Mini-Sentinel

FDA's Mini-Sentinel Program

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Harvard Pilgrim Health Care Institute
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for the Mini-Sentinel Investigators

NIH Health Care Systems Research Collaboratory Grand Rounds
February 15, 2013

Mini-Sentinel

- Congress mandated FDA develop electronic record based safety surveillance system
- Mini-Sentinel is a five year pilot project to:
  - Develop operational capacity for active medical product safety surveillance in existing automated healthcare data systems
  - Develop and evaluate scientific methods
  - Offer FDA the opportunity to evaluate safety issues
  - Assess barriers and challenges

Mini-Sentinel's key features – 1

- Governance – patient privacy, organizational expectations, etc.
- Focus on safety of marketed medical products
- Operates under FDA's public health authority – no IRB oversight
- Distributed network – no central data repository
  - Pooled analysis file are created as needed
- Coordinating center – technical expertise, libraries of protocols/programs
- Data sources
  - Administrative data, EHR, registries
  - Access to full text records to confirm exposures, outcomes, risk factors

Mini-Sentinel's key features – 2

- Evaluations
  - Safety of established products
    - Rapid assessment of new questions
    - In depth assessment of persistent questions
  - Response to regulatory action
  - Prospective assessment of accumulating experience with new products
- Methods development
  - Statistics, epidemiology, performance of detection algorithms, linkage between data sources

Mini-Sentinel's key components

- Policies
  - Privacy
  - Governance
- Data
- Infrastructure and procedures for their use at FDA, at Coordinating Center, at Partner sites
  - Standard operating procedures
  - Personnel
  - Hardware
  - Software

Mini-Sentinel partner organizations

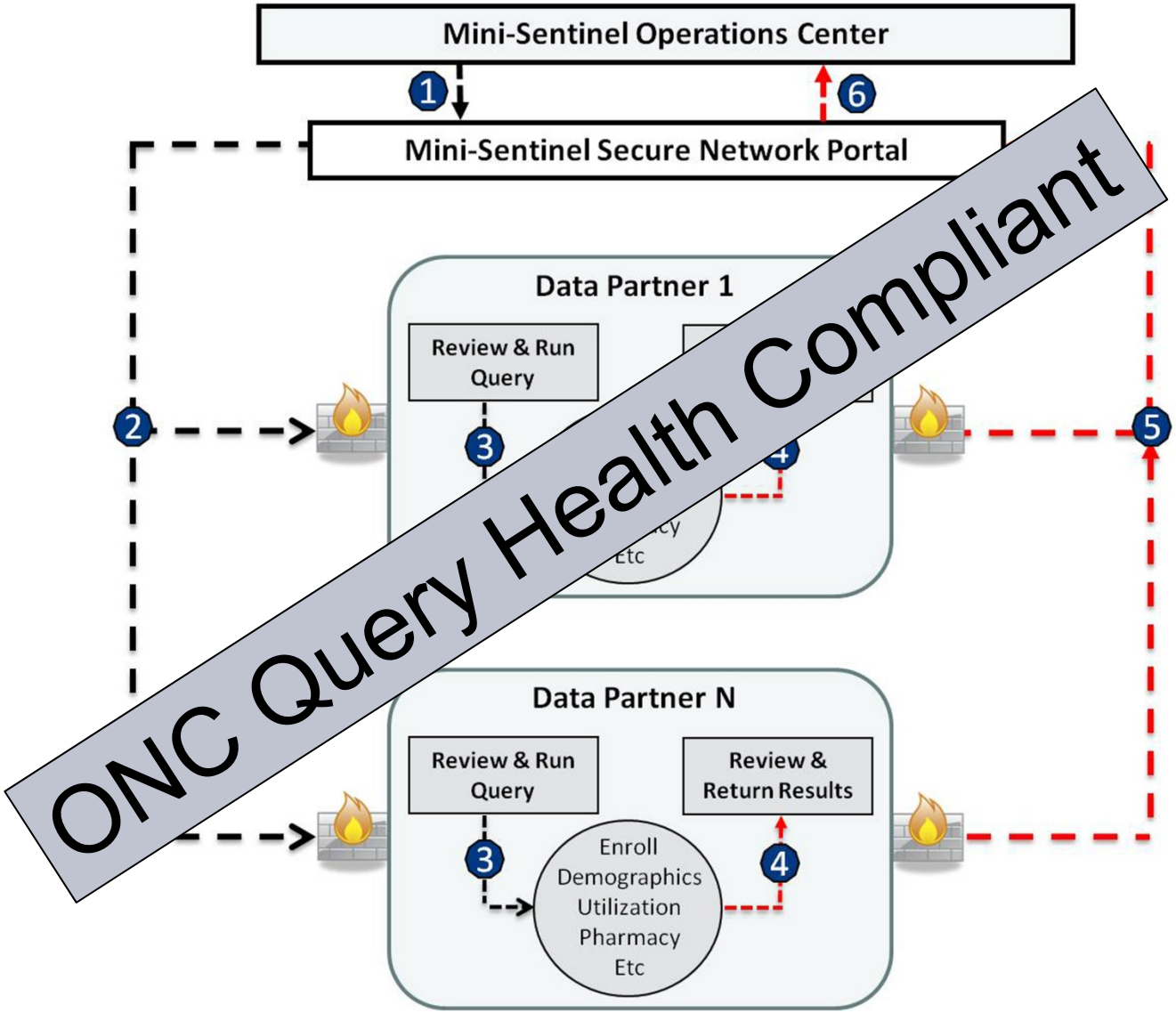
HealthCore
WellPoint
Vanderbilt School of Medicine
hmo research network
Humana
Kaiser Permanente
aetna
Outcome
Cincinnati Children's change the outcome
Optum
Penn Medicine
UAB
Duke Medicine
Critical Path Institute collaborate · innovate · accelerate
Partners Healthcare
AHIP America's Health Insurance Plans
UIC
The University of Iowa College of Public Health
Rutgers Institute for Health

Mini-Sentinel Distributed Database*

- Populations with well-defined person-time for which most medically-attended events are known
- 382 million person-years of observation time
- 3.7 billion dispensings
- 4.1 billion unique encounters
  - 46 million acute inpatient stays
- 24 million people with ≥1 laboratory test result

*As of January 2013

Mini-Sentinel Distributed Analysis



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

2- Data partners retrieve query

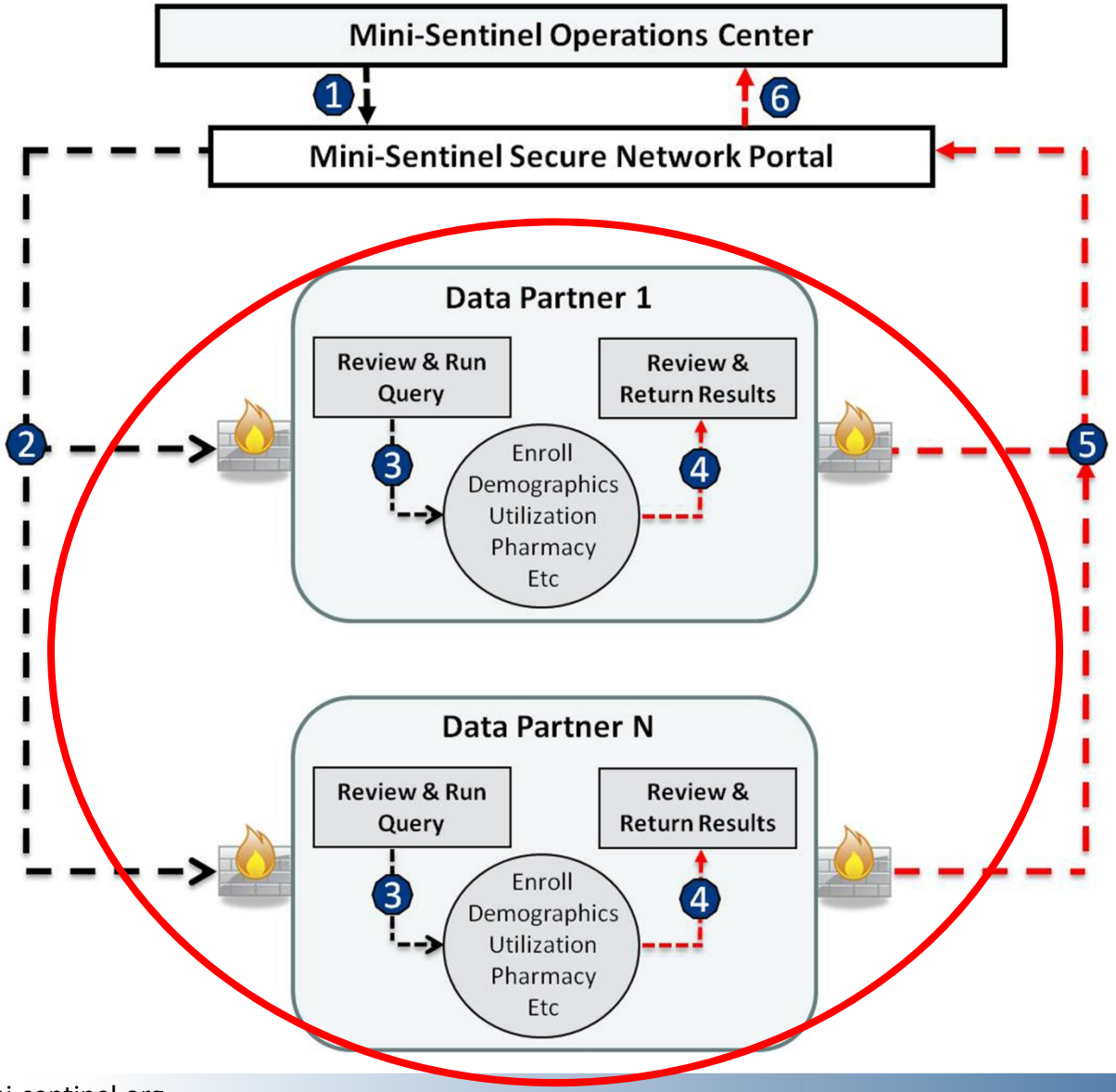
3- Data partners review and run query against their local data

4- Data partners review results

5- Data partners return results via secure network

6 Results are aggregated

Mini-Sentinel Distributed Analysis



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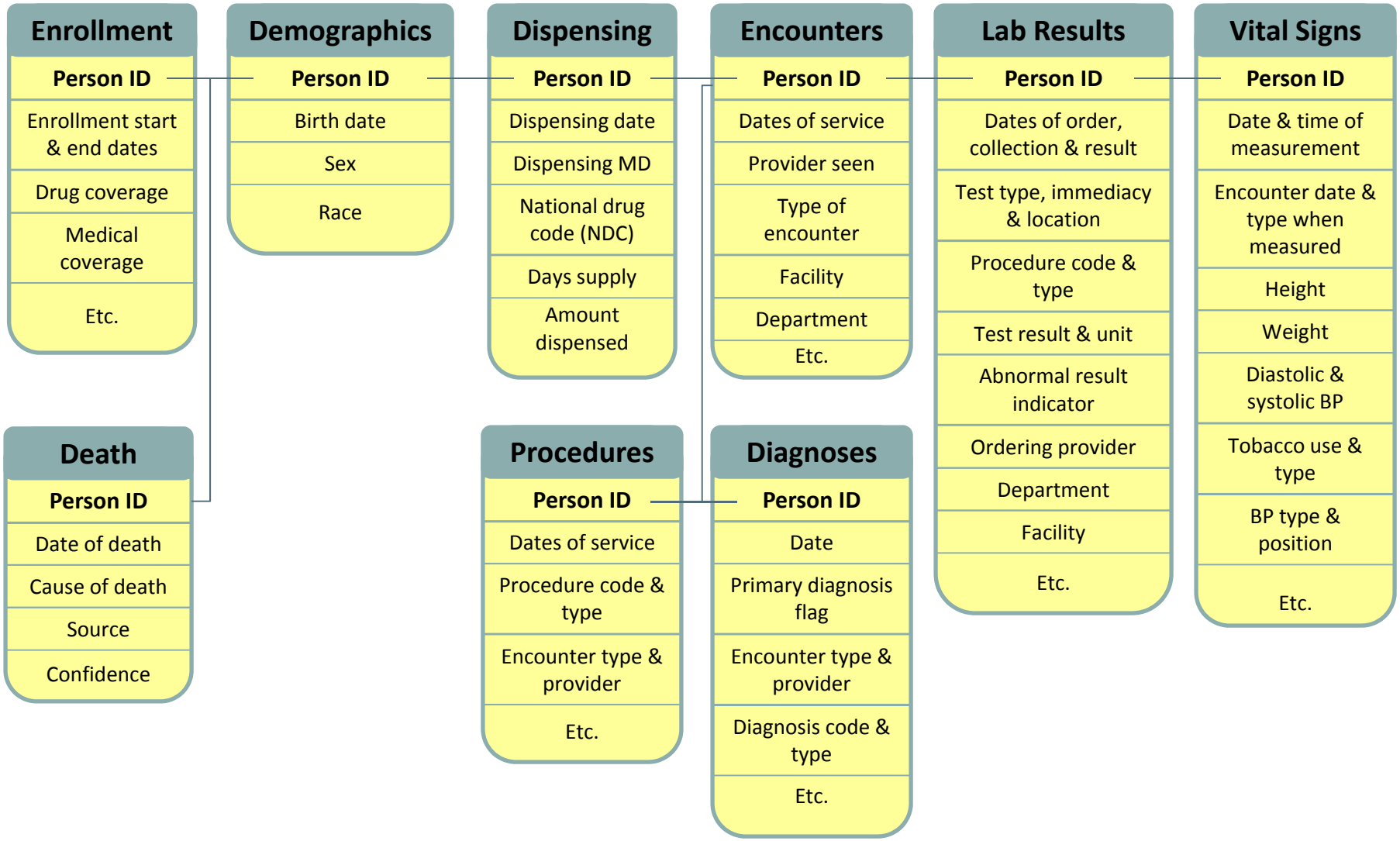
Mini-Sentinel's Data Sources

- Administrative data
  - Enrollment
  - Demographics
  - Outpatient pharmacy dispensing
  - Utilization (encounters, diagnoses, procedures)
- EHR data
  - Height, weight, blood pressure, temperature
  - Laboratory test results (selected tests)
- Registries
  - Immunization
  - Mortality (death and cause of death)

Mini-Sentinel's Common Data Model



Standard data checks for each refresh cycle

- 120 core data refreshes received through 2012
- ~400 data checks per refresh
- 100+ tables per data partner per refresh

Obs	ENCTYPE	ADATE	COUNT	PERCENT
1	AV	2000	7030952	5.1370
2	AV	2001	7454699	5.4466
3	AV	2002	8014346	5.8555
4	AV	2003	8261199	6.0358
5	AV	2004	8251011	6.0284
6	AV	2005	8857635	6.4716
7	AV	2006	9576674	6.9969
8	AV	2007	10240959	7.4823
9	AV	2008	11831682	8.6445
10	AV	2009	13785025	10.0716
11	AV	2010	14499322	10.5935
12	AV	2011	14988289	10.9508
13	ED	2000	193108	0.1411
14	ED	2001	213180	0.1558
15	ED	2002	231296	0.1690
16	ED	2003	232122	0.1696
17	ED	2004	230756	0.1686
18	ED	2005	266406	0.1946
19	ED	2006	291381	0.2129
20	ED	2007	314060	0.2295
21	ED	2008	343936	0.2513
22	ED	2009	400500	0.2926
23	ED	2010	414312	0.3027
24	ED	2011	451881	0.[illegible]
25	IP	2000	432504	0.3[illegible]
26	IP	2001	477466	0.3[illegible]
27	IP	2002	517710	0.3[illegible]
28	IP	2003	543660	0.3[illegible]
29	IP	2004	543692	0.3[illegible]
30	IP	2005	587863	0.4[illegible]

Obs	RXDATE	N
1	2000JAN	75816
2	2000FEB	68872
3	2000MAR	240058
4	2000APR	248527
5	2000MAY	261254
6	2000JUN	258289
7	2000JUL	241145
8	2000AUG	260316
9	2000SEP	252799
10	2000OCT	260813
11	2000NOV	254161
12	2000DEC	259611
13	2001JAN	275314
14	2001FEB	242270
15	2001MAR	278558
16	2001APR	260591
17	2001MAY	268647
18	2001JUN	267520
19	2001JUL	257699
20	2001AUG	279320

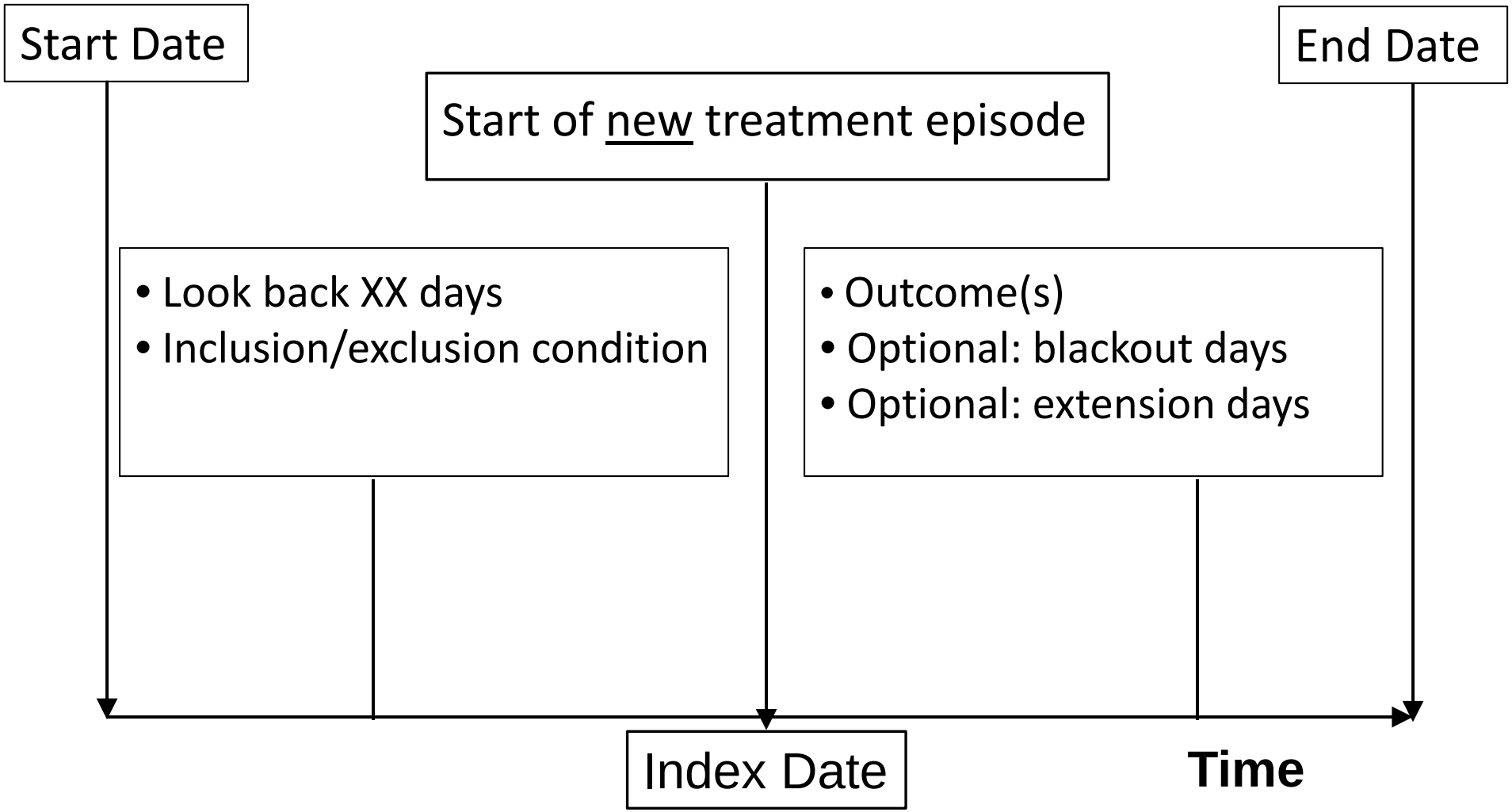
Obs	px_codetype	enctype	COUNT	PERCENT
1	09	AV	3891384	0.2061
2	09	ED	940211	0.0498
3	09	IP	7716848	0.4088
4	09	IS	168596	0.0089
5	09	OA	510196	0.0270
6	C2	AV	4906255	0.2599
7	C2	ED	325738	0.0173
8	C2	IP	392155	0.0208
9	C2	IS	18219	0.0010
10	C2	OA	222605	0.0118
11	C3	AV	212648	0.0113
12	C3	ED	5276	0.0003
13	C3	IP	7755	0.0004
14	C3	IS	269	0.0000
15	C3	OA	2030	0.0001
16	C4	AV	1364119936	72.2580
17	C4	ED	95271865	5.0466
18	C4	IP	50242438	2.6614
19	C4	IS	3914519	0.2074
20	C4	OA	27959691	1.4810
21	HC	AV	252901204	13.3963
22	HC	ED	14811325	0.7846
23	HC	IP	8125355	0.4304
[illegible]	HC	IS	1600478	0.0848
[illegible]	HC	OA	31067795	1.6457
[illegible]	ND	AV	16692216	0.8842
[illegible]	ND	ED	639229	0.0339
[illegible]	ND	IP	147970	0.0078
[illegible]	ND	IS	12924	0.0007
[illegible]	ND	OA	819916	0.0434
[illegible]	OT	AV	194765	0.0103
[illegible]	OT	ED	374	0.0000
[illegible]	OT	IP	2607	0.0001
[illegible]	OT	IS	1367	0.0001
[illegible]	OT	OA	348	0.0000

Obs	Age_group	COUNT	PERCENT
1	0.1 0-1 Yrs	602059	1.4996
2	02. 2-4 Yrs	1376997	3.4298
3	03. 5-9 Yrs	2553188	6.3595
4	04. 10-14 Yrs	2638462	6.5719
5	05. 15-18 Yrs	2135457	5.3190
6	06. 19-21 Yrs	1670742	4.1615
7	07. 22-44 Yrs	14770481	36.7906
8	08. 45-64 Yrs	11221814	27.9515
9	09. 65-74 Yrs	1854092	4.6182
10	10. 75+ Yrs	1324163	3.2982

Rapid Queries of Exposure-Outcome Pairs

- Angiotensin receptor blockers (ARBs) and celiac disease
- Drugs for smoking cessation and cardiac outcomes
- Drugs for Parkinson's disease and acute myocardial infarction or stroke
- Analeptics and severe cutaneous adverse reactions
- Oral hypoglycemics and hypersensitivity reactions
- Atypical antipsychotics and hypersensitivity reactions
- Vascular endothelial growth factor (VEGF) inhibitors and osteonecrosis of the jaw
- Direct thrombin inhibitors / warfarin and hemorrhage
- Aspirin antagonists and stroke or transient ischemic attack

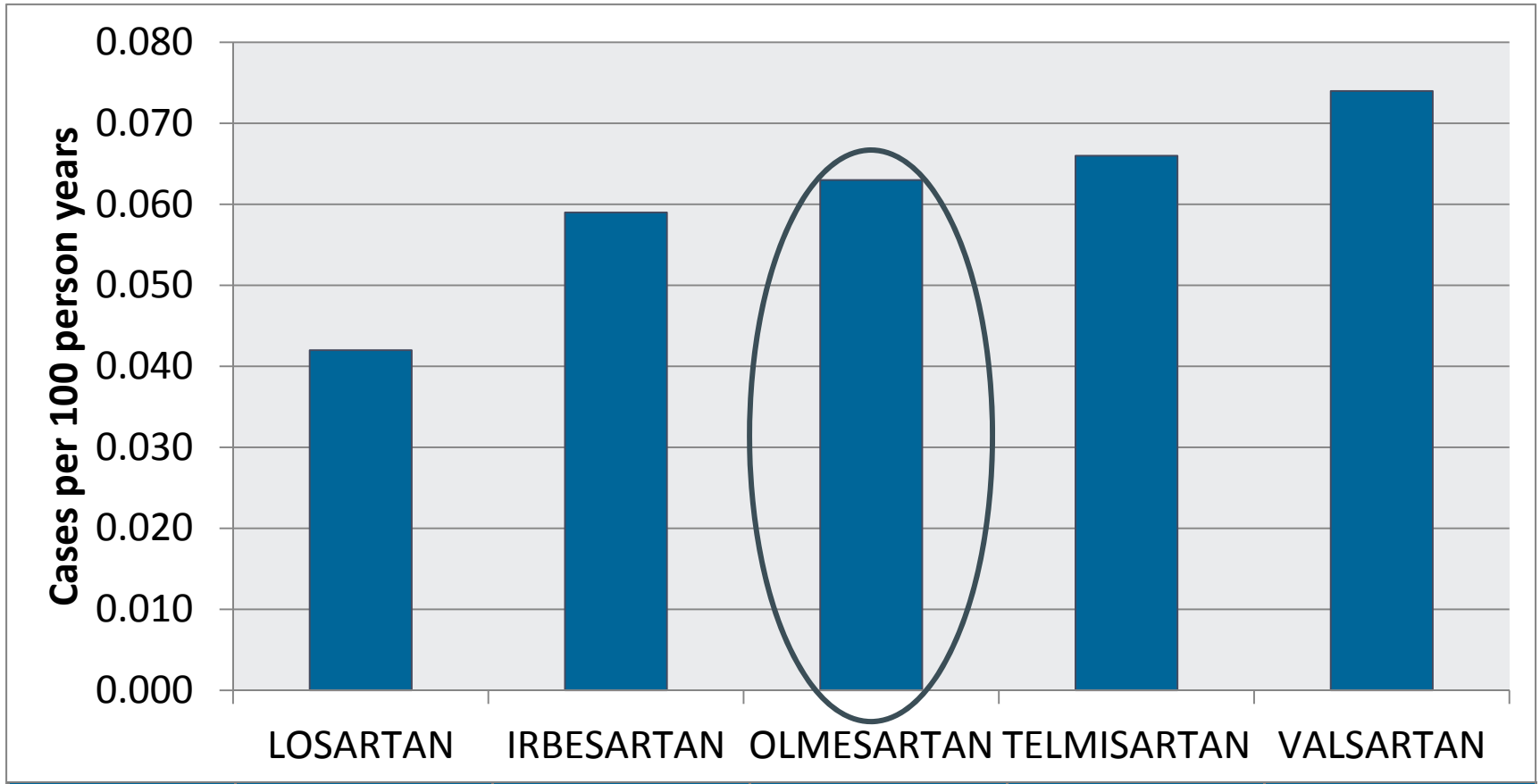
Typical Input to Modular Programs



Angiotensin Receptor Blockers and Celiac Disease

- Potential signal identified in FDA's spontaneous report database (AERS)
- Review of cases inconclusive

ARBs and celiac disease



Cases	63	10	17	5	50
New users	235,630	40,071	81,560	24,596	153,159

ARBs: New users after ≥365 day washout; Celiac Disease: 1st dx code after >365 day without diagnosis.

Limitations

- Capture of relevant GI events may be incomplete
- Potential inclusion of irrelevant events
- Patients exposed to different agents may differ with respect to risk of GI symptoms
- Majority of exposures limited to a few months duration
- Observed risk doesn't exclude excess

ARBs and Celiac Disease

i-sentinel.org/work_p

www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_Angiotensin-II-Receptor-Blockers-and-Celiac-Disease.pdf

BA Brkln Pcst Sabin Gillick HMS TAP Grnwld DmStrt Kr Dgb NYR Sox Google Reader Netflix NextBus Bookmarks

Modular Program Type: MP 3 - Drug Use – Incident Outcomes
(See online specification for details: http://www.mini-sentinel.org/data_activities/details.aspx?ID=111)

Date Posted:

Medical product exposures of interest:

This Modular Program execution included 7 unique exposures, all in the Angiotensin II Receptor Blocker (ARB) drug category. The exposures were defined using National Drug Codes (NDCs identified by FirstDataBank), limited to the oral formulations, identified in the Mini-Sentinel outpatient dispensing file. The 7 drugs included were:

- Candesartan
- Eprosartan
- Irbesartan
- Losartan
- Olmesartan
- Telmisartan
- Valsartan

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- Drug Shortages
- Postmarket Drug Safety Information for Patients and Providers
- FDA Drug Safety Newsletter
- Drug Safety Podcasts
- Safe Use Initiative
- Drug Recalls

FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa

This update is a follow-up to the FDA Drug Safety Communication of 12/7/2011: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate)

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary
References

Safety Announcement

[11-02-2012] The U.S. Food and Drug Administration (FDA) has evaluated new information about the risk of

"This assessment […used…] FDA's Mini-Sentinel pilot..."

gastrointestinal bleeding (occurring in the stomach and intestines) and intracranial hemorrhage (a type of bleeding in the brain) for new users of Pradaxa compared to new users of warfarin. This assessment was done using insurance claims and administrative data from FDA's Mini-Sentinel pilot of the Sentinel Initiative. The results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of Pradaxa do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa (the RE-LY trial).[1] (see Data Summary). FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue.

www.fda.gov/Drugs/DrugSafety/ucm326580.htm; Nov 2, 2012

One-Time Protocol-based Assessments

- ACEIs/ARBs/aliskiren and Angioedema
- Rotavirus Vaccines and Intussusception
- Influenza Vaccine and Febrile Seizures
- Influenza Vaccine and Pregnancy Outcomes
- Human Papilloma Virus Vaccine and Venous Thromboembolism

ORIGINAL INVESTIGATION

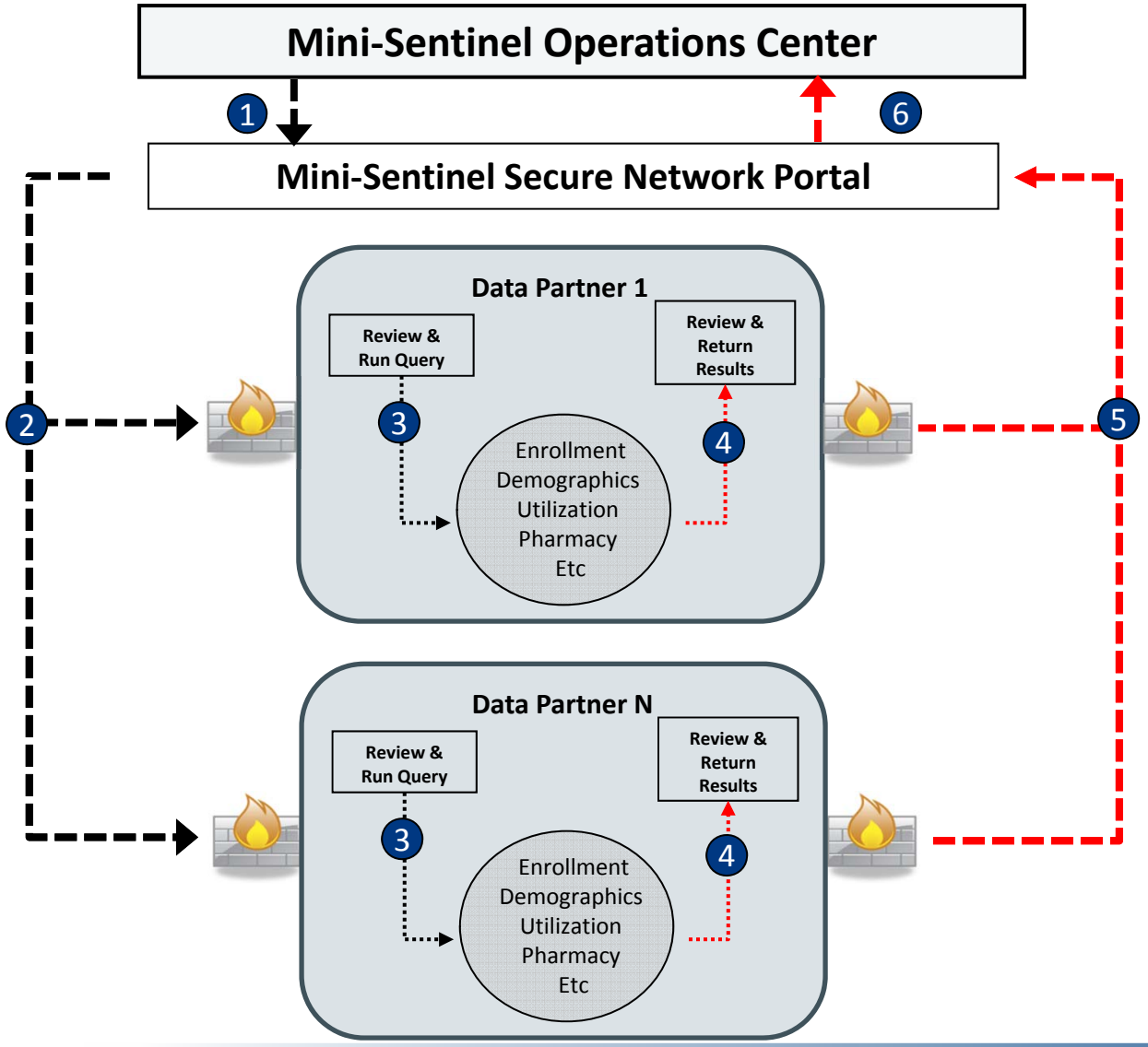
ONLINE FIRST

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

Sengwee Toh, ScD; Marsha E. Reichman, PhD; Monika Houstoun, PharmD; Mary Ross Southworth, PharmD; Xiao Ding, PhD; Adrian F. Hernandez, MD; Mark Levenson, PhD; Lingling Li, PhD; Carolyn McCloskey, MD, MPH; Azadeh Shoaibi, MS, MHS; Eileen Wu, PharmD; Gwen Zornberg, MD, MS, ScD; Sean Hennessy, PharmD, PhD

Toh Arch Intern Med.2012;172:1582-1589.

Mini-Sentinel distributed analysis



1 Workgroup creates and submits query (a computer program)

2 Data partners retrieve the query

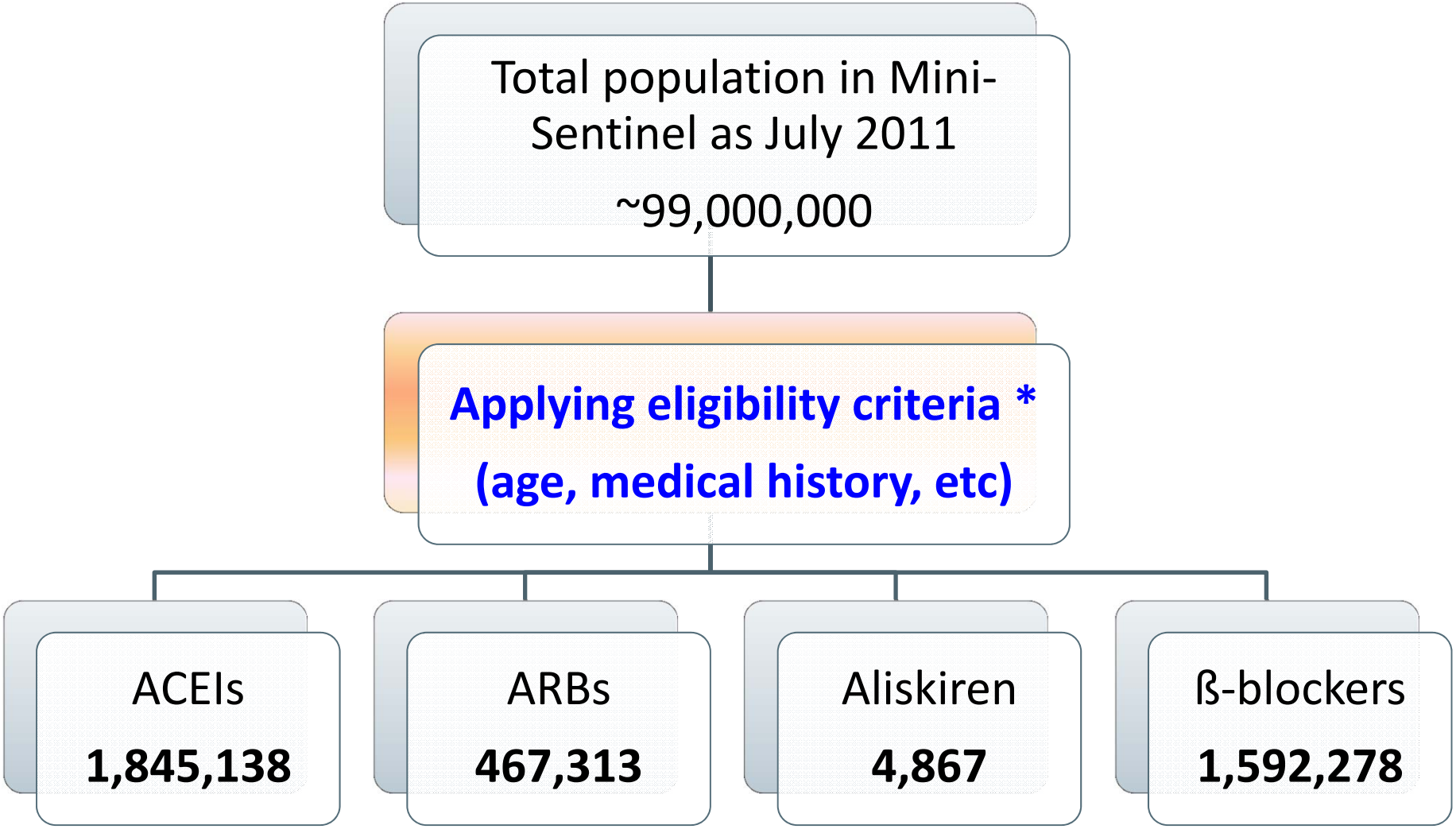
3 Data partners review and run query against their local data

4 Data partners review results

5 Data partners return results via secure network

6 Results are aggregated and returned

Cohort creation

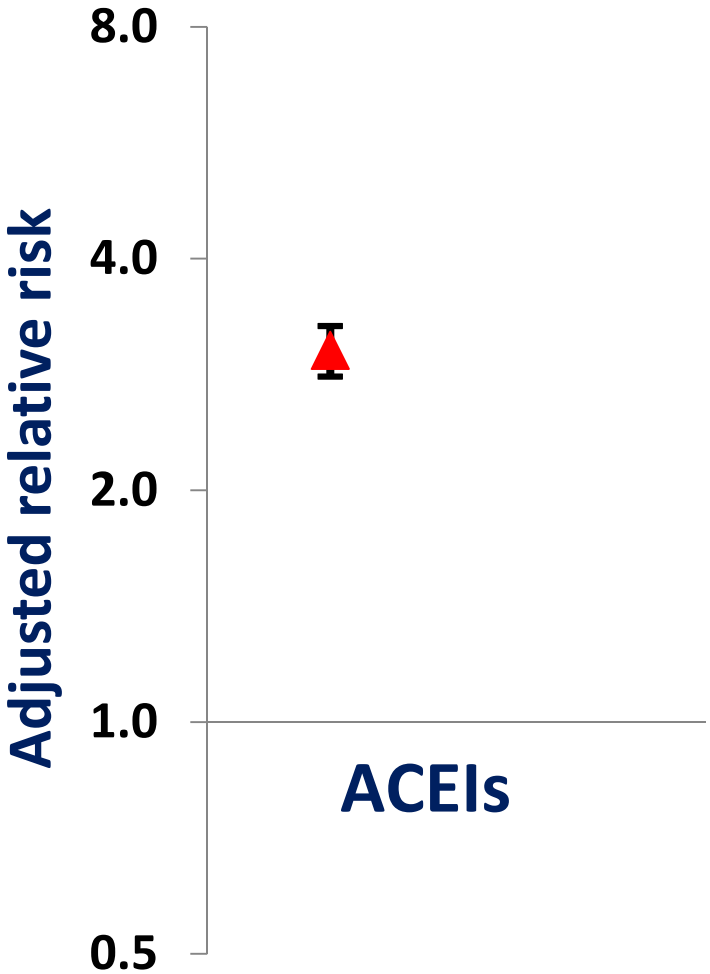


* New users with no recent exposure to any of the 4 classes and no prior angioedema

Statistical analysis

- Propensity score approach
  - Condensing information from a large number of variables
- Case-centered approach and meta-analysis
  - Needing only aggregated data to complete the analysis

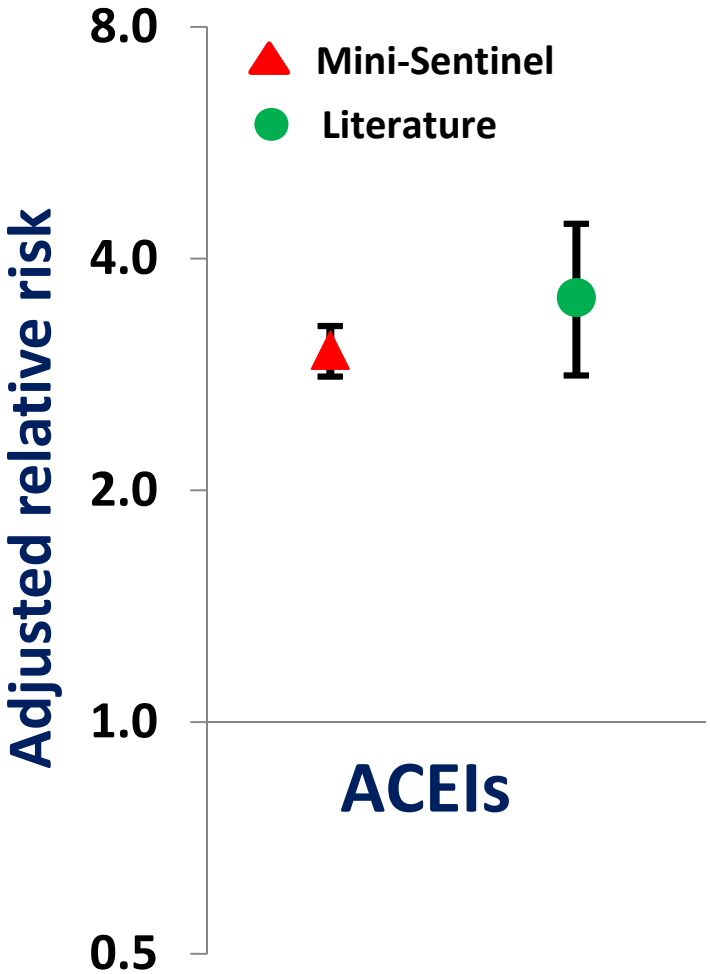
Results



* Beta-blockers as the common reference group

Toh et al, Arch Intern Med 2012;172:1582-1589

Results



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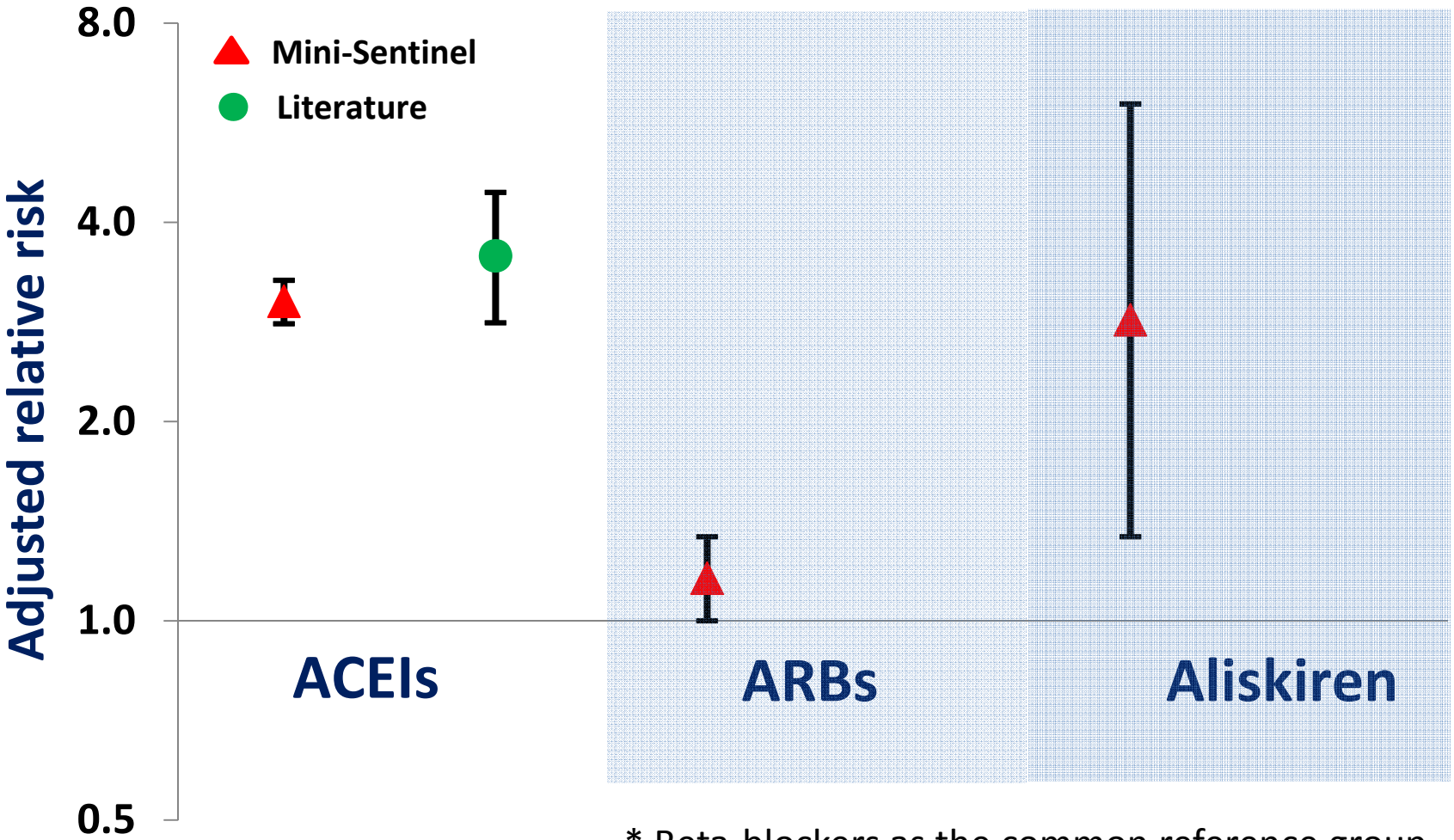

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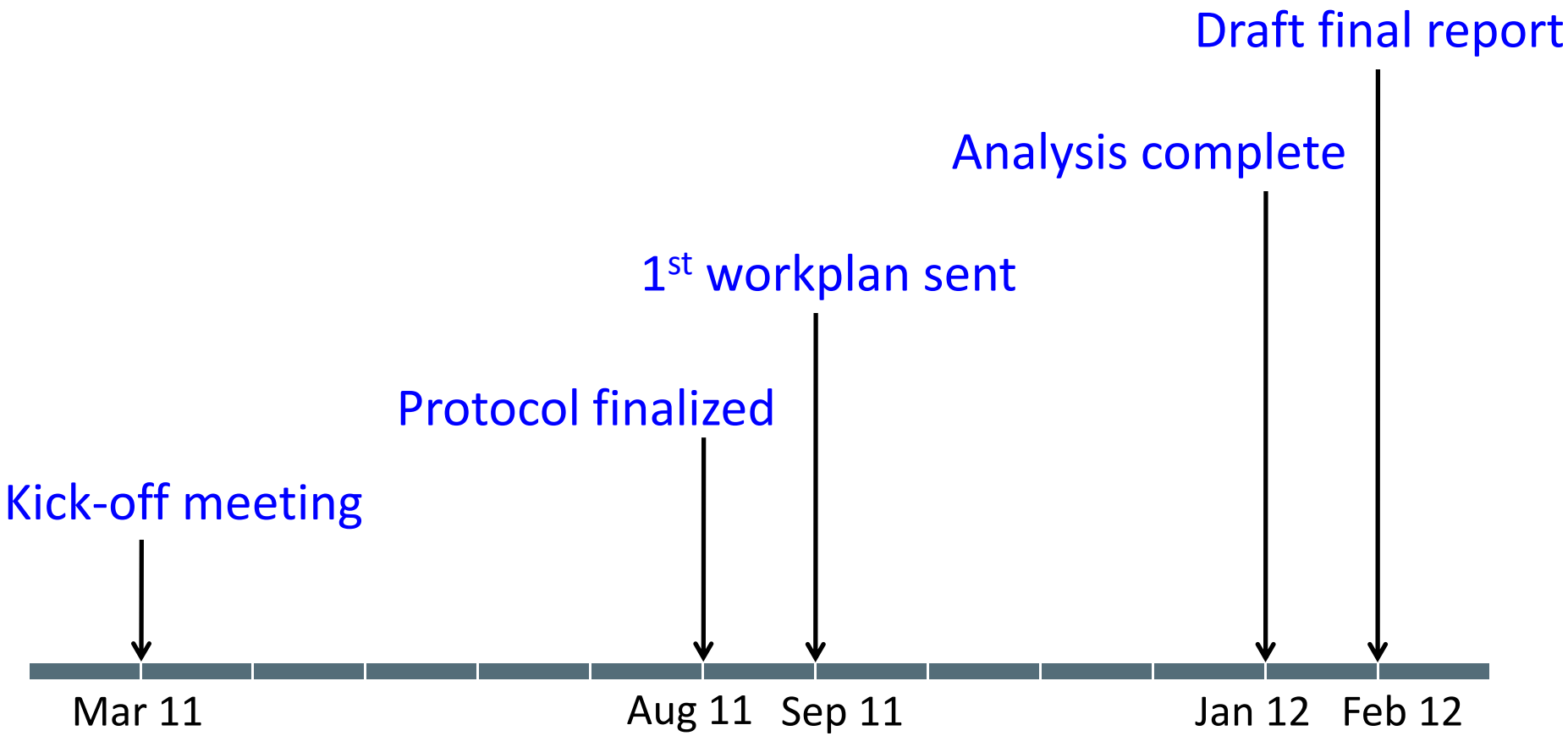
Toh et al, Arch Intern Med 2012;172:1582-1589

Timeline



Total time from start to completion: ~11 months

Conclusions

- Largest assessment on this topic to date
- Replicated known ACEIs–angioedema association
  - With much more precise risk estimates
- Provided new information on angioedema risk for
  - Aliskiren (caveat: based on 7 exposed cases)
  - ARBs

Conclusions

- Time and cost efficient study
- Robust statistical analysis did not require sharing of person-level data

An aside on distributed data analysis

Mini-Sentinel

MINI-SENTINEL METHODS

EVALUATING STRATEGIES FOR DATA SHARING AND ANALYSES IN DISTRIBUTED DATA SETTINGS

Prepared by: Jeremy A. Rassen, ScD (1), John Moran (1), Darren Toh, ScD (2), Mary K. Kowal (1), Karin Johnson, PhD (3), Azadeh Shoabi, MS, MHS (4), Tarek A. Hammad, MD, PhD, MSc, MS (5), Marsha A. Raebel, PharmD (6), John H. Holmes, PhD, (7), Kevin Haynes, PharmD, MSCE (7), Jessica Myers, PhD (1), Sebastian Schneeweiss, MD, ScD (1) and the Members of the Mini-Sentinel Strategies for Data Sharing and Analysis Workgroup

www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Evaluating-Strategies-for-Data-Sharing-and-Analyses.pdf

More results can be found here

- Report:
  http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_Angioedema-and-RAAS_Final-Report.pdf

- Manuscript:
  http://archinte.jamanetwork.com/article.aspx?articleid=1391058#qundefined

- Presentation:
  http://www.brookings.edu/events/2012/10/16-medical-product-assessment-webinar

EDITOR'S NOTE

ONLINE FIRST

"…we commend the Food and Drug Administration for developing the Mini-Sentinel…"

Risks and Benefits of Medications in Real-World Practice

All drugs have adverse effects. The challenge for practicing physicians is to determine which medications have the fewest adverse effects for a given therapeutic benefit. Unfortunately, drugs with similar indications often have not been directly compared with one another because their approvals were based on comparison with placebo or with only one member of the same or a similar class. Moreover, the comparable risks for unusual adverse effects with a group of different medications having similar indications can be even more challenging because most phase 3 efficacy trials are not powered to accurately estimate or even detect the in-

verse effect that can be life-threatening. Using the Food and Drug Administration's Mini-Sentinel program, Toh et al show that all the drugs acting on this system are not associated with the same incidence of angioedema. Specifically, the incidence was significantly higher for angiotensin-converting enzyme inhibitors and aliskiren than for angiotensin receptor blockers, and all the study drugs were associated with a greater incidence of angioedema compared with the reference category of β-blockers.

Beyond the content, we commend the Food and Drug Administration for developing the Mini-Sentinel Distributed Database; this analysis draws on medication use and

Katz. Arch Intern Med. 2012;172:1590

Protocols in the field now

- Electronic data only
  - Impact of labeling change on use of long acting beta agonists
  - Anti-diabetic drugs and acute myocardial infarction
- Electronic data plus chart review
  - Rotavirus vaccine and intussusception
  - Human papillomavirus vaccine and thromboembolism

Protocols under development

- Influenza vaccine safety
  (same season, sequential analysis)
- Metabolic effects of atypical antipsychotics in children and adolescents
- Influenza vaccine and febrile seizures
- Dabigatran and stroke / bleeding
- Influenza vaccine and birth defects, spontaneous abortion
- IV iron products and anaphylactoid reactions
- IV immune globulins and thromboembolic events

Key contributors to Mini-Sentinel's progress

- Strong collaborations between investigators and data partners
  - Creation of a community of trust with shared goals, backed by clear governance policies
  - Data partners' participation as collaborators
  - Data partners' voluntary participation on a case-by-case basis
- Distributed data network
- Focus on a relatively few well defined types of assessment
- Focus on defined populations with sufficiently complete data
  - First: Claims and administrative data, plus access to full text records
  - Then: electronic medical records, registries, …
- Rapid cycle development of capabilities

www.mini-sentinel.org

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Welcome to Mini-Sentinel

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to test and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products.

Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance.

Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise.

NEW POSTINGS

- Drugs that act on RAAS and angioedema
- Smoking cessation drugs & cardiovascular outcomes
- Angiotensin II receptor blockers & celiac disease
- Anti-diabetes drugs & acute myocardial infarction
- Mini-Sentinel Common Data Model v2.0
- MSDD At-a-Glance - December 12, 2011

www.mini-sentinel.org

The NEW ENGLAND JOURNAL of MEDICINE

February 10, 2011. Volume 364: 498-9

Perspective

Developing the Sentinel System — A National Resource for Evidence Development

Rachel E. Behrman, M.D., M.P.H., Joshua S. Benner, Pharm.D., Sc.D., Jeffrey S. Brown, Ph.D., Mark McClellan, M.D., Ph.D., Janet Woodcock, M.D., and Richard Platt, M.D.

The Food and Drug Administration (FDA) now has the capacity to "query" the electronic health information of more than 60 million people, posing specific questions in order to monitor the safety of approved medical products. This information to answer additional

convening an ongoing series of discussions among stakeholders to address the near- and long-term challenges inherent in implementing the Sentinel System.[3] In 2009, the FDA gave the Harvard Pilgrim Health Care Institute the lead role

NIH Health Care Systems Collaboratory

Home of the NIH Distributed Research Network

Millions of people. Strong collaborations. Privacy first.

A Virtual Home for Knowledge about Pragmatic Clinical Trials using Health Systems

The Collaboratory

Mini-Sentinel

Thank you!