The new reality of rapid-cycle analytics for effectiveness monitoring of drugs and devices

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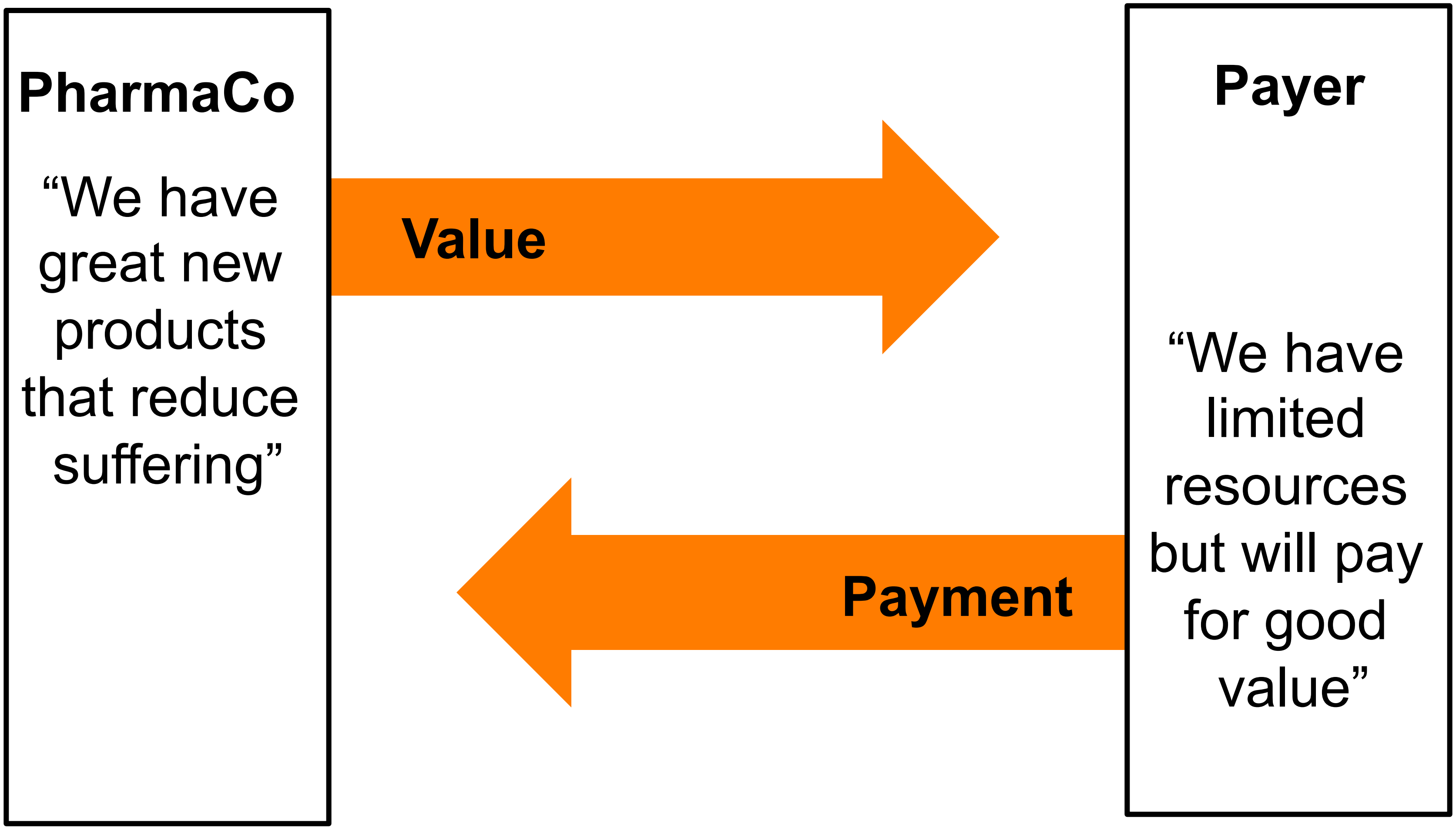
Outline

- Management Challenge
- Powerful Asset
- Where we want to be
- Rapid-cycle Analytic Solutions
- Decision Making
- Near-term Reality

Management challenge for Healthcare Payors worldwide

- Decide on coverage and payment levels for medications
- Identify delivery systems that produce high quality (HepC virus meds)
- Share risks with product manufacturers (gain sharing)
- Implement and instantaneously monitor the effect of delivery interventions (adherence improvement)

The value discussion in healthcare

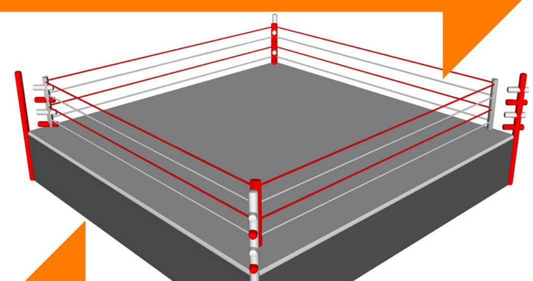


The value discussion in healthcare

PharmaCo

"We have great new products that reduce suffering"

Value



Payment

Payer

"We have limited resources but will pay for good value"

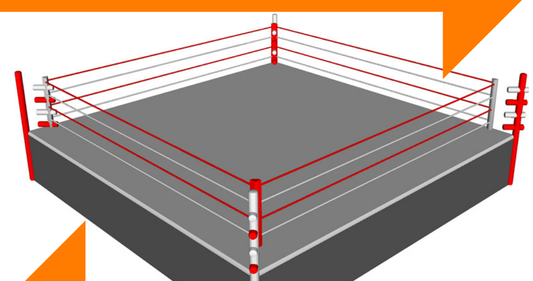
The value discussion in healthcare

PharmaCo

"We have great new products that reduce suffering"

"Payers don't believe any RWD* evidence we produce"

Value



Payment

Payer

"We have limited resources but will pay for good value"

"Pharma is presenting us with biased evidence"

* Real World Data

Consequences

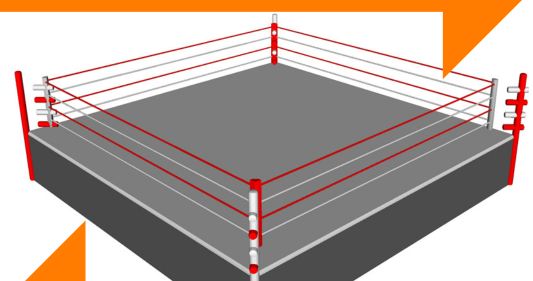
PharmaCo

"We have great new products that reduce suffering"

"Payers don't believe any evidence we produce"

Pharma misses markets

Value



Payment

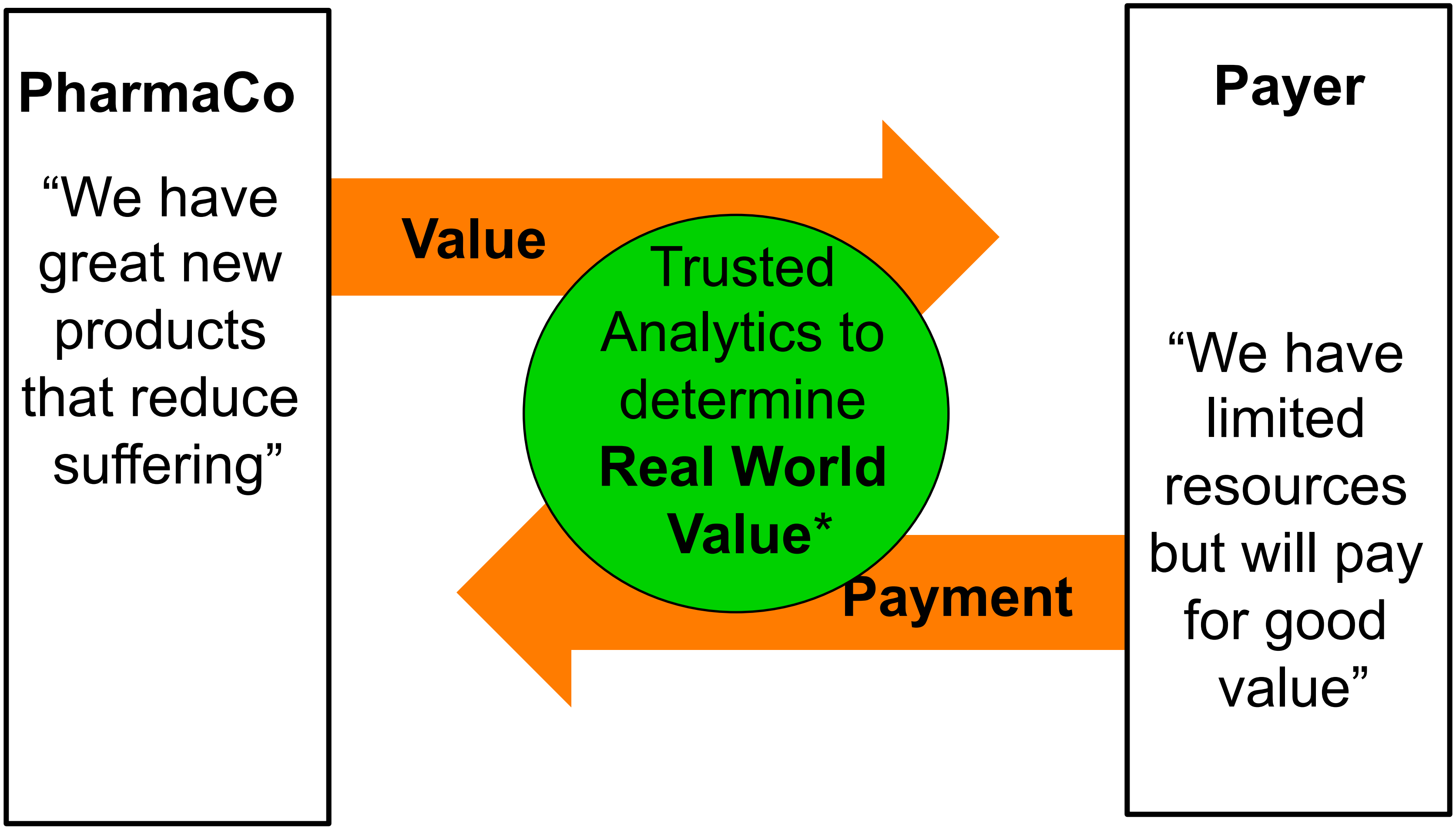
Payer

"We have limited resources but will pay for good value"

"Pharma is presenting us with biased evidence"

Payers and patients may miss true value

How can we restore trust in the conversation?



* Real world value as part of Comparative Effectiveness Research (CER)

Why can’t we just rely on RCTs?

Clinical trials are not the only way of evidence generation that really matters

- Reality:
  - Clinical trials are necessary but not sufficient
  - It is unrealistic that we will have head-to-head randomized trails

    for every intervention and

    its combinations

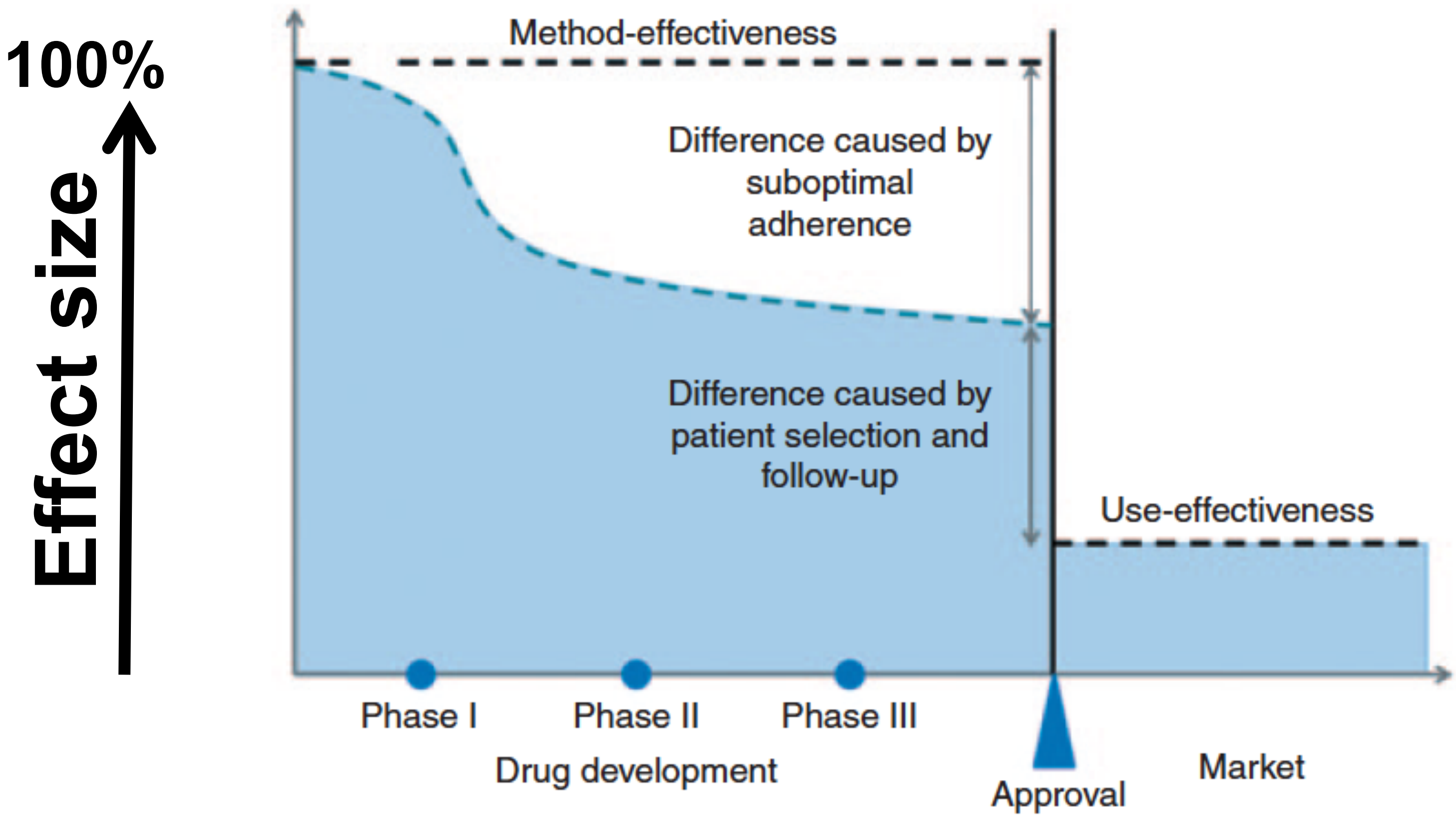
    in every patient subgroup

    that exactly mimic **routine** care
  - Most RCTs are too slow to be decision relevant
  - FDA: *Sentinel Initiative* on drug safety using electronic healthcare data of 130 million people
  - Affordable Care Act: Requires comparative effectiveness research, set up PCORI -> *PCORnet*

From Efficacy to Effectiveness

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

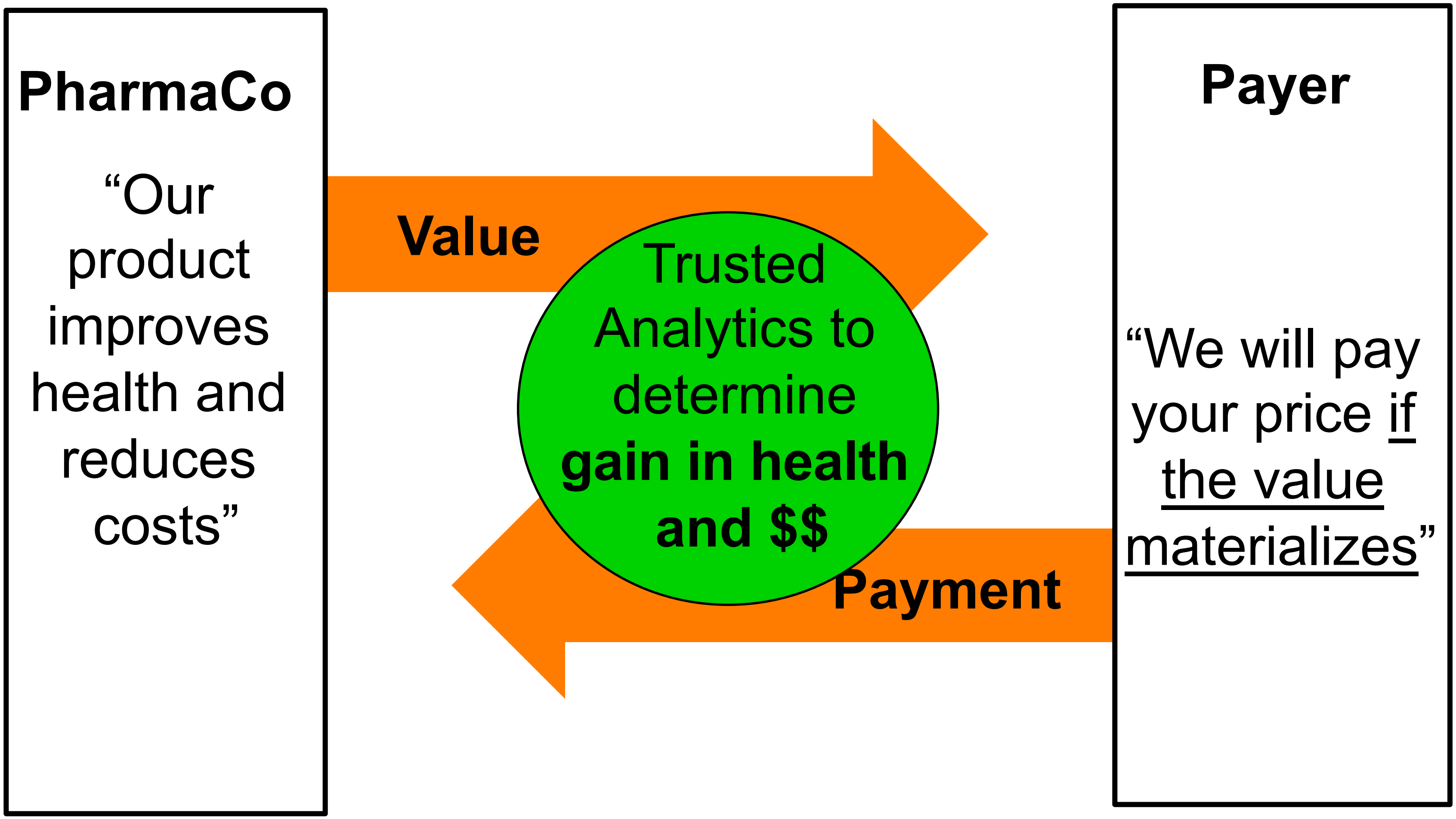
RCT | Reality of routine care



* Schneeweiss et al. JClin Epi 2013

** Vrijens & Urquhart CPT 2014

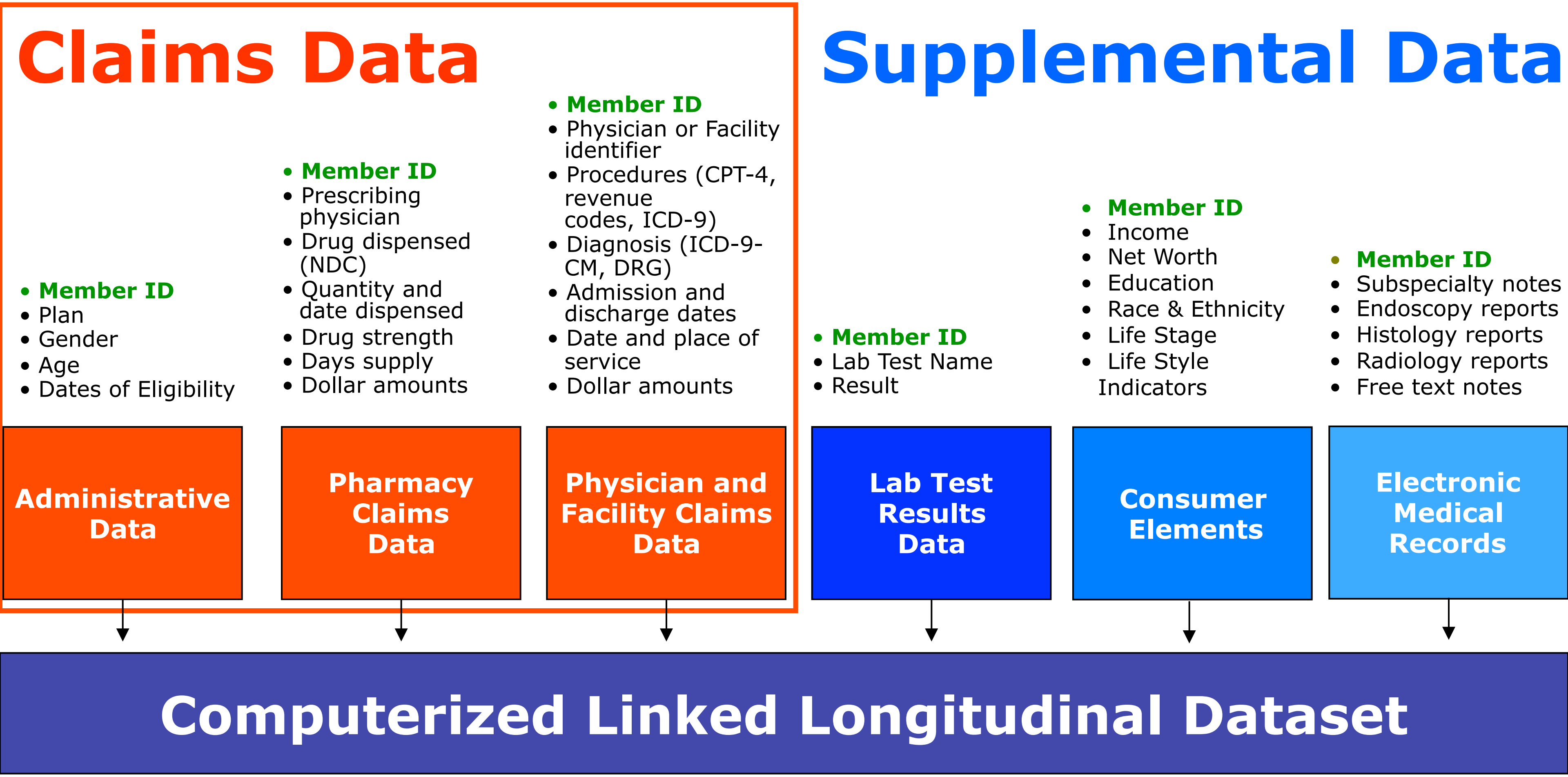
The dynamics of gain-sharing



Powerful asset: Data

Electronic health care information

- 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



Ubiquitous data, increasing pooling*

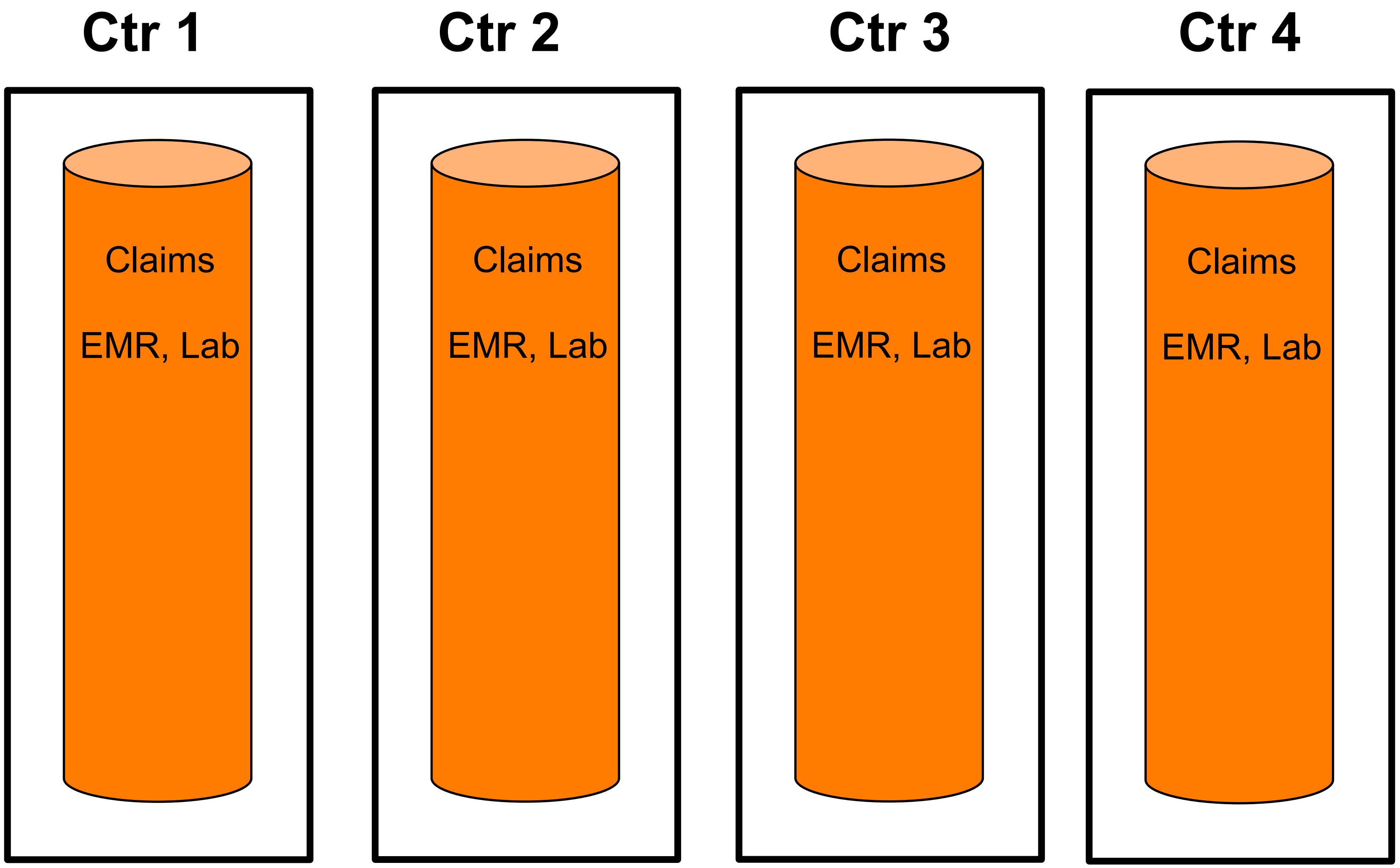
General purpose claims data	EHR data sources	In-hospital Data systems	Registries
UH	KP	Premier	Cancer (SEER)
MS	i2b2/Shrine		Cardiovascular (GWTG, etc)
WP	GE		
CMS	Humedica, Explorys		Bio repositories

Data Pooling

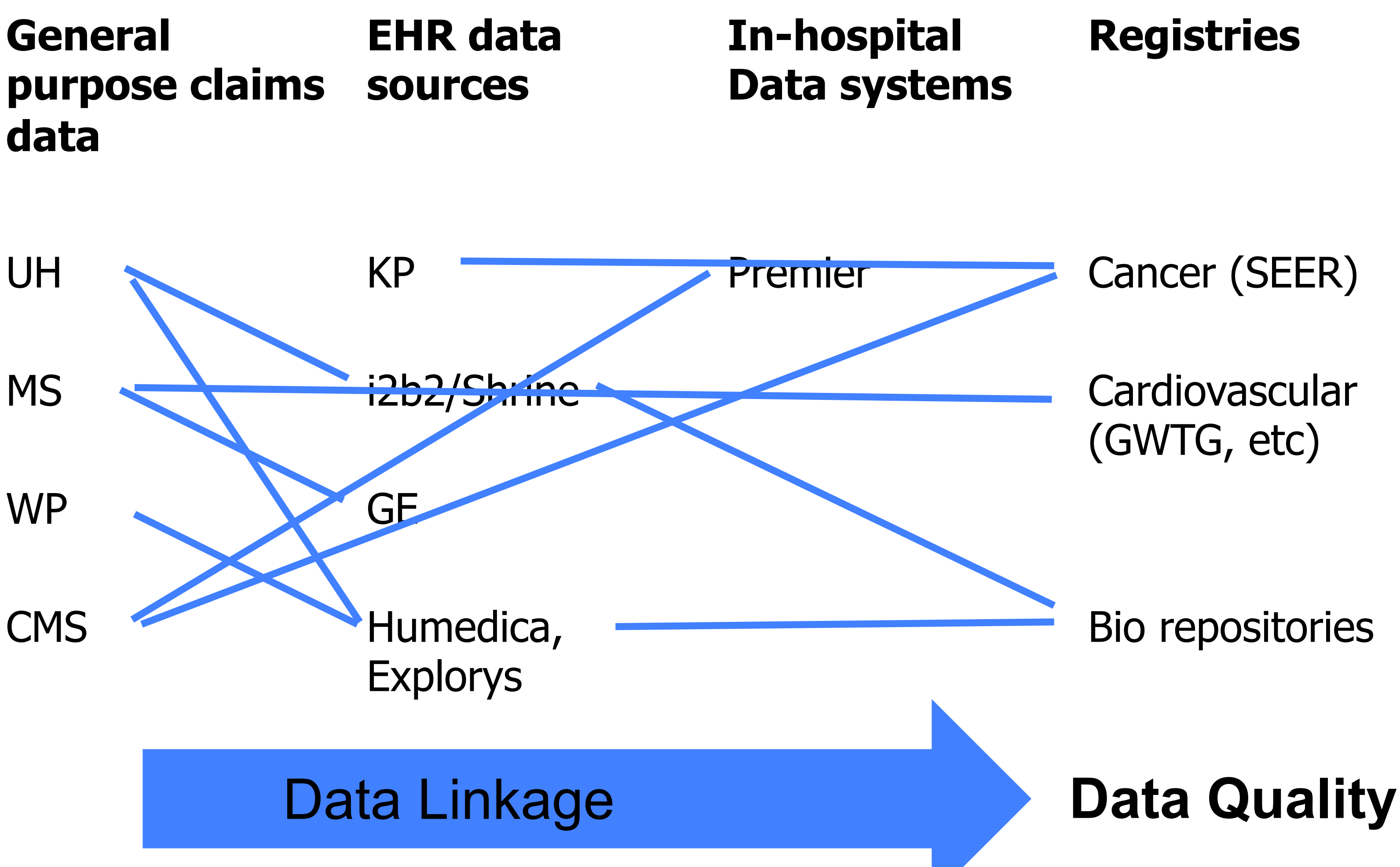
Data Quantity

* A random selection

A horizontally distributed system (Mini-Sentinel)

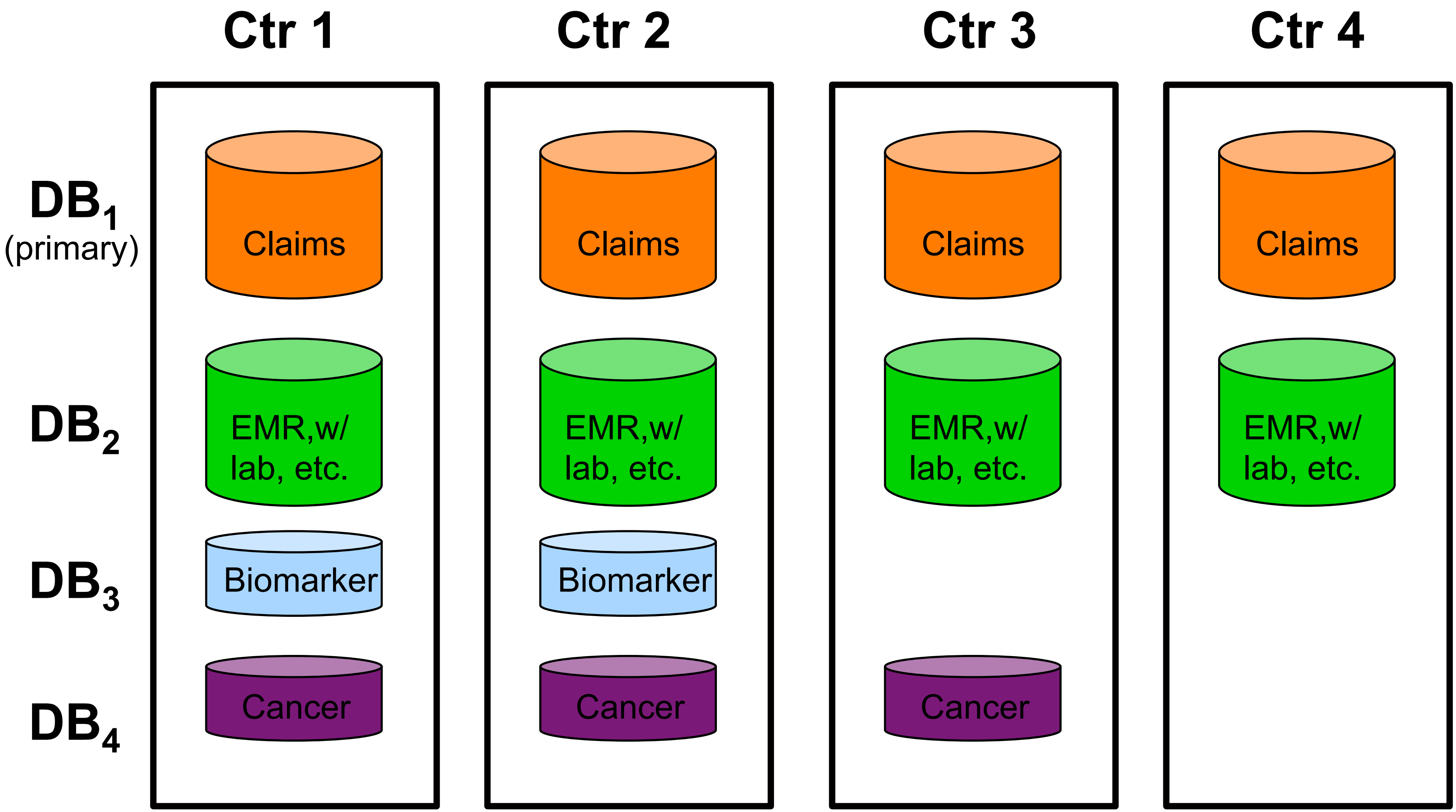


Ubiquitous data, increasing linkage*



* A random selection

A horizontally (Ctr 1-4) and vertically ($DB_{1\text{-}4}$) distributed system (PCORNet)



Secondary healthcare databases

Opportunity

- Huge amount of Data
- Longitudinal data
- Fast data refresh cycles
- Even small effects can be found
- Heterogeneity can be studied

Challenge

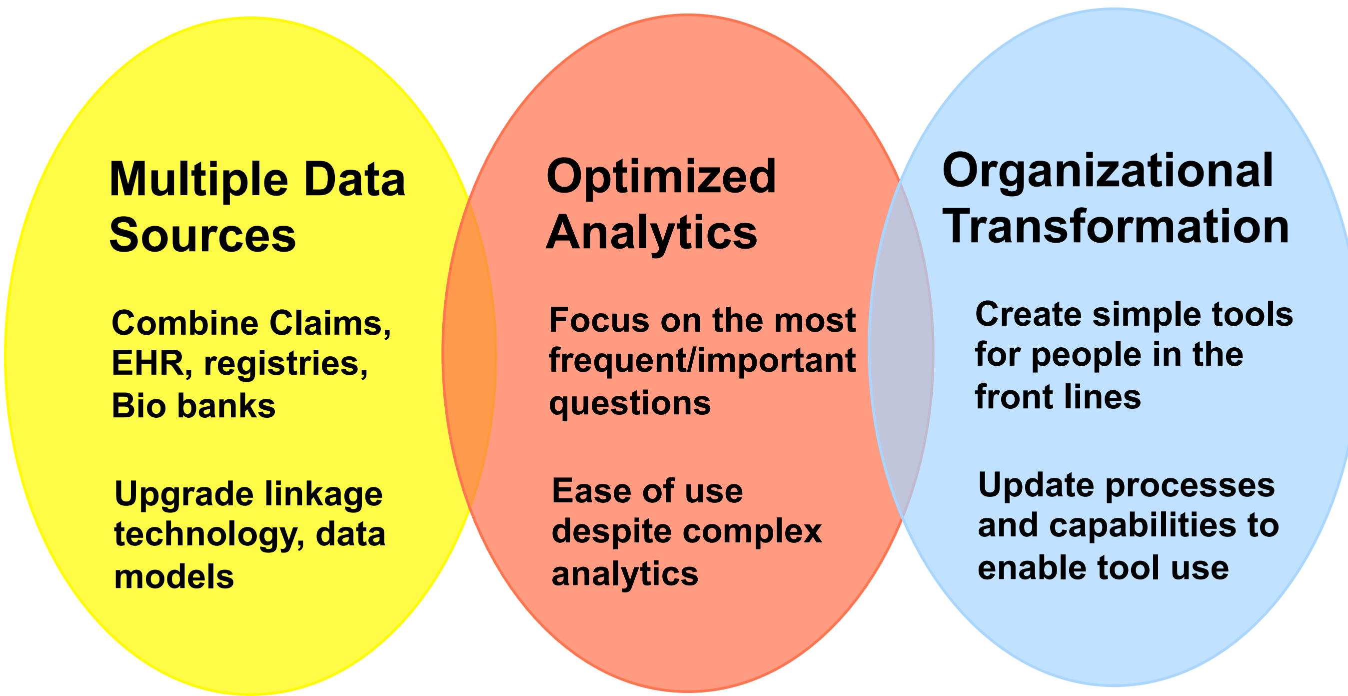
- We did not collect the data
- Not all information we want is available
- Information likely not in the format we want it to be

Where we want to be

RWD Analytics Goals for Healthcare

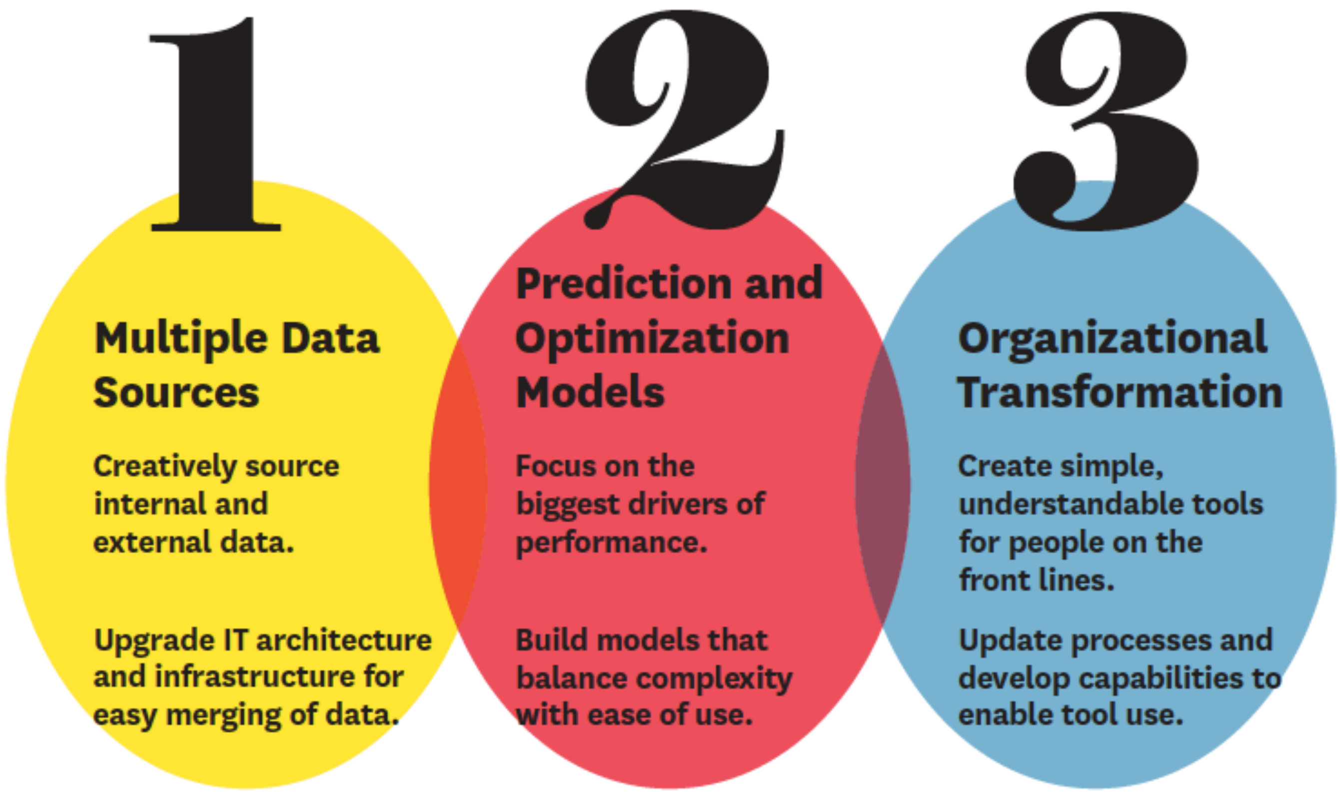
- **Analyses that support causal conclusions**
- **Analyses that**
  - run in near real-time as data refresh
  - scale to many associations of interest
  - run across multiple data sources simultaneously
  - can be conducted by moderately trained users
  - integrate well into the workflow
  - can be shared with others

Success with Big Data in Healthcare



Adapted from HBR Oct 2012

Success with Big Data `a la Harvard Business Review



HBR Oct 2012

Success with Big Data in Healthcare

Multiple Data Sources

Combine Claims, EHR, registries, Bio banks

Upgrade linkage technology, data models

Optimized Analytics

Focus on the most frequent/important questions

Ease of use despite complex analytics

Organizational Transformation

Create simple tools for people in the front lines

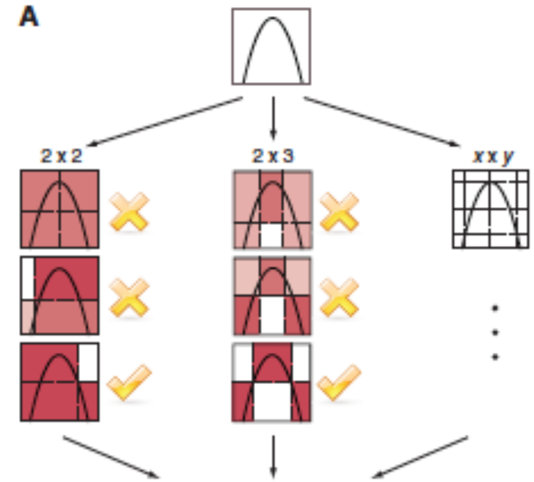
Update processes and capabilities to enable tool use

Adapted from HBR Oct 2012

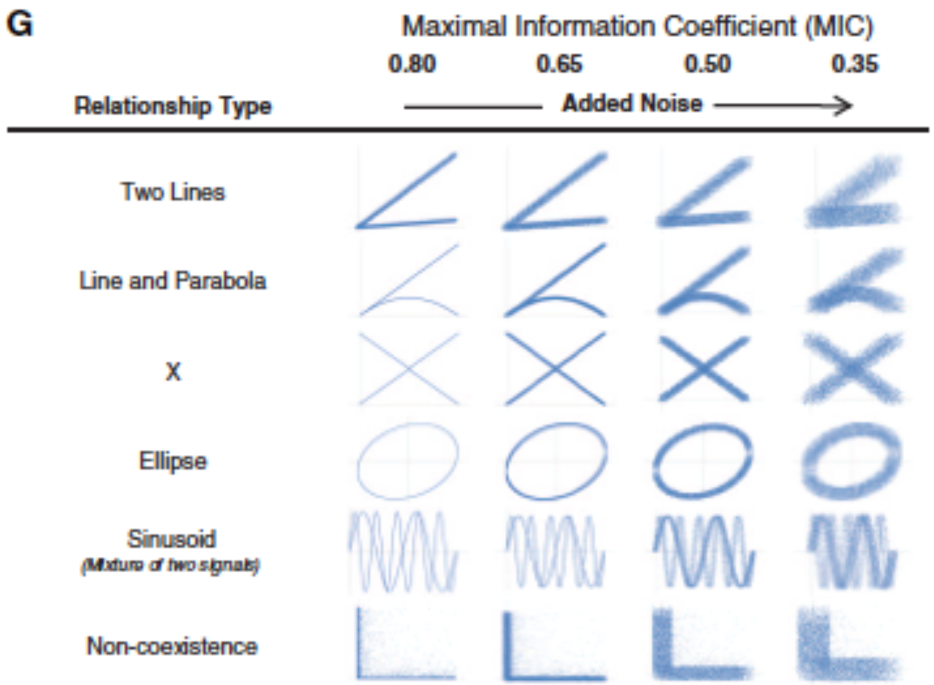
Detecting Novel Associations in Large Data Sets

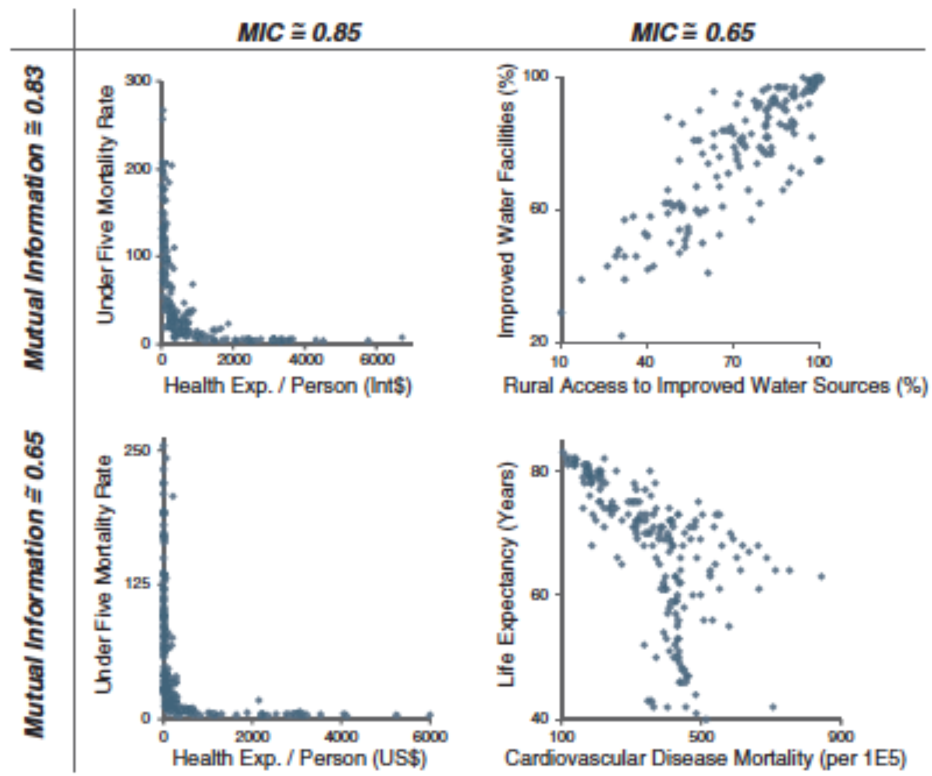
David N. Reshef,[1,2,3*†] Yakir A. Reshef,[2,4*†] Hilary K. Finucane,[5] Sharon R. Grossman,[2,6] Gilean McVean,[3,7] Peter J. Turnbaugh,[6] Eric S. Lander,[2,8,9] Michael Mitzenmacher,[10‡] Pardis C. Sabeti[2,6‡]

A



G





Minimal Components of Causal inference:

1) Temporality
2) Health Status (confounders)
3) Exposures
4) Outcomes

Health Status

Claims data
(In+ outpatient Dx)

EHR data
(clinical parms, lifestyle, QoL)

Registry data
(PRO)

Exposure

Claims data
(drug dispensing)

EHR data
(prescrib. details)

Registry data
(Device id#)

Outcomes

Claims data
(hosp. for MI via ICD-9 codes)

EHR data
(Functional status via nat. language processing)

Registry data
(PRO)

Time

Reproducible causal analyses: Why do guidelines fail us?

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2008; **17**: 200–208
Published online 17 September 2007 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1471

ISPE COMMENTARY

Guidelines for good pharmacoepidemiology practices (GPP)†

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 June 2013
EMA/95098/2010 Rev.2

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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

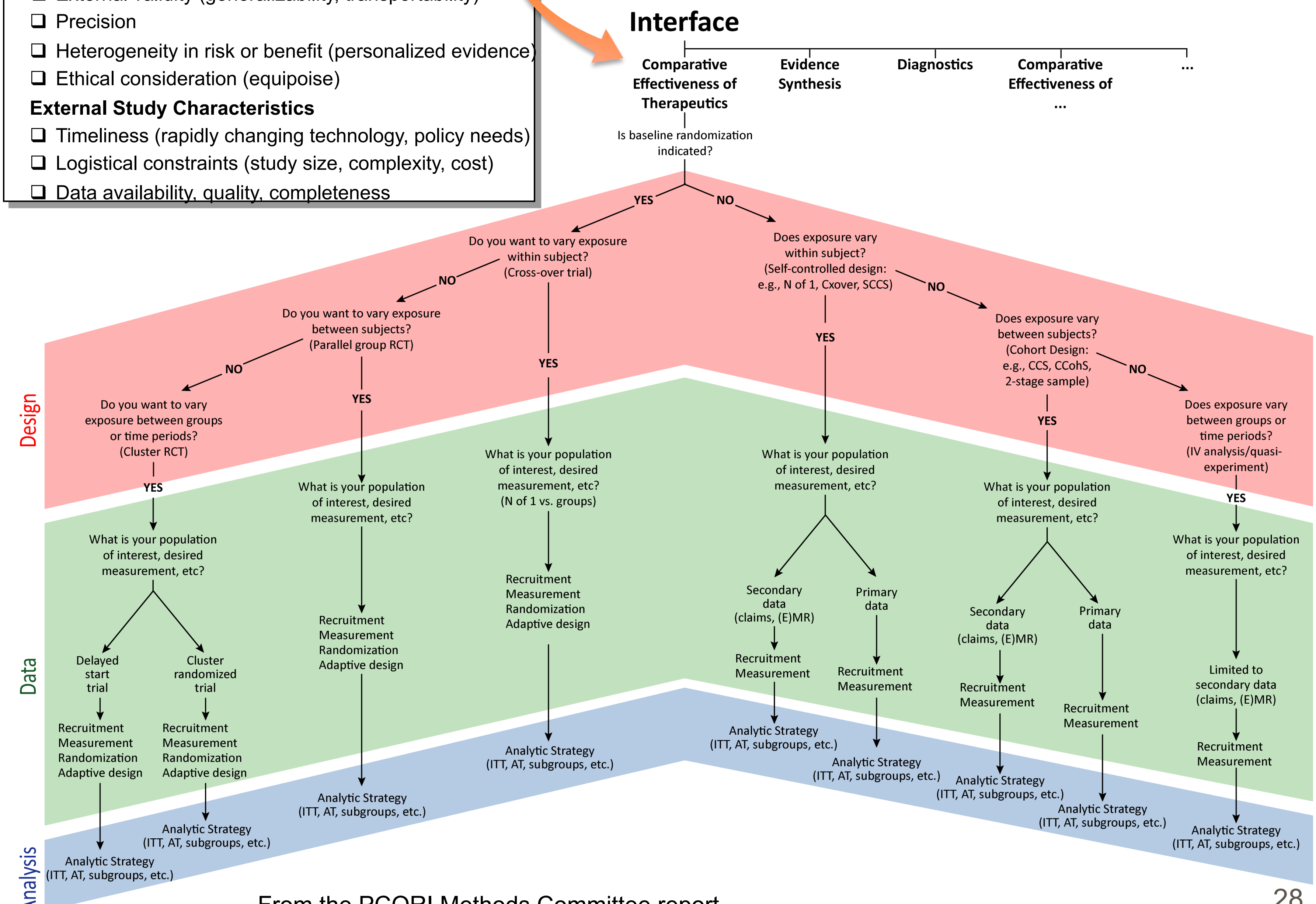
Nancy A. Dreyer, PhD; Sebastian Schneeweiss, MD; Barbara J. McNeil, MD; Marc L. Berger, MD; Alec M. Walker, MD; Daniel A. Ollendorf, MPH; and Richard E. Gliklich, MD; for the GRACE Initiative

Intrinsic Study Characteristics

- ❑ Internal validity (bias)
- ❑ External validity (generalizability, transportability)
- ❑ Precision
- ❑ Heterogeneity in risk or benefit (personalized evidence)
- ❑ Ethical consideration (equipoise)

External Study Characteristics

- ❑ Timeliness (rapidly changing technology, policy needs)
- ❑ Logistical constraints (study size, complexity, cost)
- ❑ Data availability, quality, completeness



From the PCORI Methods Committee report

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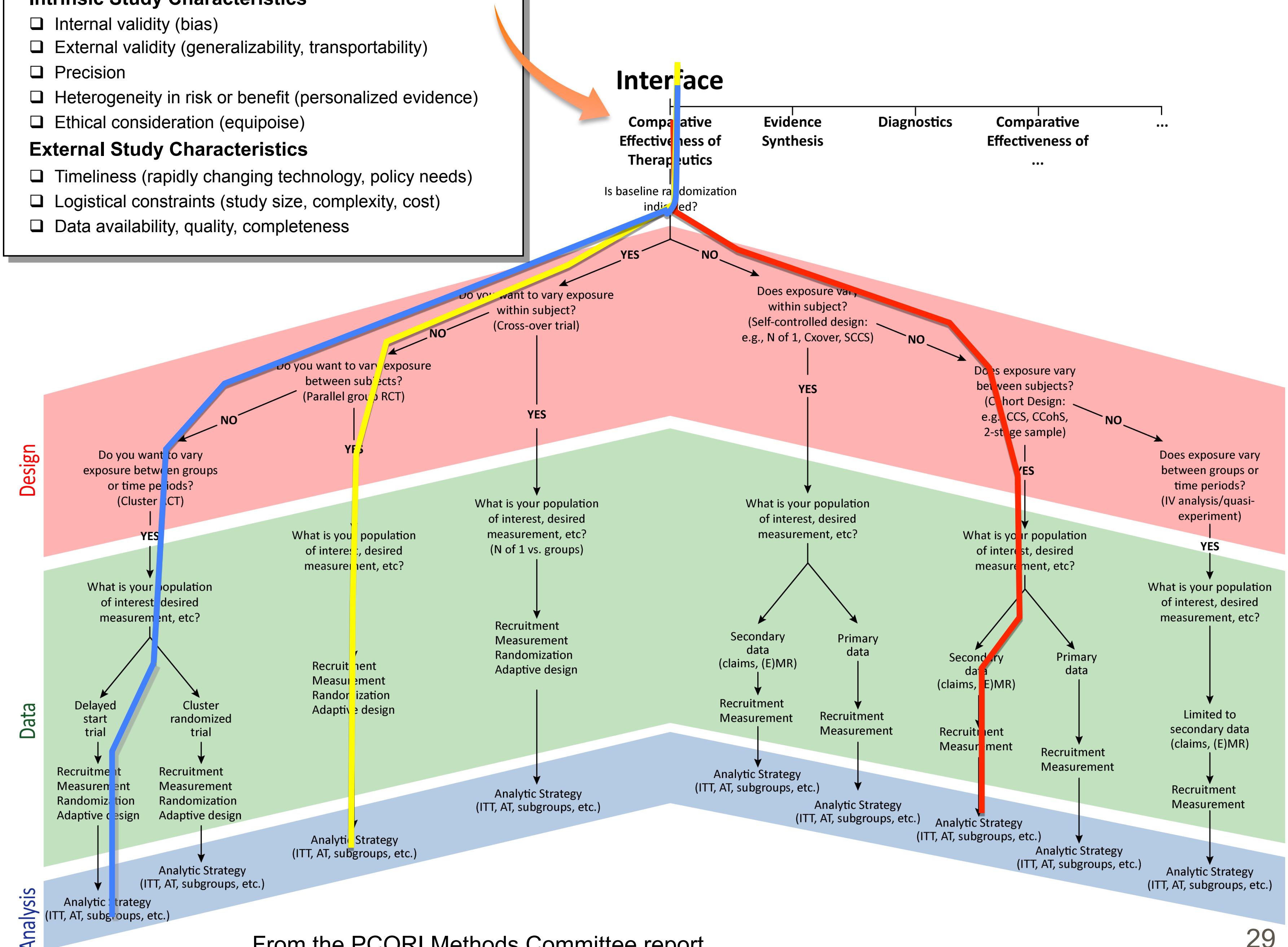
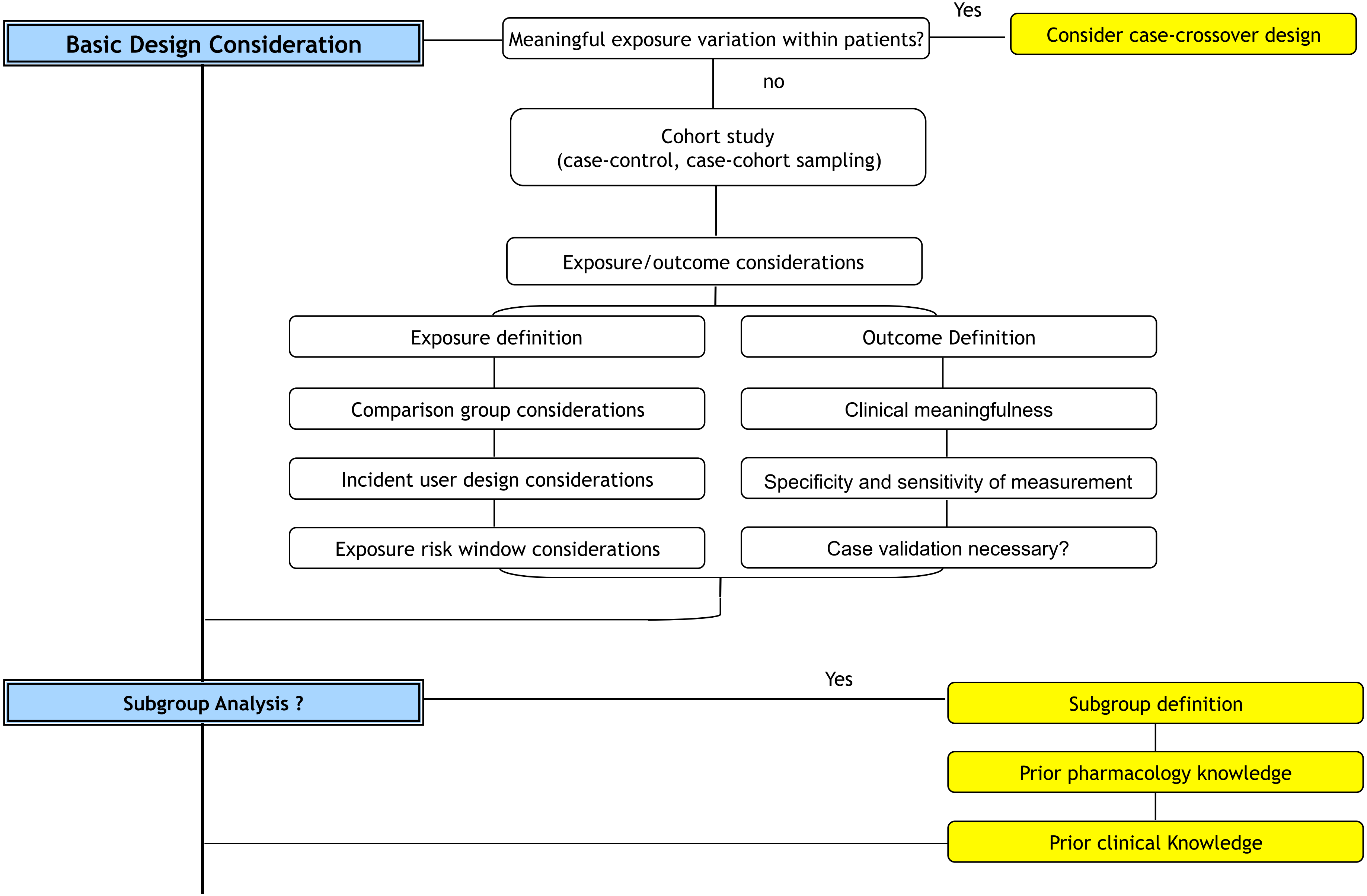


From the PCORI Methods Committee report

A basic study design approach



Schneeweiss Pharmacoepi Drug Safety 2010

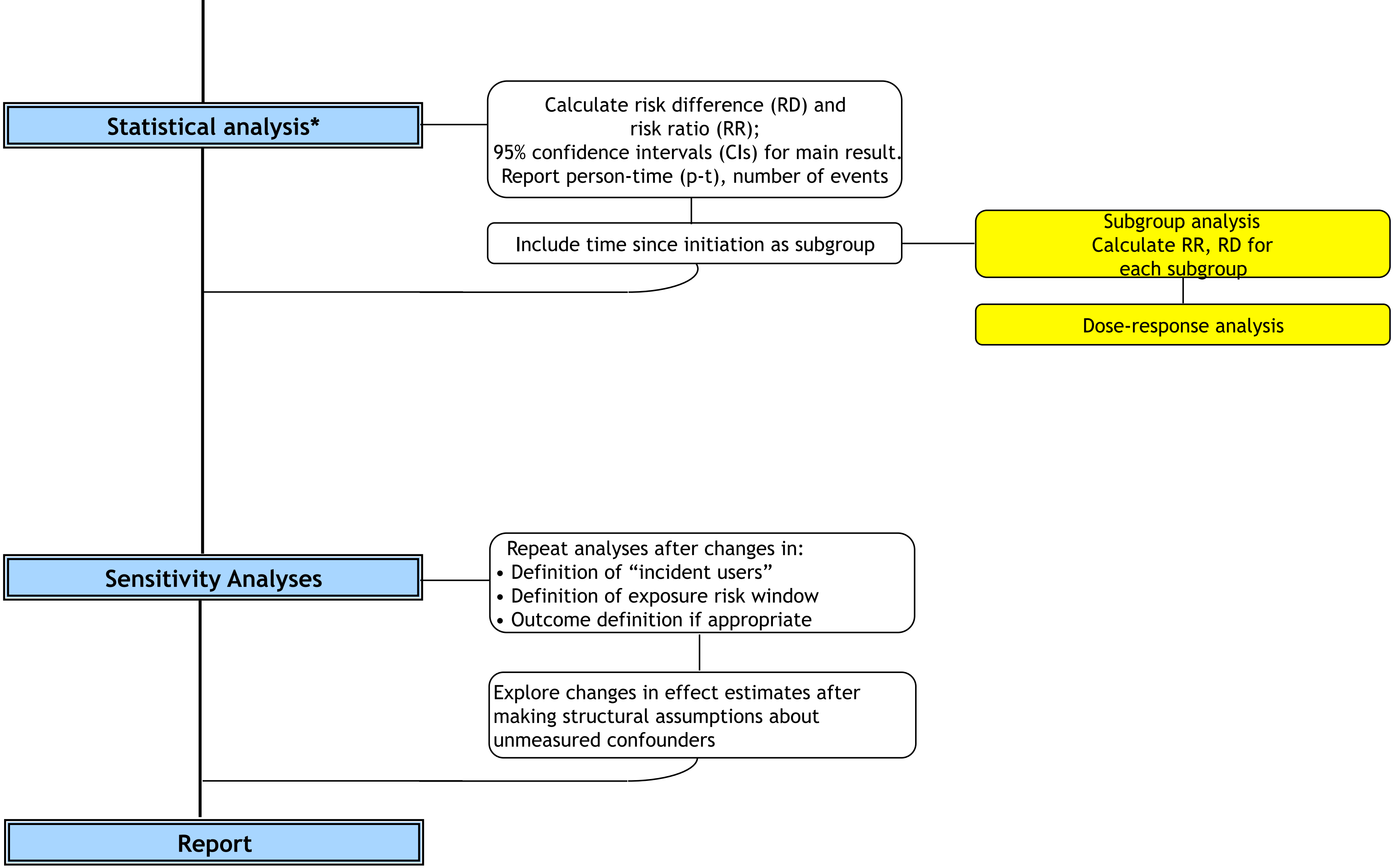
Balancing Patient Characteristics

- Defining covariates based on clinical knowledge
- Defining additional covariates empirically (high-dimensional proxy adjustment)
- Demonstrate covariate distributions by treatment group with RDs and 95% CIs
- Supplemental covariate information required that is not available in primary data source?
  - Yes → Collect additional information in subpop.
    - 2-stage sampling
    - External data source
      - -(PS Calibration)
      - - Multiple imputation

Propensity score (PS) analysis

- Missing covariate values in EMRs?
  - Yes → Multiple imputation
- Estimating propensity score
- Graphically explore PS distribution by treatment group
- Explore effect measure modification by PS: tabulate RR, RD for each PS stratum
- Effect measure modification by PS?
  - Yes → Trim 5% of patients on each end of PS distribution or **match by PS**
- •Stratify by PS deciles
  •Match on PS (1:1, 1:n, 1:n:m)
- Demonstrate covariate balance by treatment group with RDs and 95% CIs

Schneeweiss Pharmacoepi Drug Safety 2010



*For illustration purposes only an analysis after PS matching is shown.

Schneeweiss Pharmacoepi Drug Safety 2010

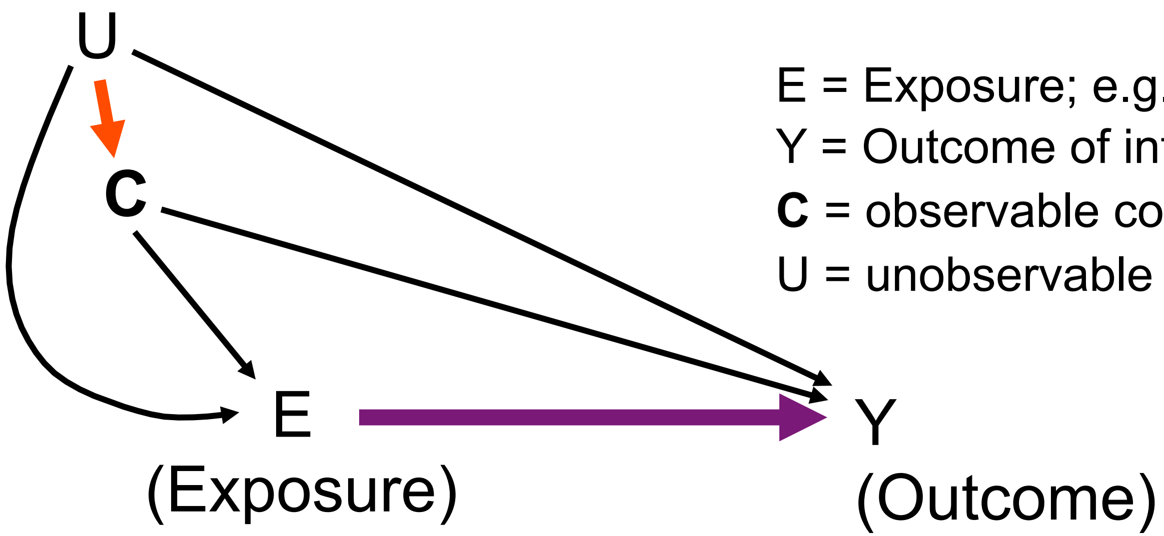
Longitudinal insurance claims databases

```
---------- ID=********** dob=**/**/1948 sex=M eligdt=1/2000 indexdt=6/2001  ------------------

Service  Site of                     ___________Drug or Procedure________   _________Diagnosis_____
Date     Service  Prov Type          Code   Description                     * Code   Description
---------------------------------------------------------------------------------------------------
10/01/00 OFFICE   Family Practice    90658  INFLUENZA VIRUS VACC/SPLIT         V048  VACC FOR INFLUEN
10/01/00 Rx       Pharmacy                  CIPROFLOXACIN 500MG TABLETS              10
11/05/00 OFFICE   Family Practice    17110  DESTRUCT OF FLAT WARTS, UP         0781  VIRAL WARTS
11/07/00 Rx       Pharmacy                  CIPROFLOXACIN 500MG TABLETS              10
01/15/01 Rx       Pharmacy                  CIPROFLOXACIN 500MG TABLETS              10
06/25/01 OFFICE   Emerg Clinic       99070  SPECIAL SUPPLIES                * 84509  SPRAIN OF ANKLE
                                                                              E927   ACC OVEREXERTION
06/30/01 OFFICE   Orthopedist        99204  OV,NEW PT.,DETAILED H&P,LOW     * 72767  RUPT ACHILL TEND
06/30/01 OFFICE   Internist/Gener    99202  OV,NEW PT.,EXPD.PROB-FOCSD      * 84509  SPRAIN OF ANKLE
         OUTPT HP Anesthesiologis    01472  REPAIR OF RUPTURED ACHILLES     * 84509  SPRAIN OF ANKLE
                  Hospital           27650  REPAIR ACHILLES TENDON          * 84509  SPRAIN OF ANKLE
                                     85018  BLOOD COUNT; HEMOGLOBIN         * 84509  SPRAIN OF ANKLE
                  Orthopedist        27650  REPAIR ACHILLES TENDON          * 84509  SPRAIN OF ANKLE
06/30/01 OFFICE   Orthopedist        29405  APPLY SHORT LEG CAST            * 72767  RUPT ACHILL TEND
07/30/01 OFFICE   Orthopedist        29405  APPLY SHORT LEG CAST            * 72767  RUPT ACHILL TEND
08/13/01 OFFICE   Orthopedist        L2116  AFO TIBIAL FRACTURE RIGID       * 72767  RUPT ACHILL TEND
```

Longitudinal patterns of codes of any type (Dx, Px, Rx, Lx etc.) are proxies of disease activity, severity and general health state.

Unobservable confounding and proxy measures



E = Exposure; e.g.
Y = Outcome of interest
C = observable confounder (serves as a proxy)
U = unobservable confounder

Unobserved confounder	Observable proxy	Coding
Very frail health	Use of **oxygen canister**	CPT-4:
Acutely sick but not that bad off	Receiving a **code for hypertension** during a hospital stay	ICD-9:
Health seeking behavior	**Regular check-up** visit; regular screening exams	ICD-9, CPT-4 # GP visits
Fairly health senior	Receiving the **first lipid-lowering medication** at age 70	NDC
Chronically sick	Regular visits with specialist, hospitalization; many prescription drugs	# specialist visits, NDC

Three main data dimensions

Data type

Structured health data:
- Inpatient Diagnoses *
- Outpatient Diagnoses *
- Inpatient Procedures **
- Outpatient Procedures **
- Medication dispensings ***
- Lab test results

Unstructured text notes

Frequency/ Intensity

- Once
- Sporadic
- Frequent

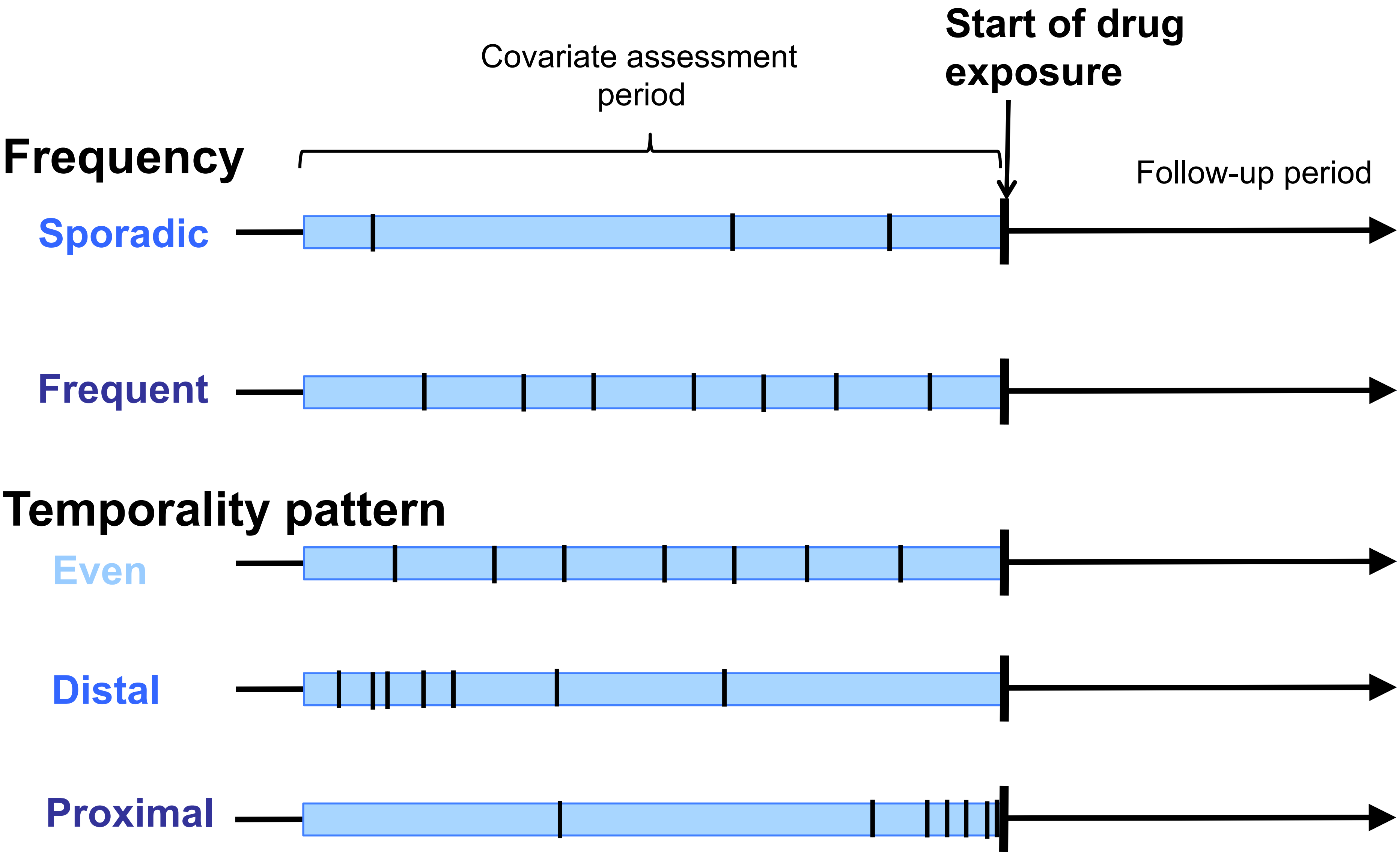
Temporality

- Proximal to exposure
- Evenly distributed
- Distal to exposure start

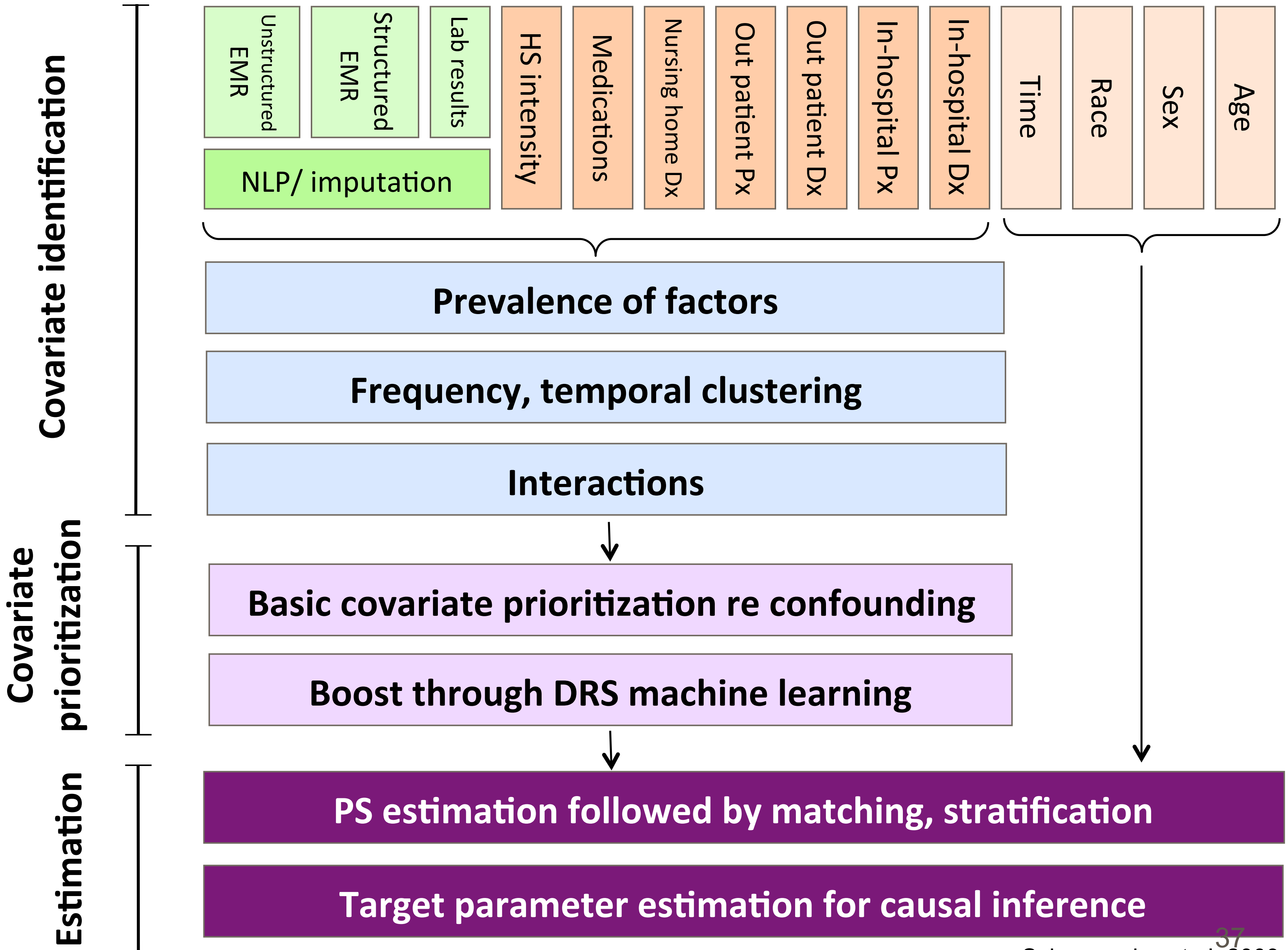
Standard coding examples: * ICD: International classification of disease; ** CPT: Current procedure terminology; *** NDC: National Drug Code, ATC: Anatomical Therapeutic Classification

Schneeweiss et al. 2009, Rassen et al 2011

Confounding frequency and temporality patterns



High-dimensional data adjustment



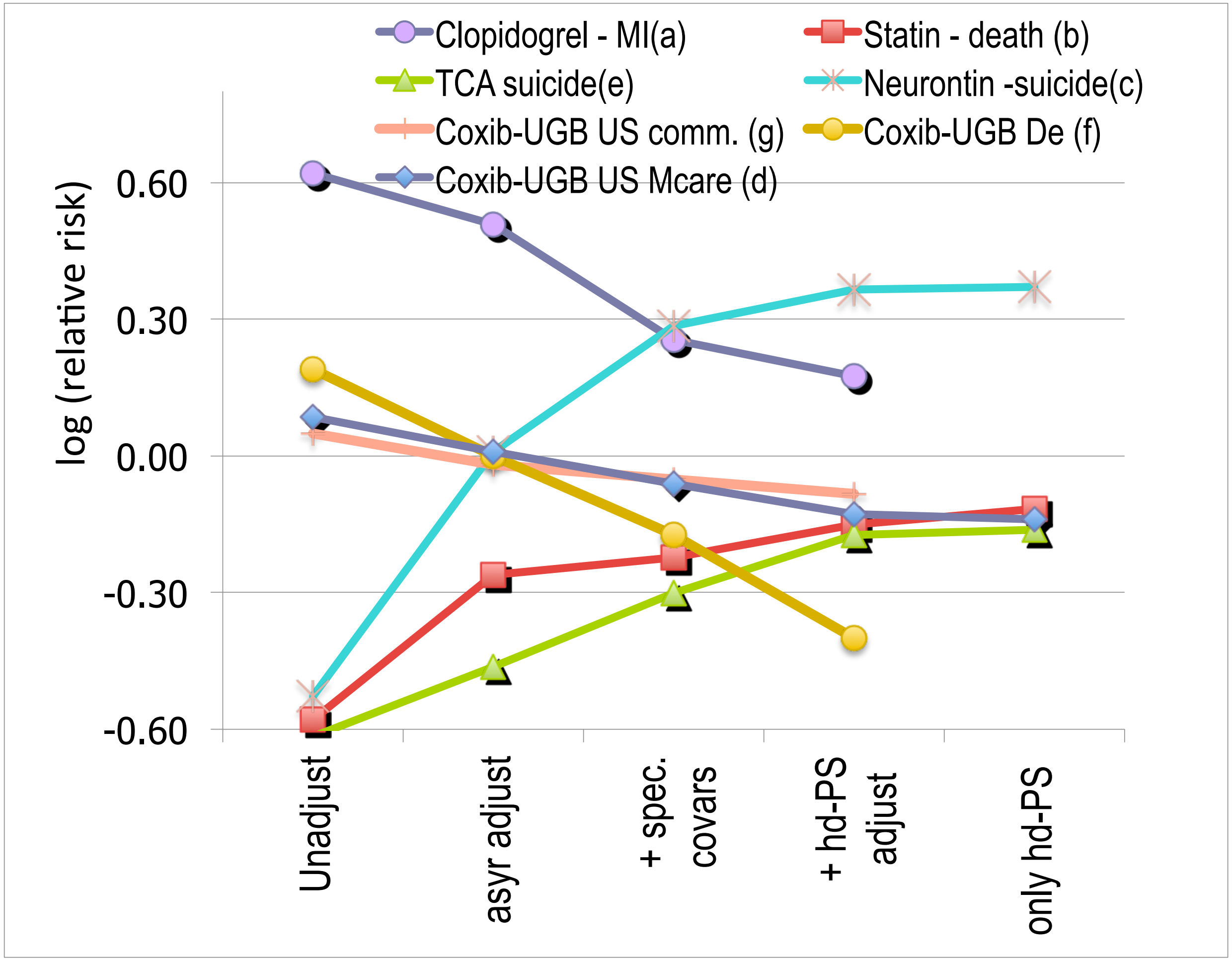
Schneeweiss et al. 2009,

Performance in empirical database studies

Data sources

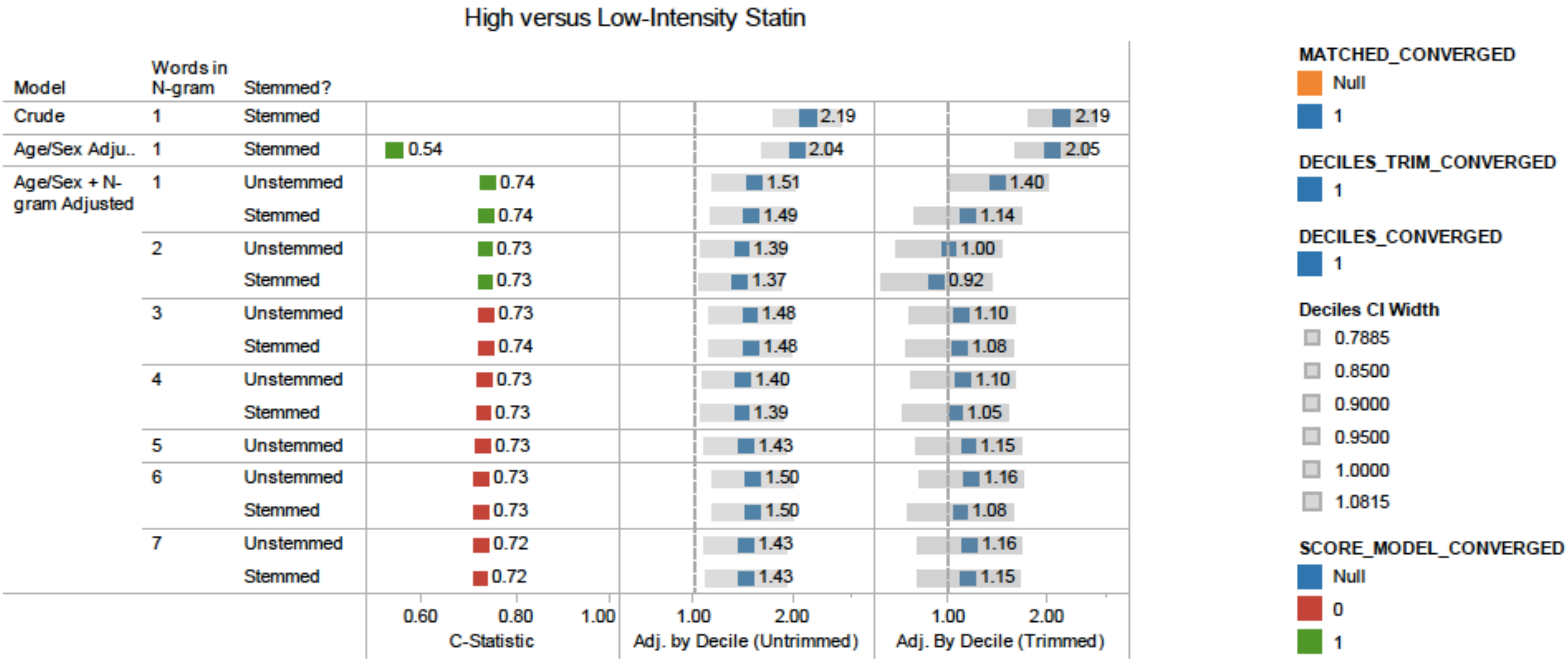
<u>Claims databases:</u>
U.S. Medicare
U.S. commercial
Canada
Germany

<u>HER databases:</u>
United Kingdom
Regenstrief



(a) Rassen JA, et al.. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention. Circulation 2009;120:2322-9.
(b + d) Schneeweiss S, et al.. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512–22.
(c) Patorno E, et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA 2010;303:1401-9
(e) Schneeweiss S, et al. The comparative safety of antidepressant agents in children regarding suicidal acts. Pediatrics 2010;125: 876–88
(f) Garbe E, et al. High-dimensional versus conventional propensity scores in a comparative effectiveness study of coxibs and reduced upper gastrointestinal complications. Eur J Clin Pharmacol. 2012 Jul 5.
(g) Le, et al. Effects of aggregation of drug and diagnostic codes on the performance of the hdPS algorithm. BMC Med Res Methodology 2013;13:142.

Performance of algorithmic EHR word stem adjustment



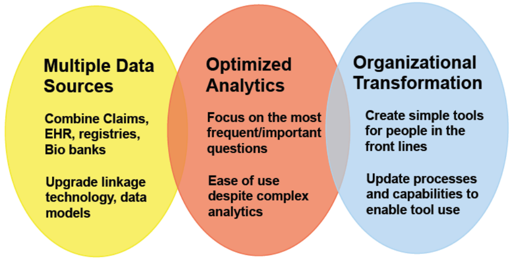
<u>1 Word:</u>
leukocytosi
oxycontin
haptic
extracrani
scleral
splenomengali
valium
cardizem

<u>2 Words:</u>
site cervix
categori within
specimen
categori
peripher edema
maxillari sinus
differenti diagnos
high hpv

<u>3 Words:</u>
specimen site cervix
site cervix endocervix
categori within normal
impress ct abdomen
or 3 view
white female a
exam ct abdomen

Rassen et al. 2013

Success with Big Data in Healthcare



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  - run in near real-time as data refresh
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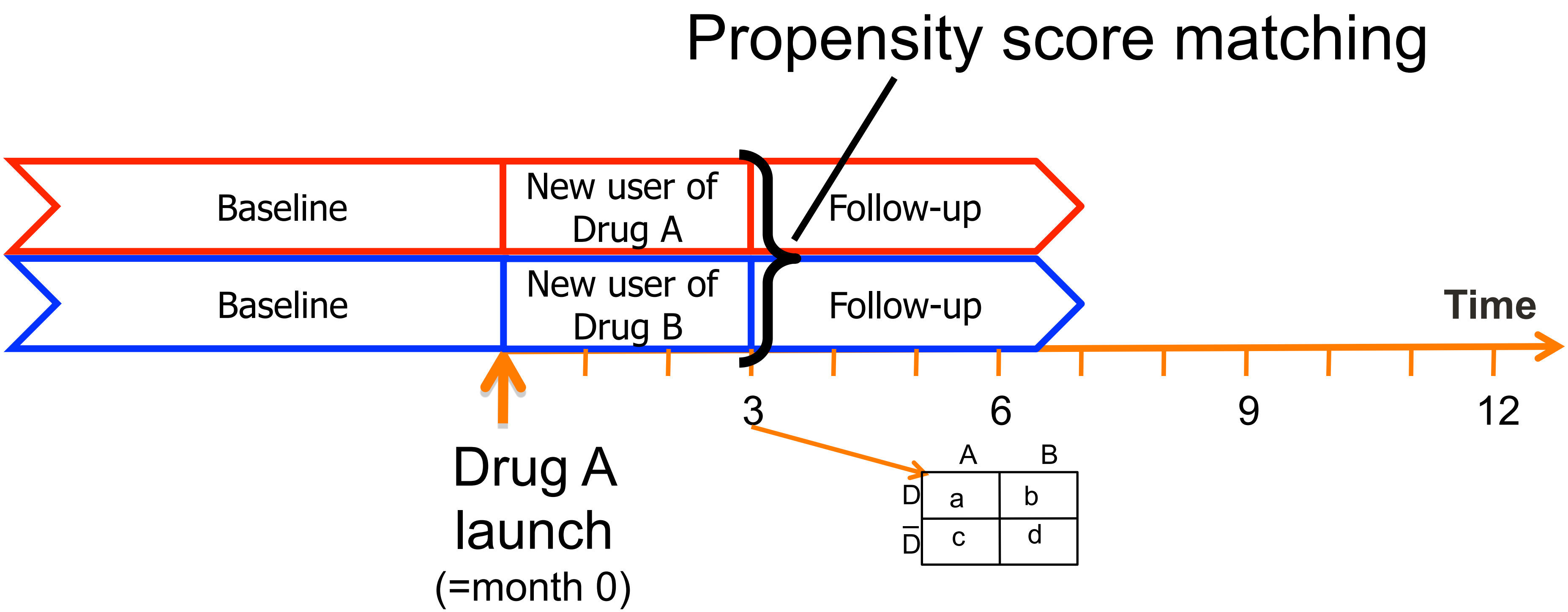
Evidence generation as data refresh

A sequential cohort design



Schneeweiss et al. CPT 2011

Evidence generation as data refresh

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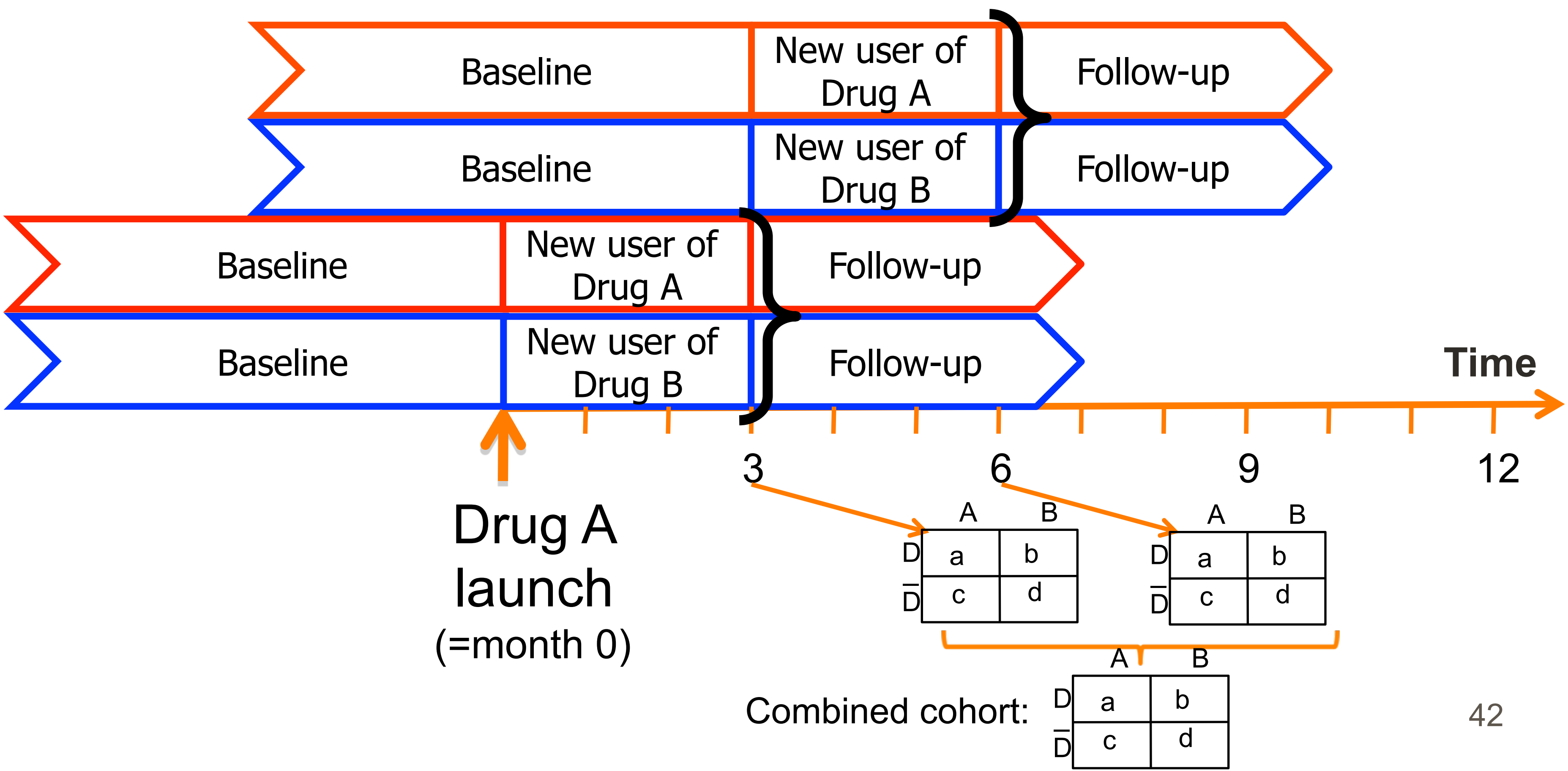

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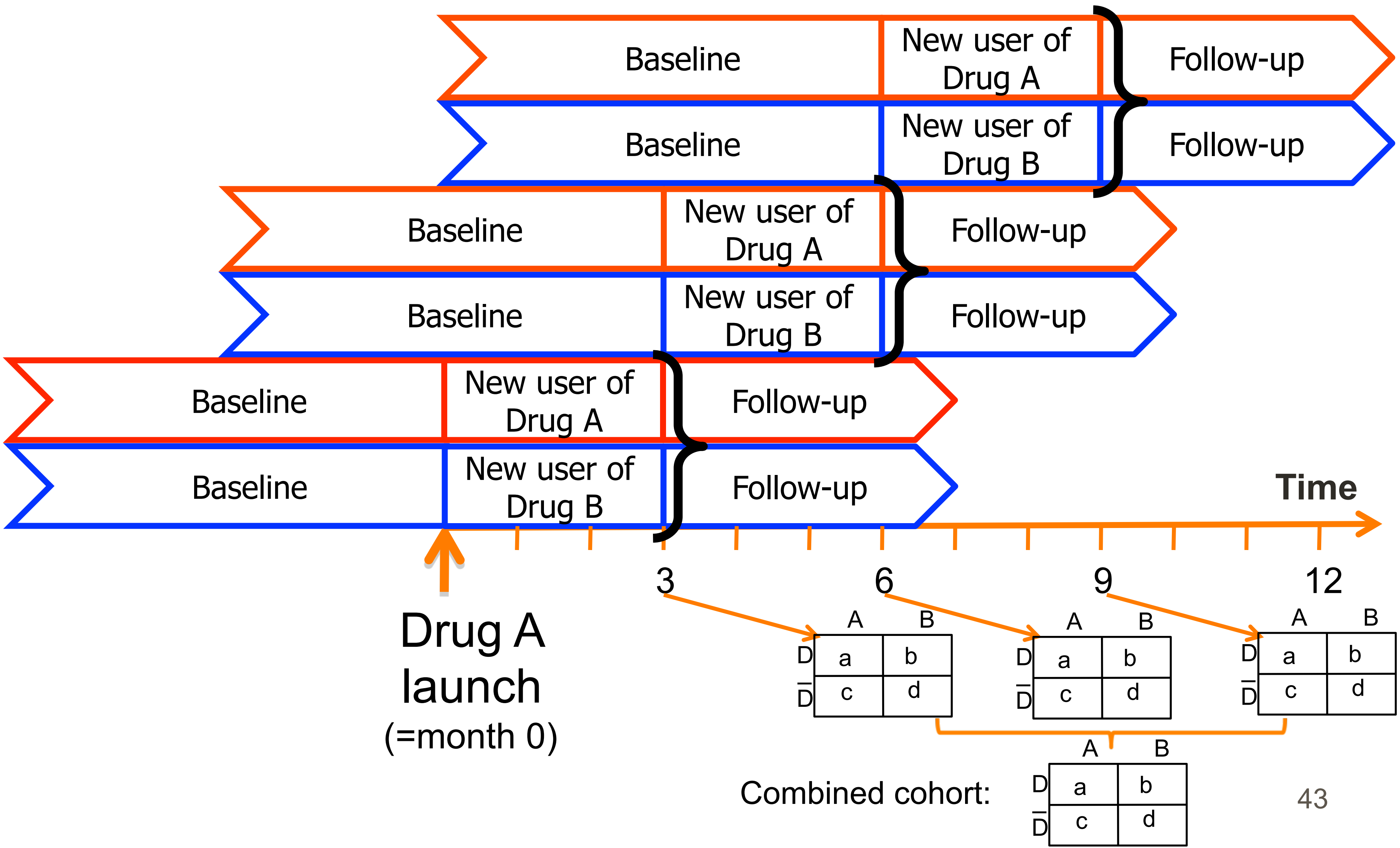
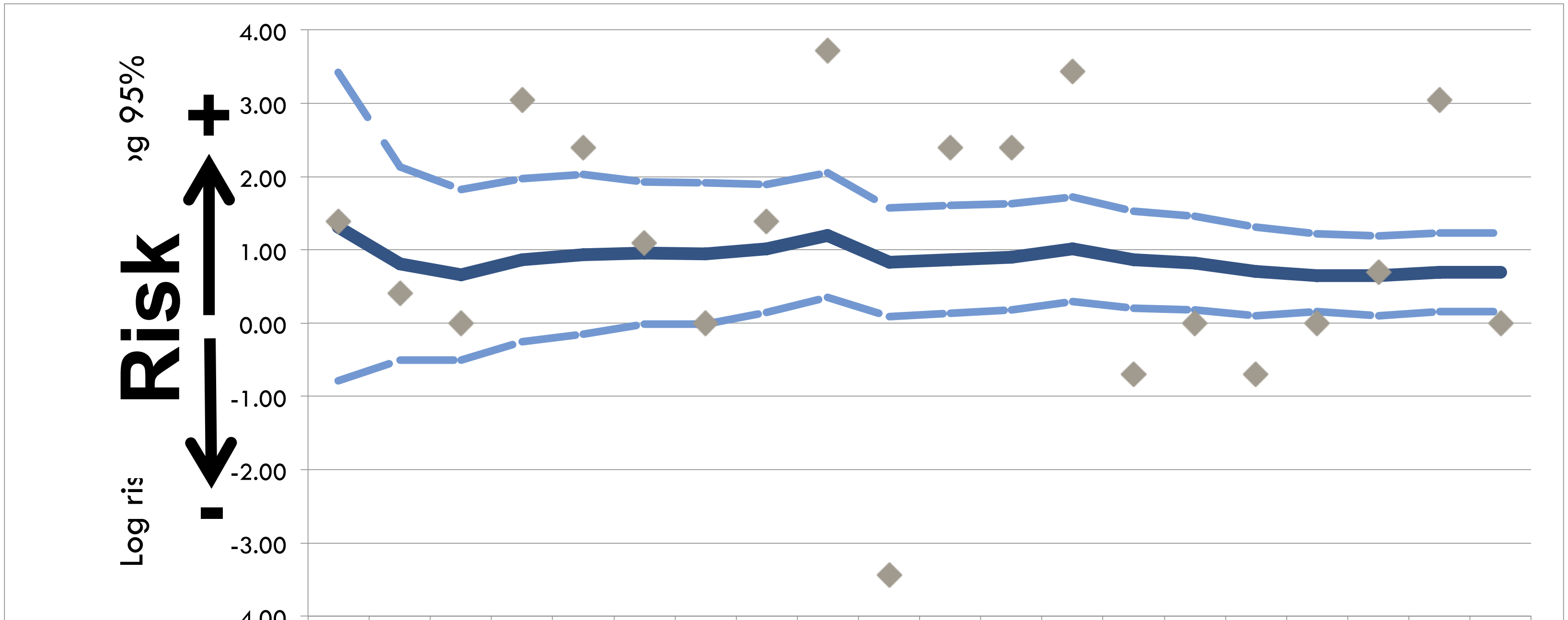


Output of cumulating data in a monitoring system



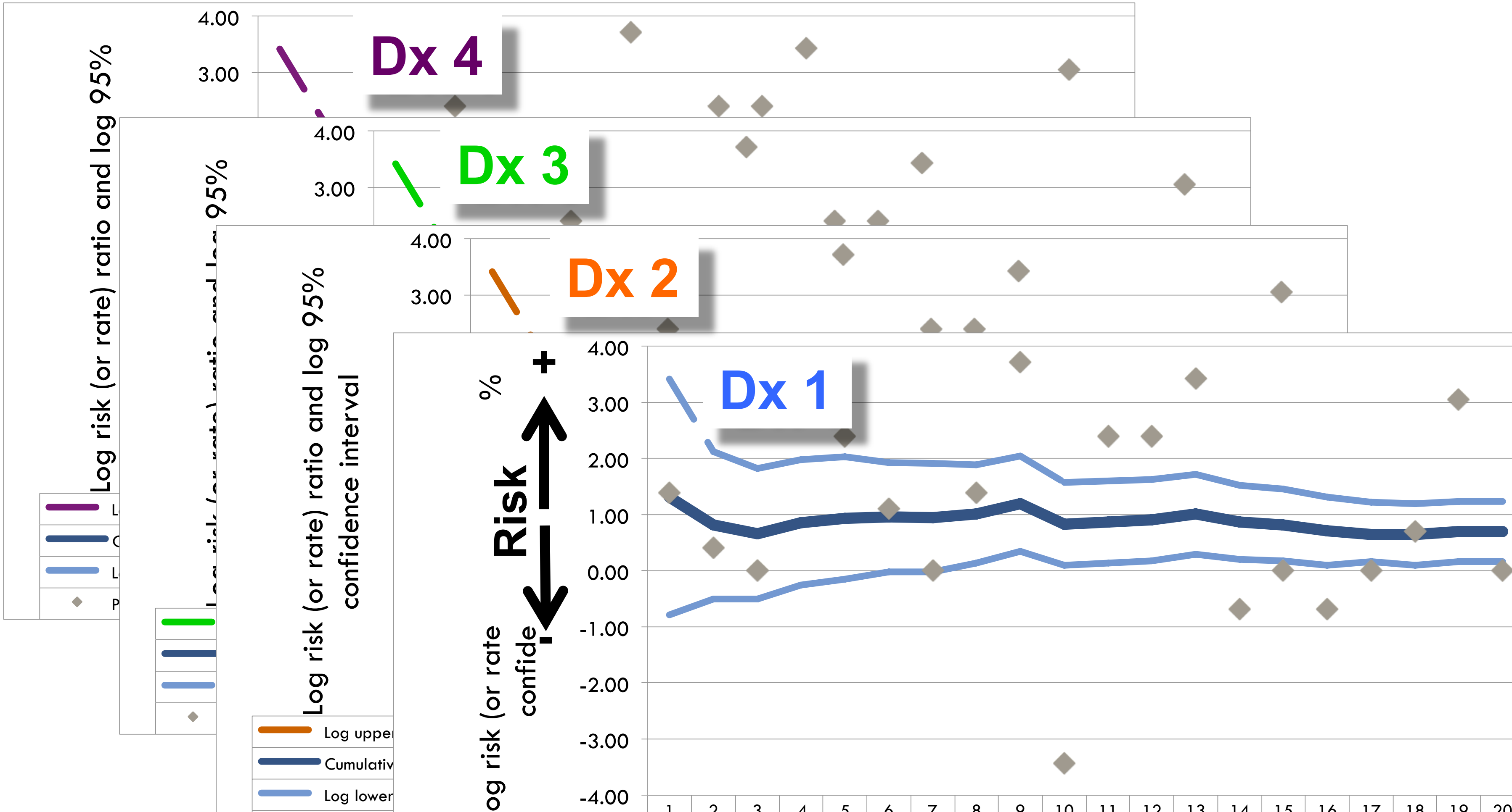
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Log upper 95% CI	3.42	2.13	1.82	1.97	2.03	1.93	1.91	1.89	2.05	1.57	1.60	1.63	1.72	1.53	1.46	1.31	1.22	1.19	1.23	1.23
Cumulative lnRR	1.32	0.81	0.66	0.86	0.94	0.96	0.95	1.02	1.20	0.83	0.87	0.90	1.01	0.86	0.82	0.71	0.64	0.65	0.70	0.69
Log lower 95% CI	-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

	A	B
D	a	b
$\bar{D}$	c	d

	A	B
D	a	b
$\bar{D}$	c	d

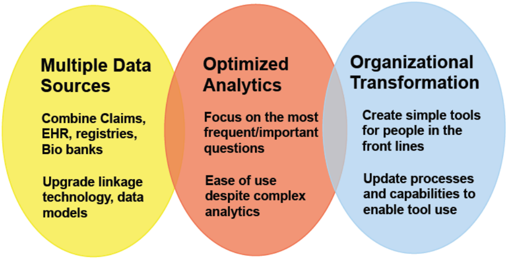
	A	B
D	a	b
$\bar{D}$	c	d

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

Success with Big Data in Healthcare



- **Analyses that support causal conclusions**
- **Analyses that**
  - run in near real-time as data refresh
  - scale to many associations of interest
  - run across multiple data sources simultaneously
  - can be conducted by moderately trained users
  - integrate well into the workflow
  - can be shared with external partners

Speed is a relative measure!

Mini-Sentinel and Regulatory Science — Big Data Rendered Fit and Functional

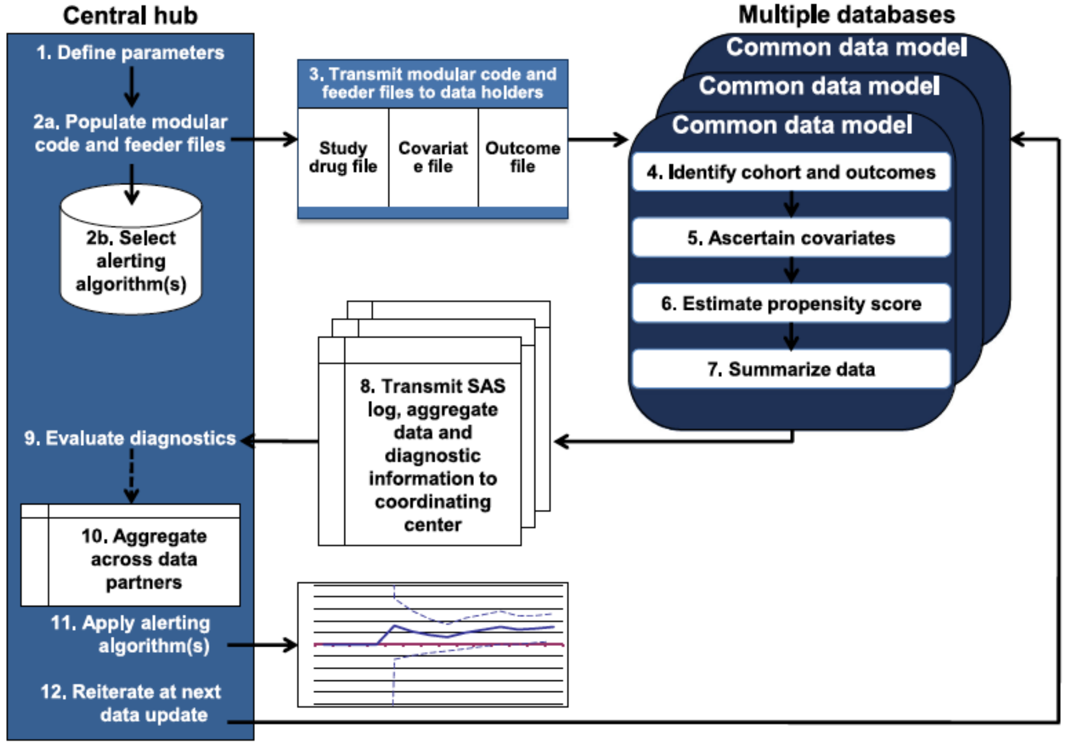
Bruce M. Psaty, M.D., Ph.D., and Alasdair M. Breckenridge, M.D.

N ENGL J MED 370;23 NEJM.ORG JUNE 5, 2014

study design. With the MSDD in place, a full-scale observational study to evaluate the association between angioedema and drugs targeting the renin–angiotensin system was designed, conducted, and completed in 11 months.[1]

Decision makers need this done in hours !

FDA Mini Sentinel PROMPT modules

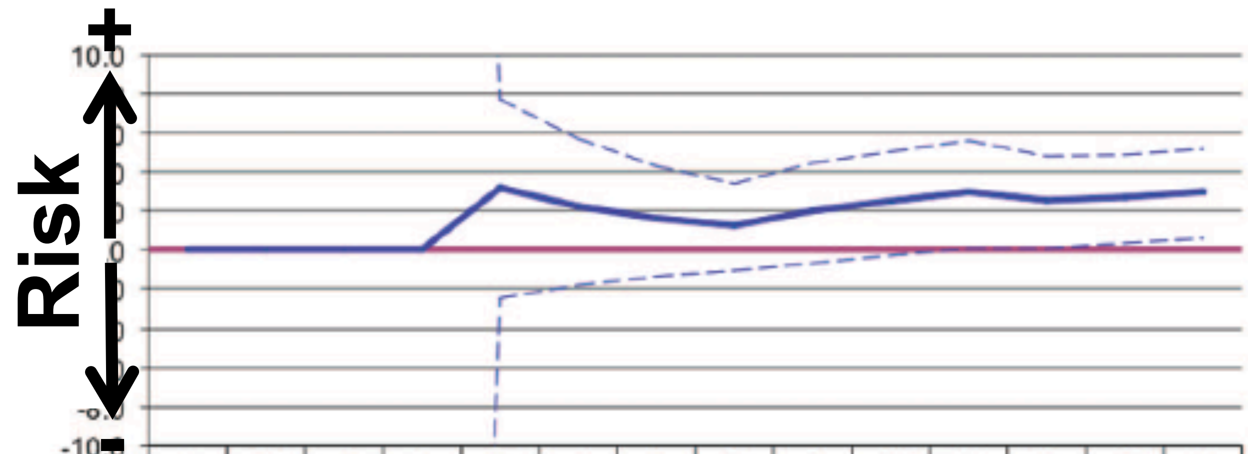


A modular, prospective, semi-automated drug safety monitoring system for use in a distributed data environment

Joshua J. Gagne*, Shirley V. Wang, Jeremy A. Rassen and Sebastian Schneeweiss

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02120, USA

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

Group 1, p=0.20

Group 1, p=0.10
Group 3, α=0.40

Group 1, p=0.05
Group 2, α=0.30
Group 3, α=0.20
Group 4, p=0.05

Rhabdomyolysis added to label

Baycol launched

First published case report

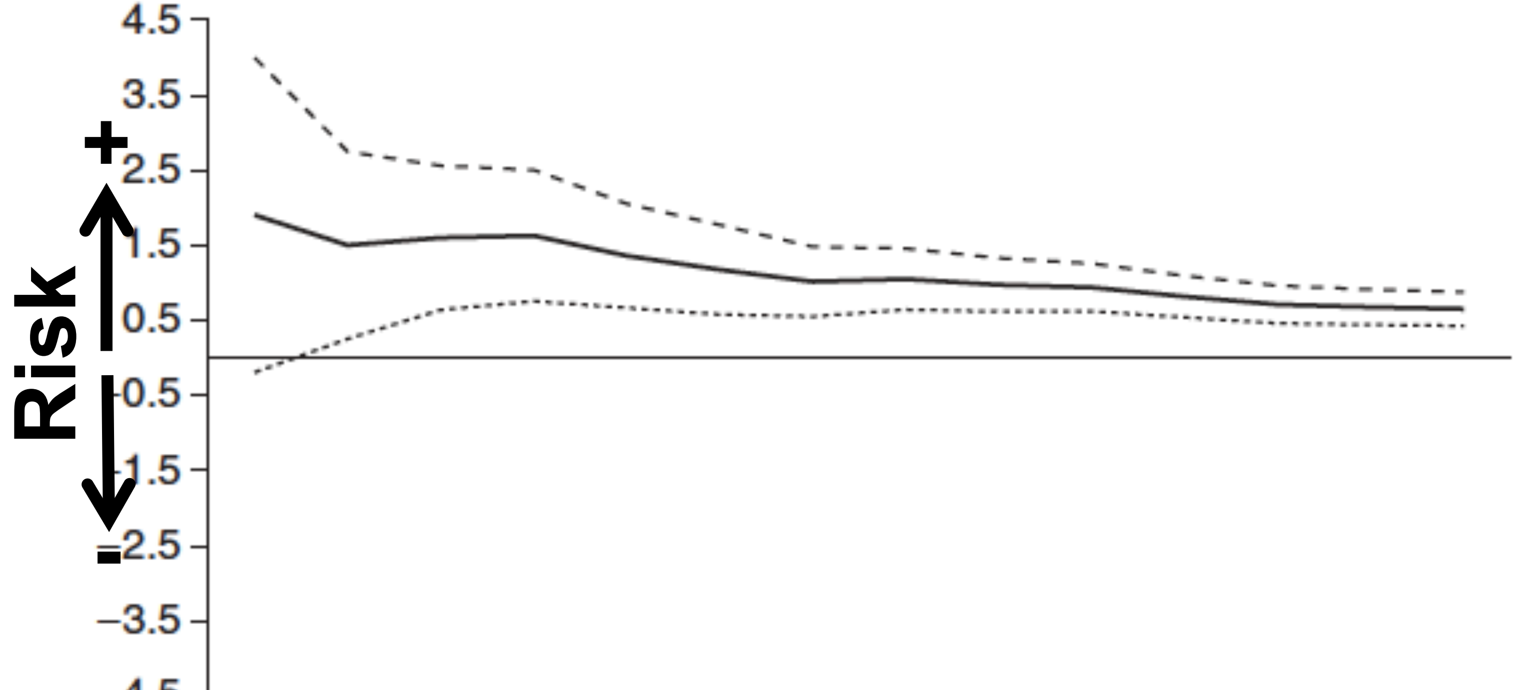
Baycol withdrawn

Manufacturer receives 6 case reports

Manufacturer completes observational study that fails to detect association

Gagne et al Epidemiology 2011

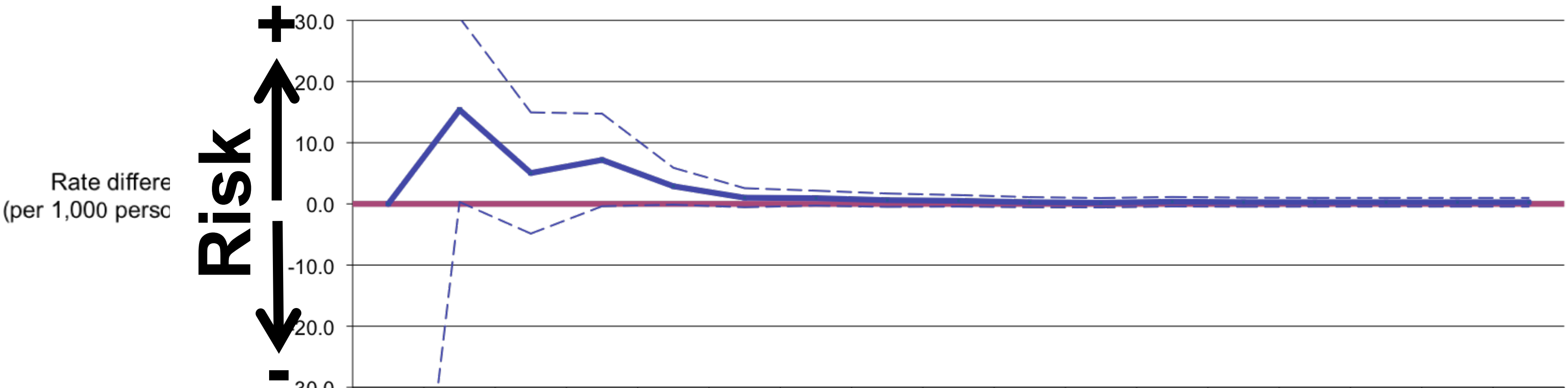
Monitoring for angioedema among initiators of lisinopril vs. ARBs



	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14
- - - lnRR UL	4.00	2.75	2.56	2.50	2.05	1.77	1.48	1.46	1.33	1.26	1.09	0.96	0.91	0.88
—— lnRR	1.90	1.50	1.60	1.63	1.36	1.18	1.02	1.05	0.97	0.94	0.82	0.71	0.68	0.65
------ lnRR LL	–0.19	0.25	0.64	0.76	0.67	0.58	0.55	0.64	0.62	0.62	0.54	0.46	0.44	0.43
Lisinopril events	7	14	25	31	40	47	69	93	115	142	172	194	216	231
ARB events	1	3	5	6	10	14	24	31	41	52	71	89	103	113

Wahl et al. Drug Safety 2012

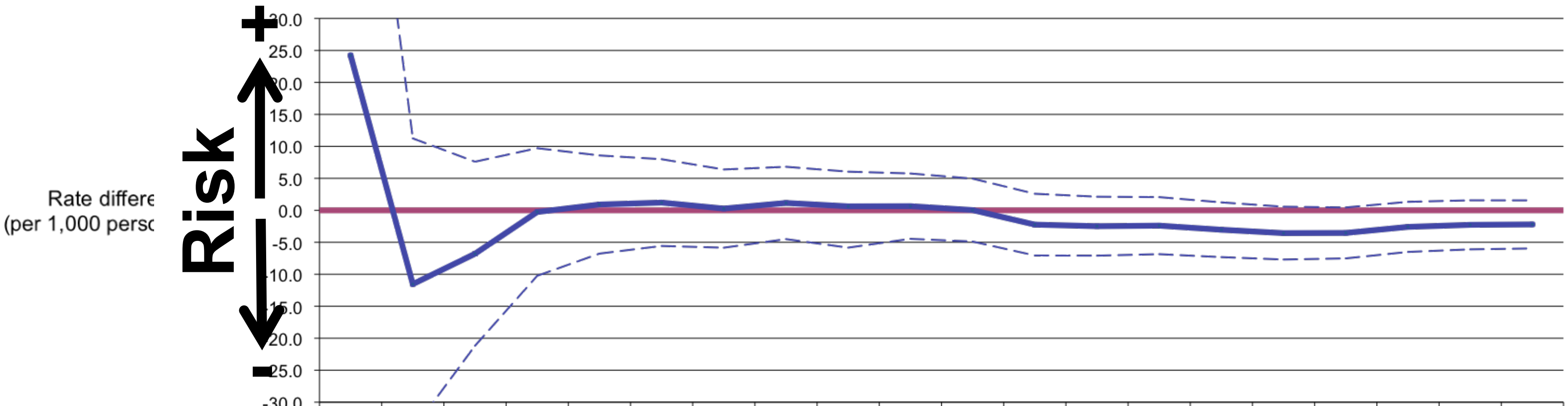
Monitoring for hepatotoxicity among initiators of telithromycin (Ketek) vs. azithromycin (Zithromax)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Lower 95% confidence interval	-99.00	0.31	-4.86	-0.38	-0.13	-0.55	-0.28	-0.49	-0.44	-0.55	-0.58	-0.42	-0.47	-0.45	-0.45	-0.45	-0.45
Cumulative rate difference	0.00	15.37	5.05	7.18	2.89	1.01	0.94	0.60	0.50	0.27	0.19	0.35	0.27	0.27	0.26	0.26	0.26
Upper 95% confidence interval	99.00	30.44	14.96	14.75	5.90	2.56	2.16	1.70	1.44	1.10	0.96	1.13	1.02	0.98	0.98	0.98	0.98
Cumulative events: telithromycin	0	4	6	11	13	14	18	18	19	20	20	23	23	23	23	23	23
Cumulative events: azithromycin	0	0	3	4	5	8	10	12	13	16	17	17	18	18	18	18	18
Cumulative person-years: telithromycin	13	260	593	994	2761	5917	8508	9840	11830	14237	15561	16101	17011	17615	17698	17710	17720
Cumulative person-years: azithromycin	21	260	593	1029	2745	5888	8477	9793	11760	14159	15482	15806	16697	17309	17397	17409	17416

Gagne et al CPT 2012

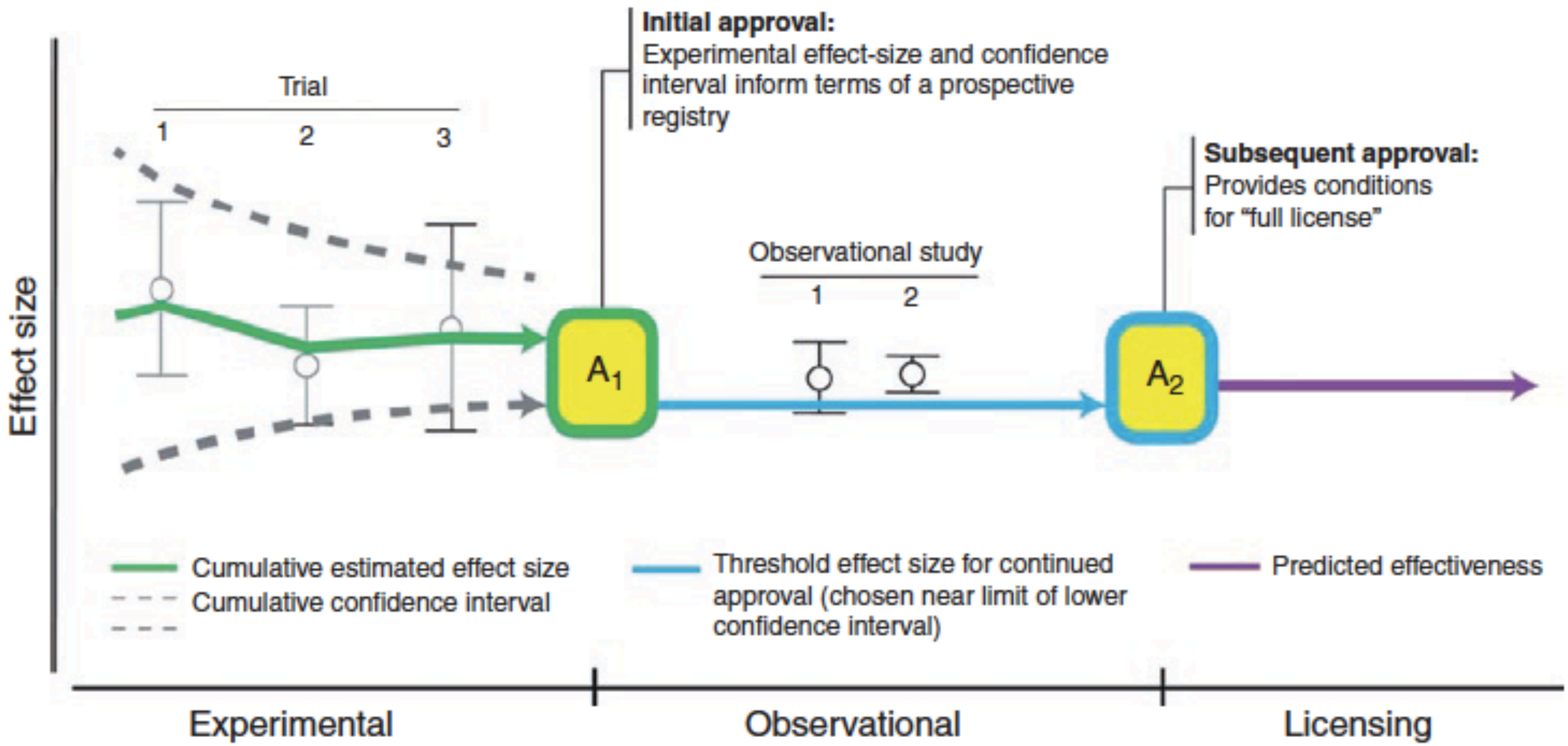
Monitoring for diabetes among initiators of rosuvastatin (Crestor) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-38.29	-34.33	-21.18	-10.24	-6.77	-5.57	-5.85	-4.51	-5.84	-4.46	-4.88	-7.06	-7.09	-6.86	-7.32	-7.69	-7.52	-6.51	-6.10	-5.96
Cumulative rate difference	24.22	-11.54	-6.79	-0.26	0.90	1.21	0.27	1.15	0.62	0.65	0.04	-2.24	-2.48	-2.40	-3.04	-3.57	-3.54	-2.59	-2.27	-2.21
Upper 95% confidence interval	86.74	11.25	7.60	9.71	8.58	7.99	6.39	6.81	6.04	5.76	4.96	2.59	2.13	2.06	1.24	0.56	0.45	1.33	1.56	1.55
Cumulative events: rosuvastatin	13	30	56	127	199	267	321	370	403	424	446	501	560	630	681	731	782	821	841	859
Cumulative events: atorvastatin	11	40	70	135	208	283	354	406	454	481	517	614	688	774	849	922	985	1013	1032	1055
Cumulative person-years: rosuvastatin	144	700	1482	3094	4983	6489	7905	9090	10039	10745	11482	12563	13941	15251	16581	17867	19161	19839	20480	21098
Cumulative person-years: atorvastatin	167	735	1570	3268	5329	7086	8776	10265	11488	12393	13322	14578	16131	17710	19248	20729	22210	23036	23814	24580

Gagne et al CPT 2012

Application: Adaptive Licensing



Eichler et al. CPT 2012

Active Safety Monitoring of Newly Marketed Medications in a Distributed Data Network: Application of a Semi-Automated Monitoring System

JJ Gagne[1], RJ Glynn[1,2], JA Rassen[1],

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 Rassen[1]

Early Steps in the Development of a Claims-Based Targeted Healthcare Safety Monitoring System and Application to Three Empirical Examples

Peter M. Wahl,[1] *Joshua J. Gagne,*[1] *Thomas E. Wasser,*[2] *Debra F. Eisenberg,*[2] *J. Keith Rodgers,*[2] *Gregory W. Daniel,*[2] *Marcus Wilson,*[2] *Sebastian Schneeweiss,*[1] *Jeremy A. Rassen,*[1] *Amanda R. Patrick,*[1] *Jerry Avorn*[1] and *Rhonda L. Bohn*[2,3]

Using high-dimensional propensity scores to automate confounding control in a distributed medical product safety surveillance system

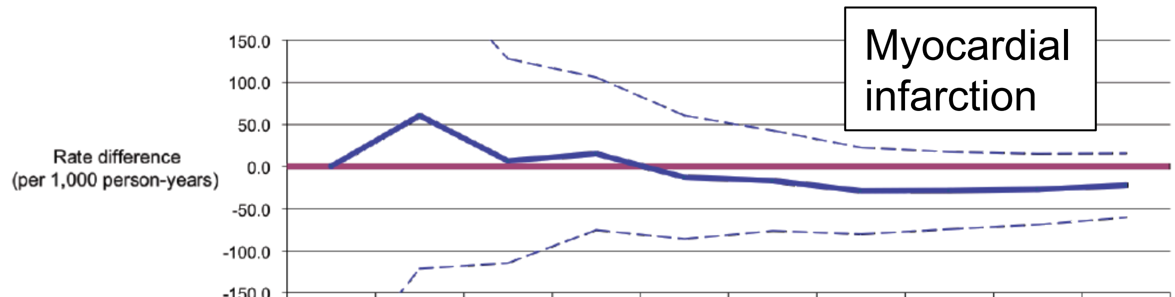
Typical value judgment:
Efficacy (benefit) - Harm Assessment

	RCT	Observational
Information on Benefit	Chance Representative ness **Benefit Assessment**	Chance Bias Representative ness
Information on Harm	Chance Bias Representative ness	Chance Bias Representative ness **Harm Assessment**

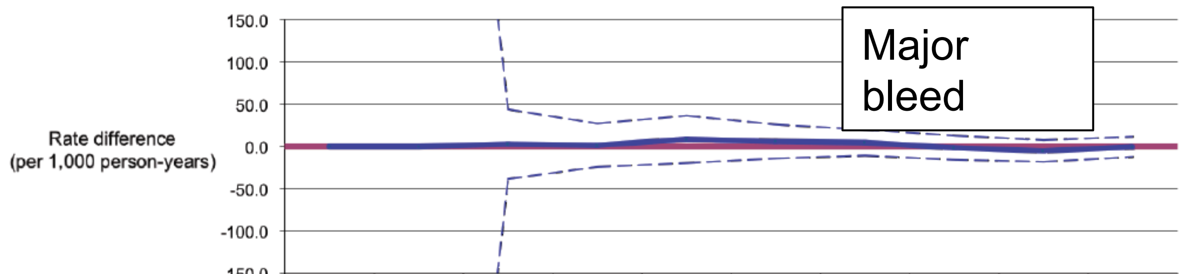
Net benefit

Clopidogrel vs. prasogrel:

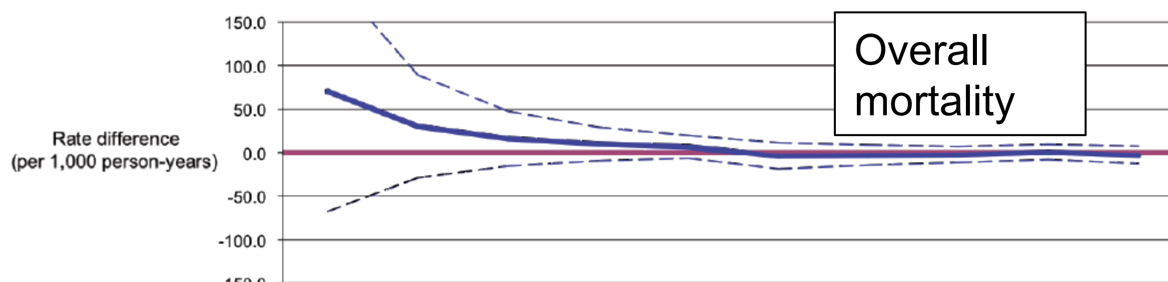
MI prevention vs. bleed



	(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



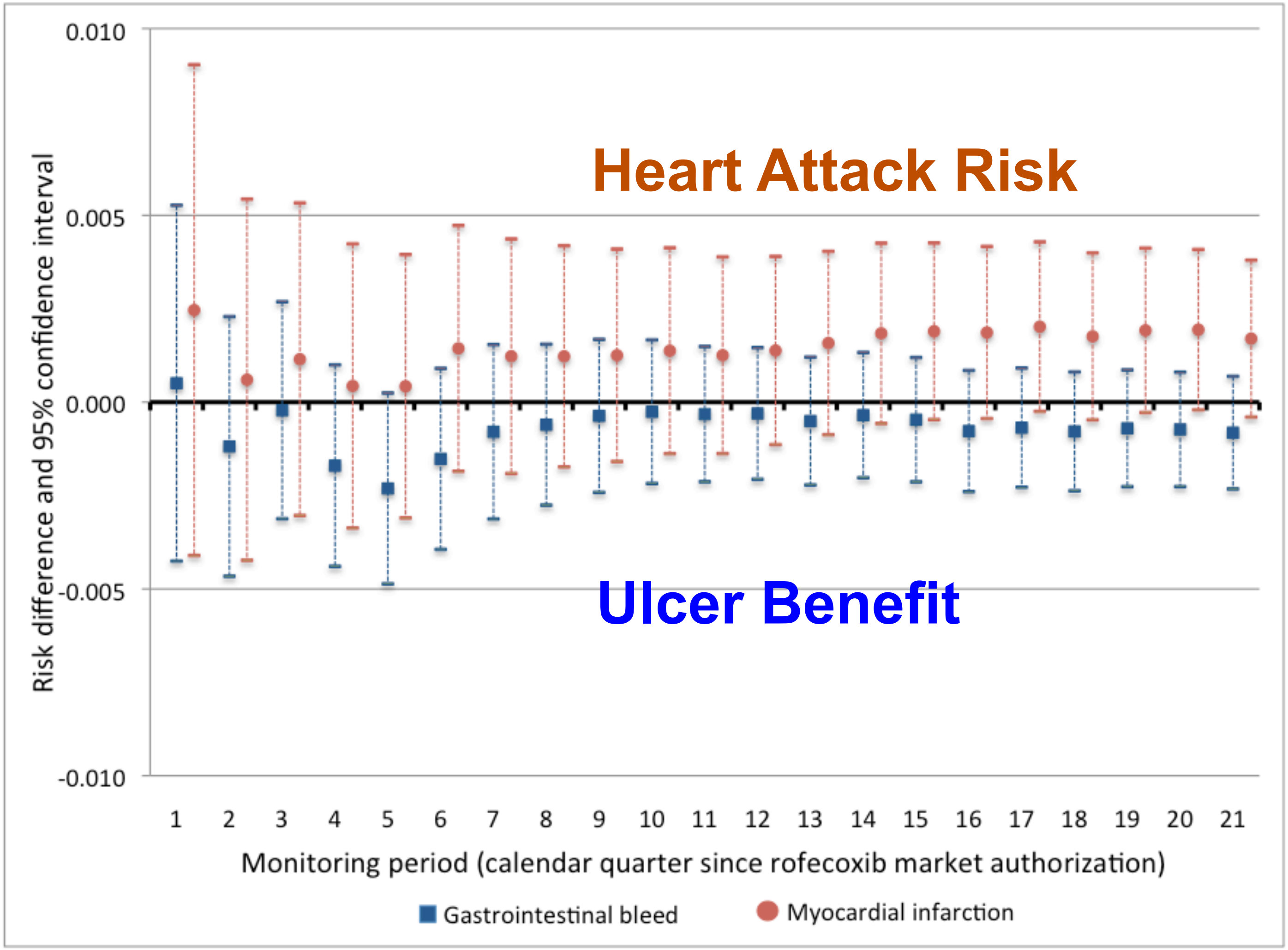
	(1) 9/09-2/10	(2) 3/10-4/10	(3) 5/10-6/10	(4) 7/10-8/10	(5) 9/10-10/10	(6) 11/10-12/10	(7) 1/11-2/11	(8) 3/11-4/11	(9) 5/11-6/11	(10) 7/11-8/11
Lower 95% confidence interval	-999.00	-999.00	-38.39	-24.28	-19.66	-14.13	-10.92	-15.72	-18.13	-12.38
Cumulative rate difference	0.00	0.00	2.66	1.35	8.34	5.81	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

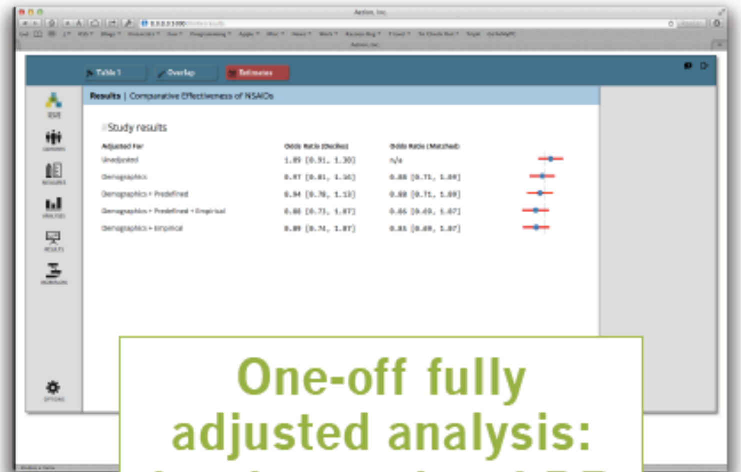
Gagne et al Drug Saf 2014

Net Benefit
Rofecoxib vs. NSAIDs

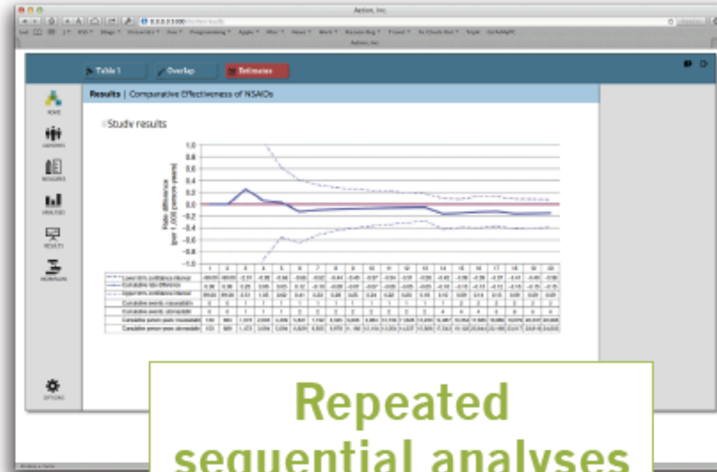


Gagne et al. ViH 2013

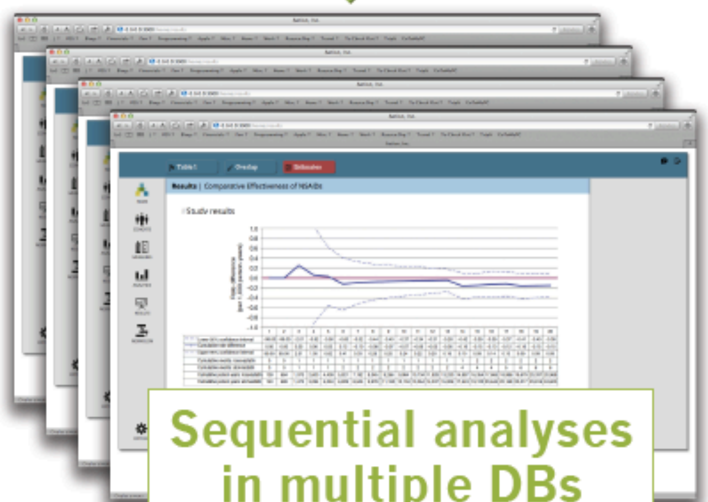
Scalability across multiple Databases



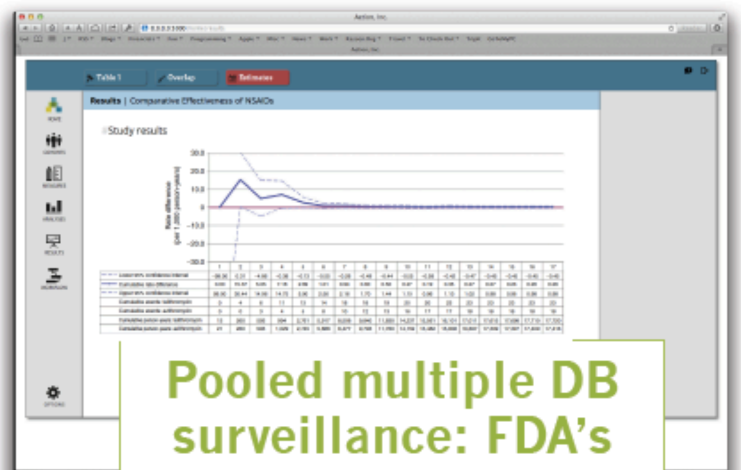
One-off fully adjusted analysis: local or national DB



Repeated sequential analyses



Sequential analyses in multiple DBs



Pooled multiple DB surveillance: FDA's Mini Sentinel

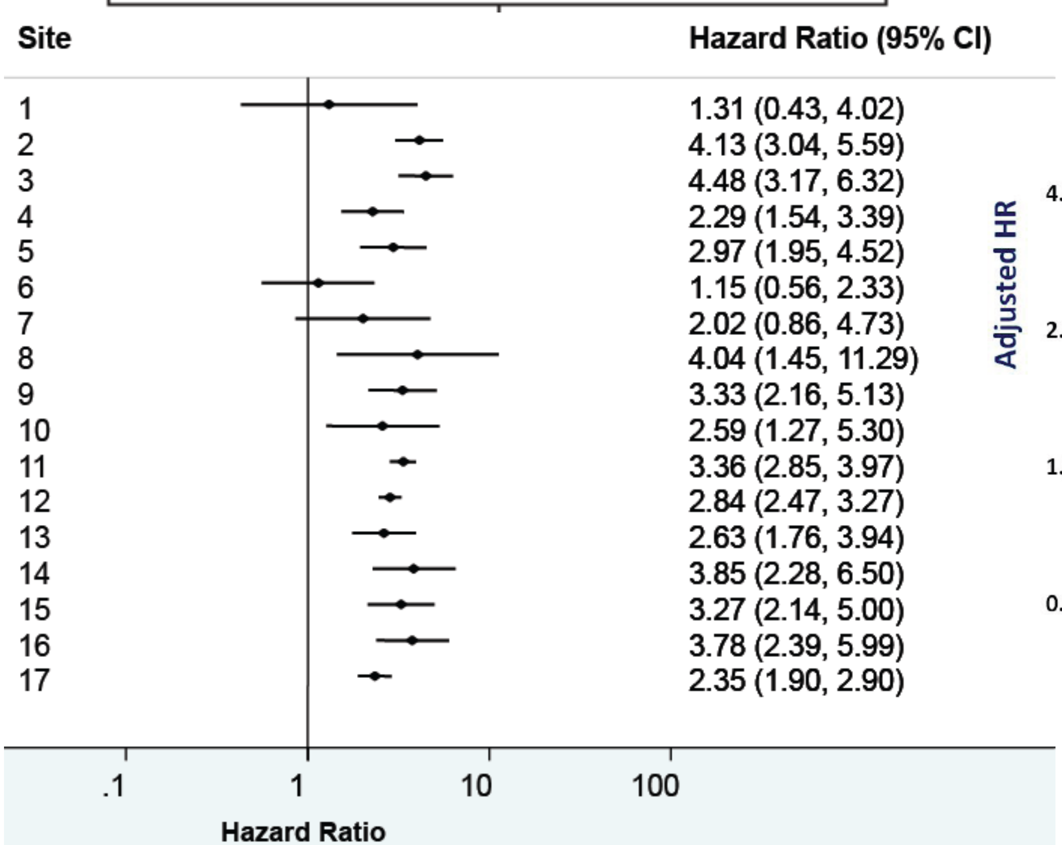
FDA Mini Sentinel system: Size

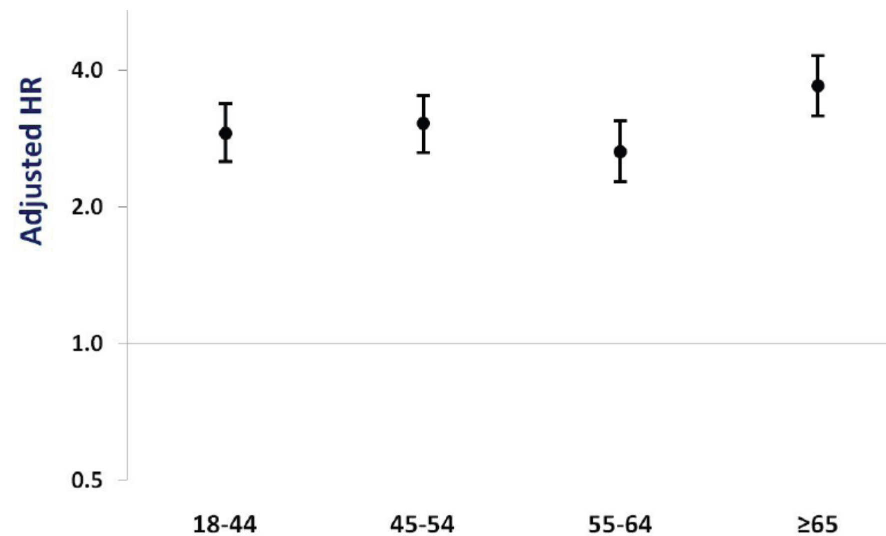
ORIGINAL INVESTIGATION

Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System

Sengwee … orth, PharmD;
Xiao Din… lcCloskey, MD, MPH;
Azadeh S… , PharmD, PhD

65 006 161 Health plan members aged ≥ 18 y from 17 Mini-Sentinel data partners between 1/1/2001 and 12/31/2010





FDA Mini Sentinel system: Speed

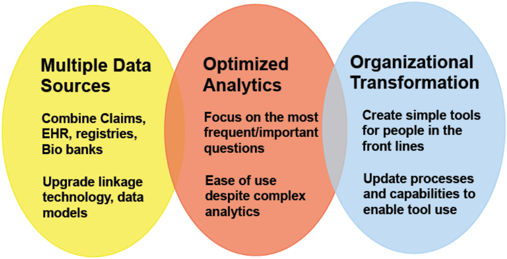
Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

Success with Big Data in Healthcare



- **Analyses that support causal conclusions**
- **Analyses that**
  - run in near real-time as data refresh
  - scale to many associations of interest
  - run across multiple data sources simultaneously
  - can be conducted by moderately trained users
  - integrate well into the workflow
  - can be shared with external partners

Rapid-cycle analytics and decision making

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

Safety monitoring & false decision making

False positive alerts:

Societal cost:

- Withholding a safe and effective drug from some selected patient groups or from all.

Causes:

- Lack of confounder control
- Multiple testing

Alert generation process:

- Process ctrl rules
- Sequential testing (SPRT)
- Gamma shrinkage
- Estimation projection
- Disproportionality measures

False negative alerts:

Societal cost:

- Exposing patients to an unnecessary risk
- Marketing with inappropriate risk information

Causes:

- Lack of confounder control
- Insufficient precision

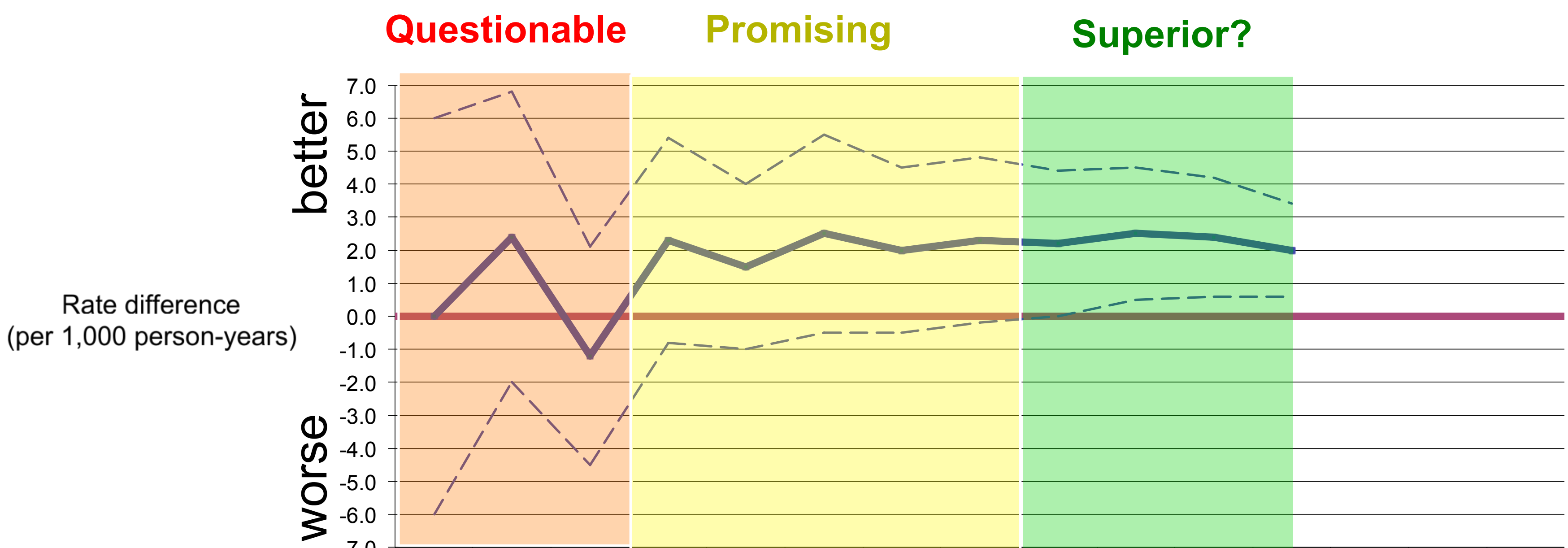
Correct ("true") alerts:

Societal gain:

- Makes new risk information available quickly
- Removes or restricts unsafe medications quickly

Avorn, Schneeweiss NEJM 2010

Decision-making with rapid-cycle evaluation using healthcare databases



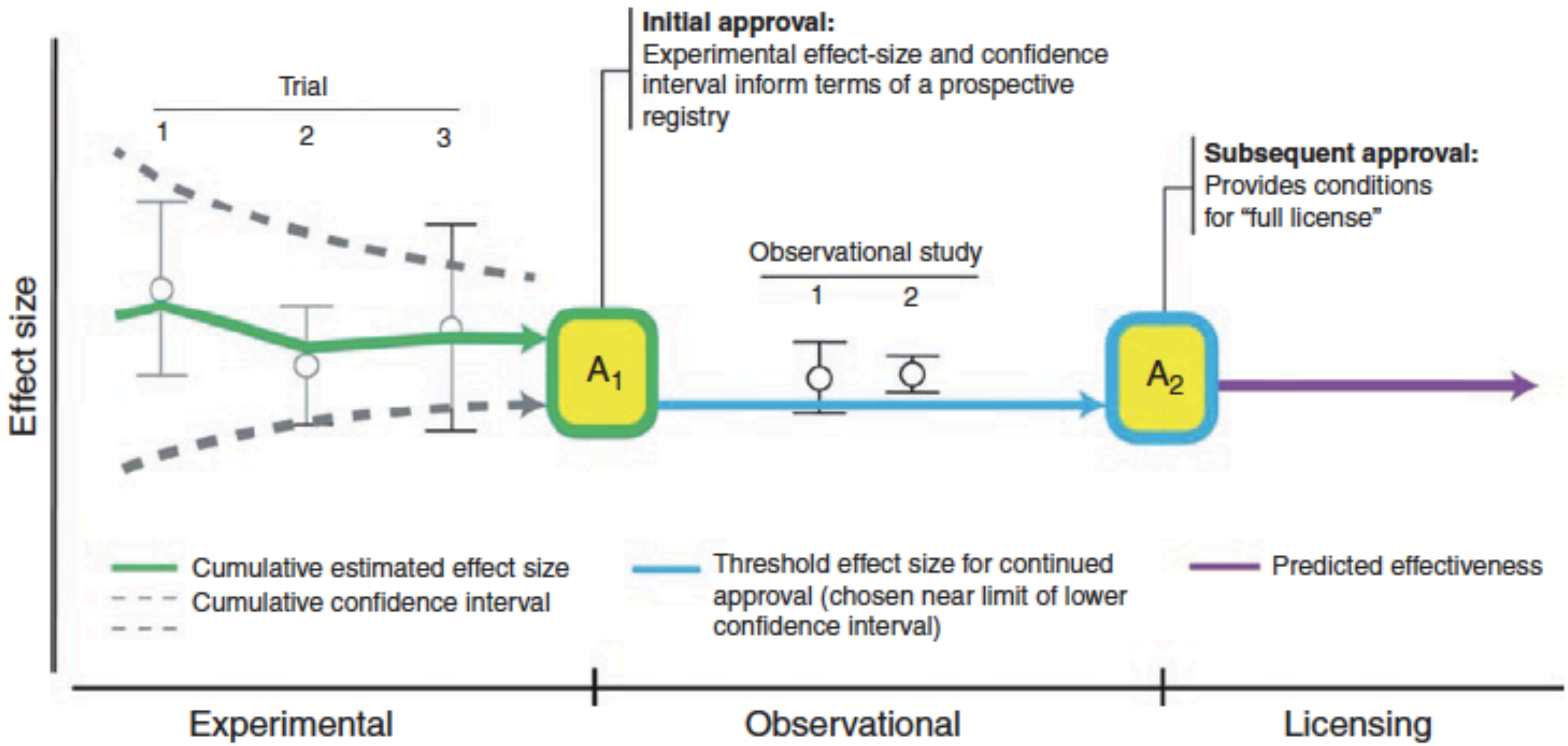
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Lower 95% confidence interval	-6.00	-2.00	-4.50	-0.80	-1.00	-0.50	-0.50	-0.20	0.00	0.50	0.60	0.60			
Cumulative rate difference	0.00	2.40	-1.20	2.30	1.50	2.50	2.00	2.30	2.20	2.50	2.40	2.00			
Upper 95% confidence interval	6.00	6.80	2.10	5.40	4.00	5.50	4.50	4.80	4.40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

Questionable:
- Investigate subgroup effects
- Continue evaluation

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

Superior:
- Widely disseminate

Reminder: Adaptive Licensing

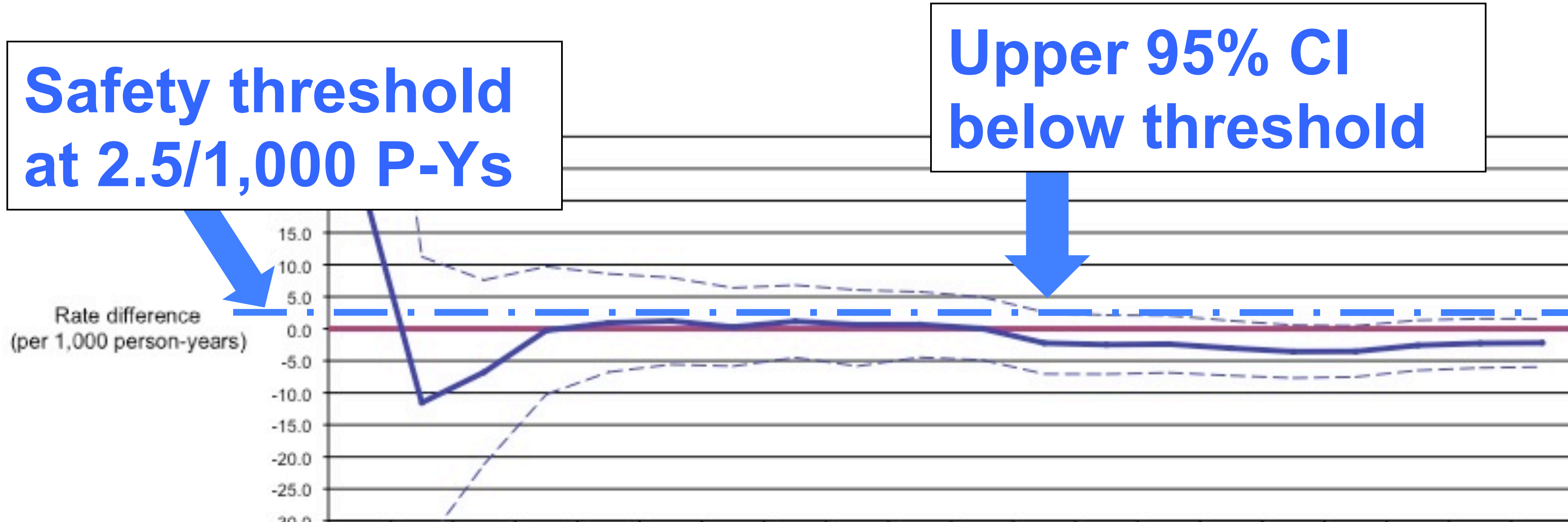


Eichler et al. CPT 2012

When should we stop monitoring?
… and conclude a drug is effective/safe?

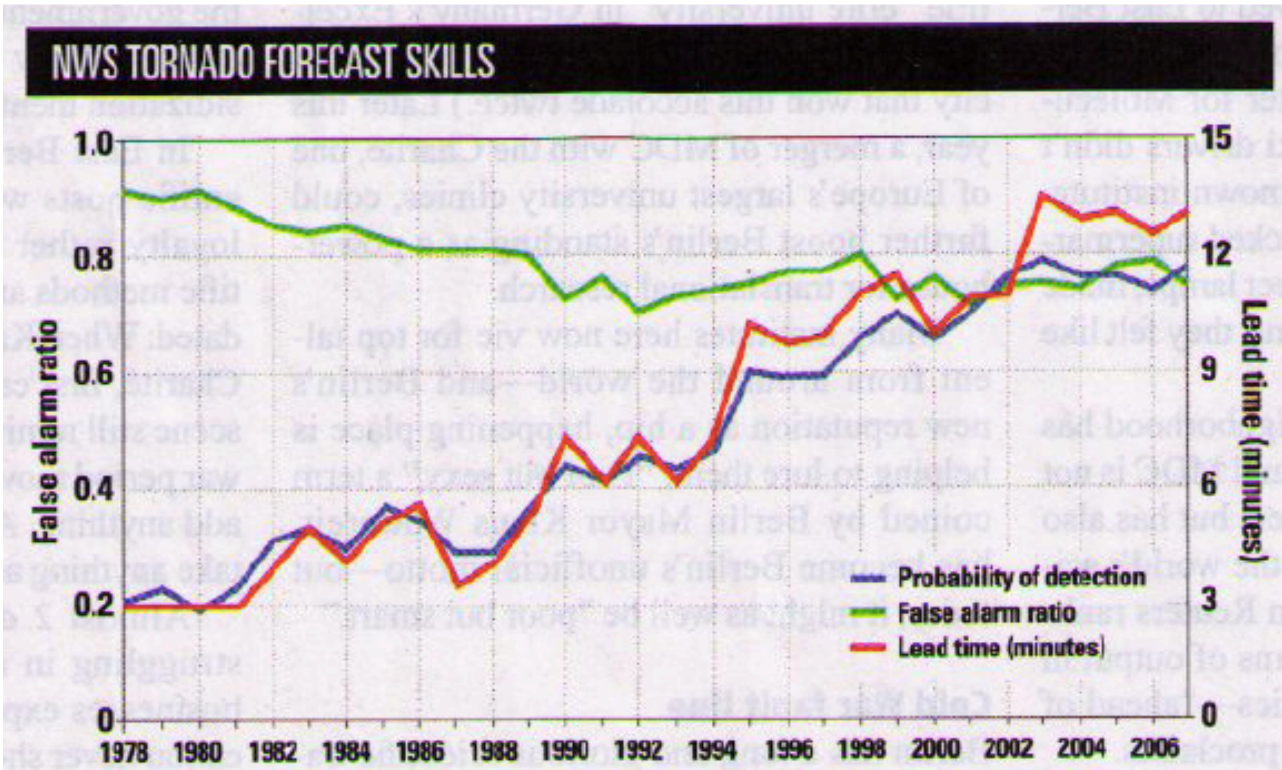
- Need a threshold of acceptable safety
  - Acceptable to whom?
- If monitoring is inexpensive, largely automated, why ever stop?
  - Safe at this point with today's usage pattern
  - Evaluation of risk management programs

Rosuvastatin and DM



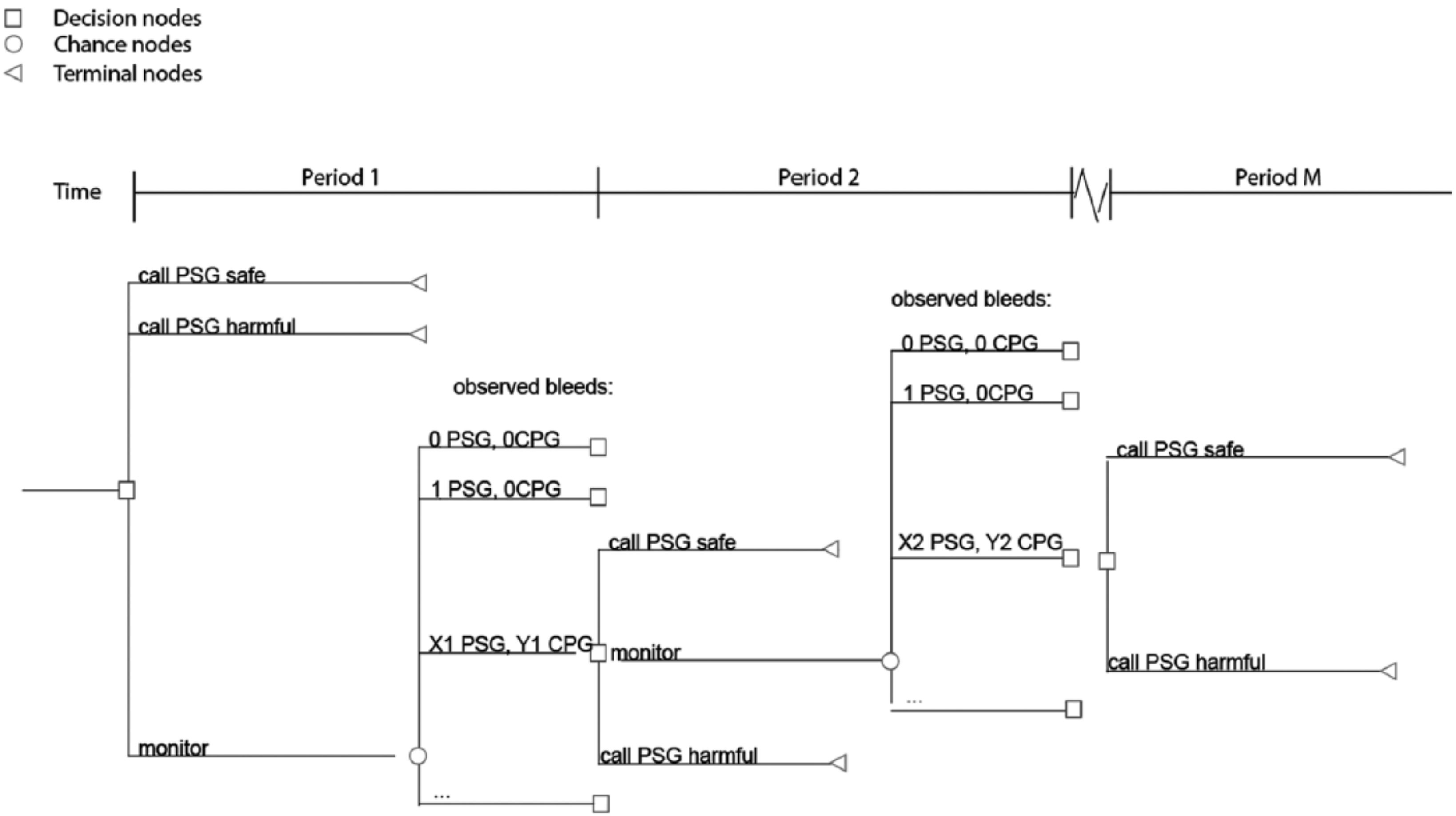
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-38.29	-34.33	-21.18	-10.24	-6.77	-5.57	-5.85	-4.51	-5.84	-4.46	-4.88	-7.06	-7.09	-6.86	-7.32	-7.69	-7.52	-6.51	-6.10	-5.96
Cumulative rate difference	24.22	-11.54	-6.79	-0.26	0.90	1.21	0.27	1.15	0.62	0.65	0.04	-2.24	-2.48	-2.40	-3.04	-3.57	-3.54	-2.59	-2.27	-2.21
Upper 95% confidence interval	86.74	11.25	7.60	9.71	8.58	7.99	6.39	6.81	6.04	5.76	4.96	2.59	2.13	2.06	1.24	0.56	0.45	1.33	1.56	1.55
Cumulative events: rosuvastatin	13	30	56	127	199	267	321	370	403	424	446	501	560	630	681	731	782	821	841	859
Cumulative events: atorvastatin	11	40	70	135	208	283	354	406	454	481	517	614	688	774	849	922	985	1013	1032	1055
Cumulative person-years: rosuvastatin	144	700	1482	3094	4983	6489	7905	9090	10039	10745	11482	12563	13941	15251	16581	17867	19161	19839	20480	21098
Cumulative person-years: atorvastatin	167	735	1570	3268	5329	7086	8776	10265	11488	12393	13322	14578	16131	17710	19248	20729	22210	23036	23814	24580

What level of false decision making is acceptable?



Progress, or not. The U.S. National Weather Service has increased its tornado warning time (lead time, red), thanks to Doppler radar. But the false alarm ratio—how often forecasters warned of a tornado that never appeared—hasn't budged in 20 years.

Ongoing decision making via Sequential value of information (VOI)



Patrick A et al. MDM 2013

Near-term Reality: Opportunities

- Maturing monitoring methodology
- Maturing software technology
- Some standardization
- Increasing pooling of databases
- Increasing linking of databases
  - Claims w/ EMR, w/ pathology, w/ imaging, w/ genetics

- Let’s make sure we wont drown in data but make meaningful and targeted use

Near-term Reality: Challenges

- Bias in non-randomized analyses of healthcare data
  - Surveillance-related biases
  - Selection-related biases

  Jointly agree on standards!
- Separate accurate effect estimation from decision making
- Need to better understand implications of continuous decision making
- Governance (Mini Sentinel, PCORNet)
- Data privacy confusion: research vs. quality improv't
- Value communication of Real World Data analytics

Mini-Sentinel and Regulatory Science — Big Data Rendered Fit and Functional

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The Mini-Sentinel, which costs about 6 cents per capita per year, protects privacy, maintains transparency, and provides an essential public health service.

Some papers that cover this talk

- Schneeweiss S. et al. Comparative effectiveness research of newly marketed medications. Clin Pharm & Ther 2011
- Gagne JJ et al. Active safety monitoring of newly marketed medications in a distributed data network: Application of a semi-automated monitoring system. Clin Pharm & Ther 2012
- Song F et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 2003
- Schneeweiss S. Developments in comparative effectiveness research. Clin Pharm & Ther 2007
- Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. Pharmaceopi Drug Safety 2010