FDA's Mini-Sentinel Program to Evaluate the Safety of Marketed Medical Products

Progress and Direction

Richard Platt
Harvard Pilgrim Health Care Institute
Harvard Medical School
for the Mini-Sentinel Investigators

January 31, 2013

2009

Mini-Sentinel

- Develop scientific operations for active medical product safety surveillance
- Create a coordinating center with continuous access to automated healthcare data systems, and the following capabilities:
  - Develop and evaluate scientific methods that might later be used in a fully-operational Sentinel System.
  - Offer FDA the opportunity to evaluate safety issues in existing automated healthcare data system(s) and learn more about barriers and challenges.

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

DukeMedicine

CRITICAL PATH INSTITUTE
collaborate · innovate · accelerate

PARTNERS HEALTHCARE

AHIP
America's Health Insurance Plans

UIC

THE UNIVERSITY OF IOWA COLLEGE OF PUBLIC HEALTH

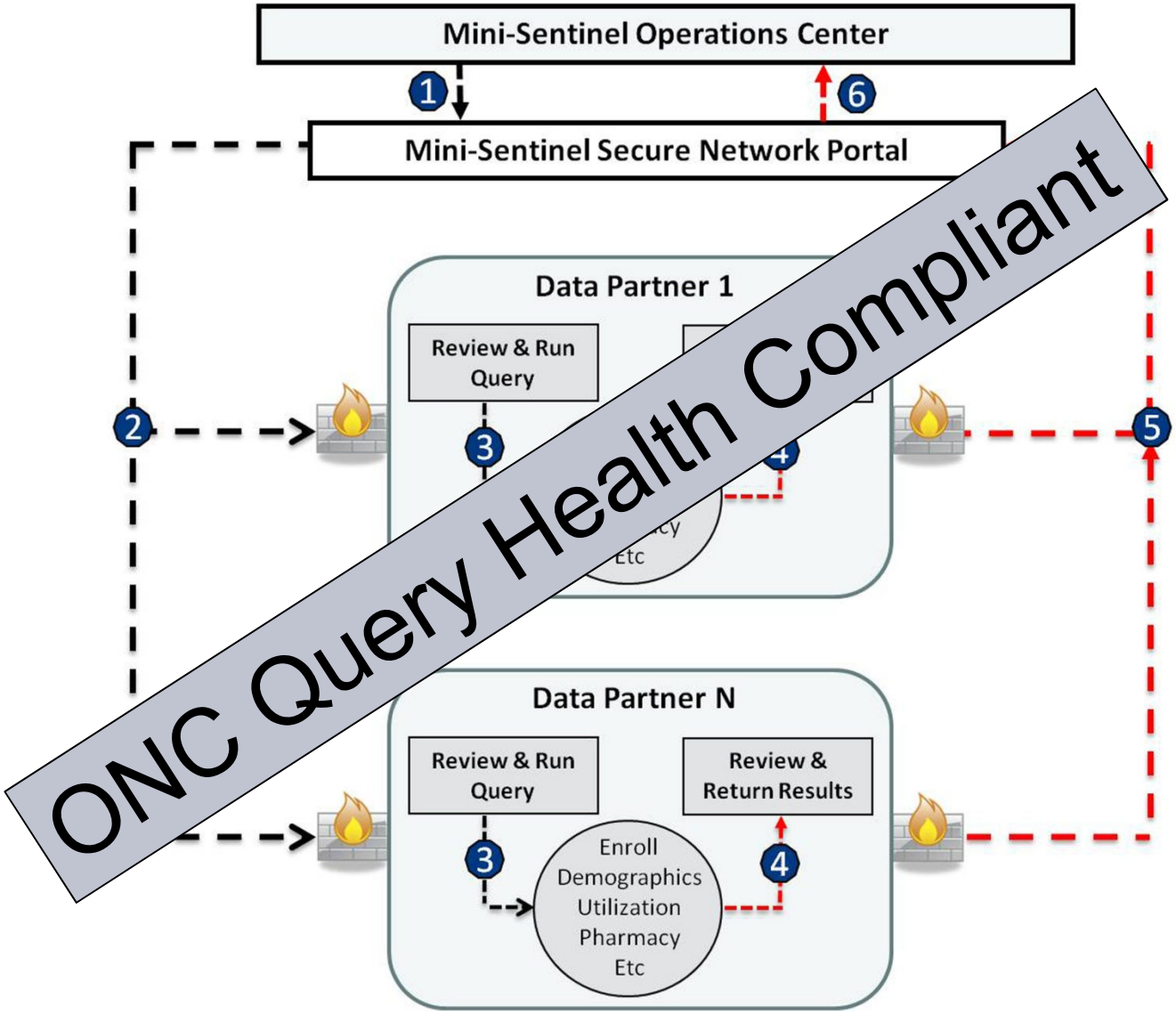
RUTGERS
Institute for Health

Initial needs

- Policies
  - Privacy
  - Governance
- Data model
- Procedures at FDA, at Coordinating Center, at Partner sites
  - White papers
  - Standard operating procedures
- Infrastructure at FDA, at Coordinating Center, at Partner sites
  - Personnel
  - Hardware
  - Software

Everything!

Mini-Sentinel Distributed Analysis



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

2- Data partners retrieve query

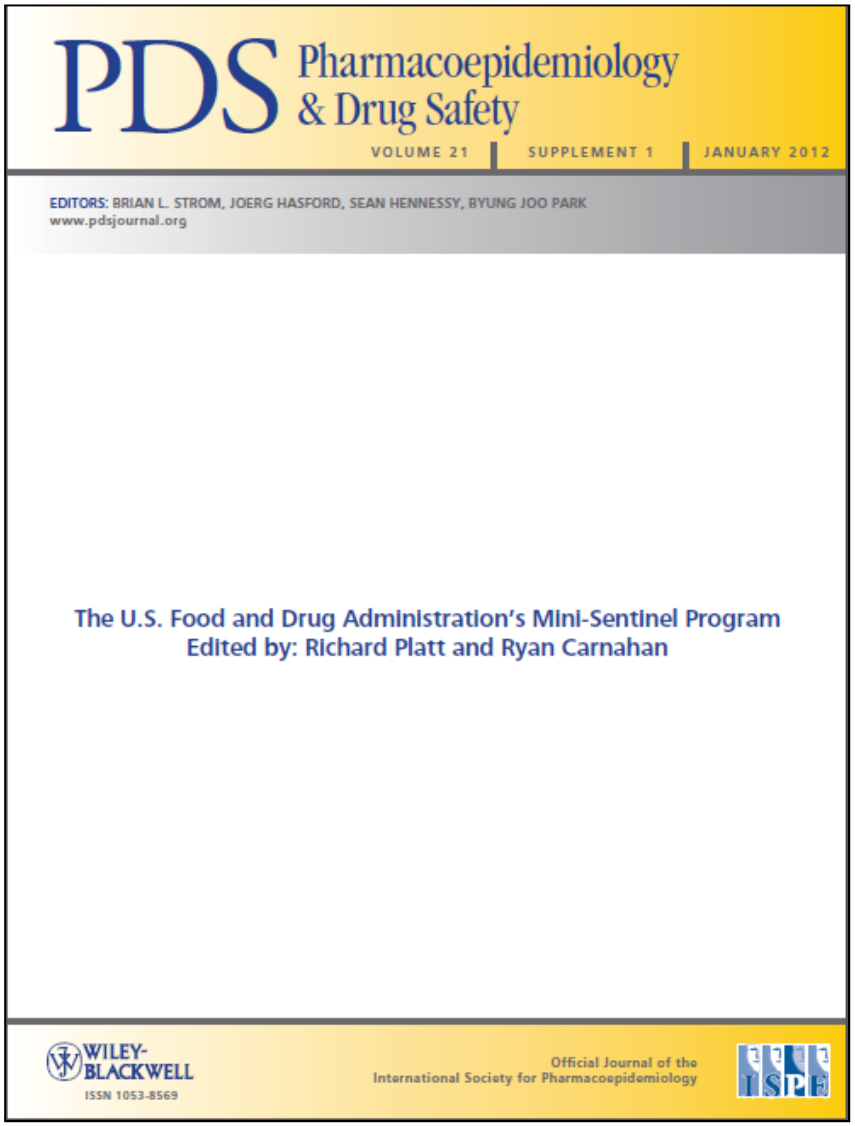
3- Data partners review and run query against their local data

4- Data partners review results

5- Data partners return results via secure network

6 Results are aggregated

Mini-Sentinel Journal Supplement



- Supplement to Pharmacoepidemiology and Drug Safety
- 34 peer reviewed articles
- Goals, organization, privacy policy, data systems, systematic reviews, stats/epi methods, record retrieval and review, protocols for drug/vaccine studies...
- Open access!
- http://onlinelibrary.wiley.com/doi/10.1002/pds.v21.S1/issuetoc

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

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

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.

EDITOR'S NOTE

ONLINE FIRST

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

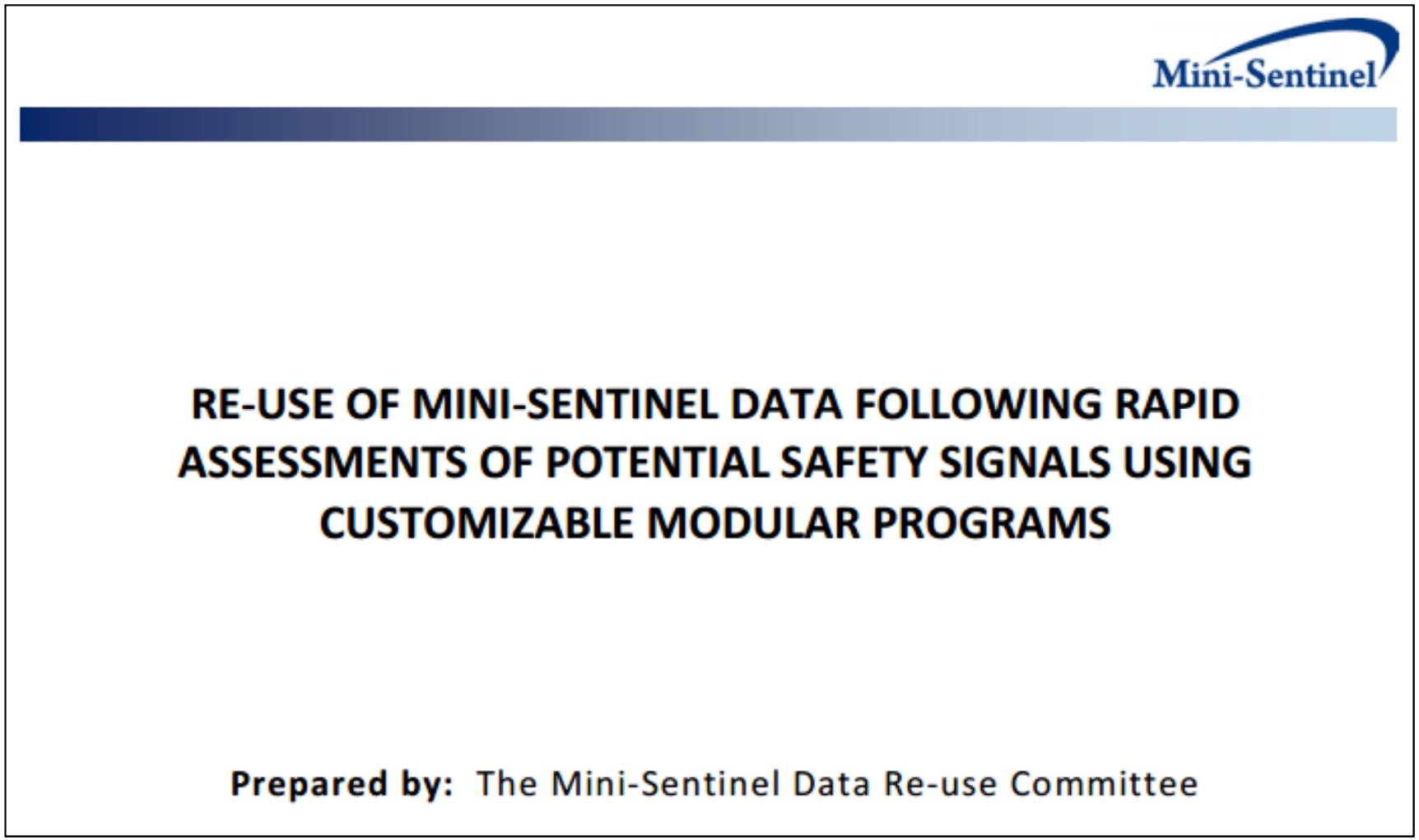
Risks and Benefits of Medications in Real-World Practice

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-

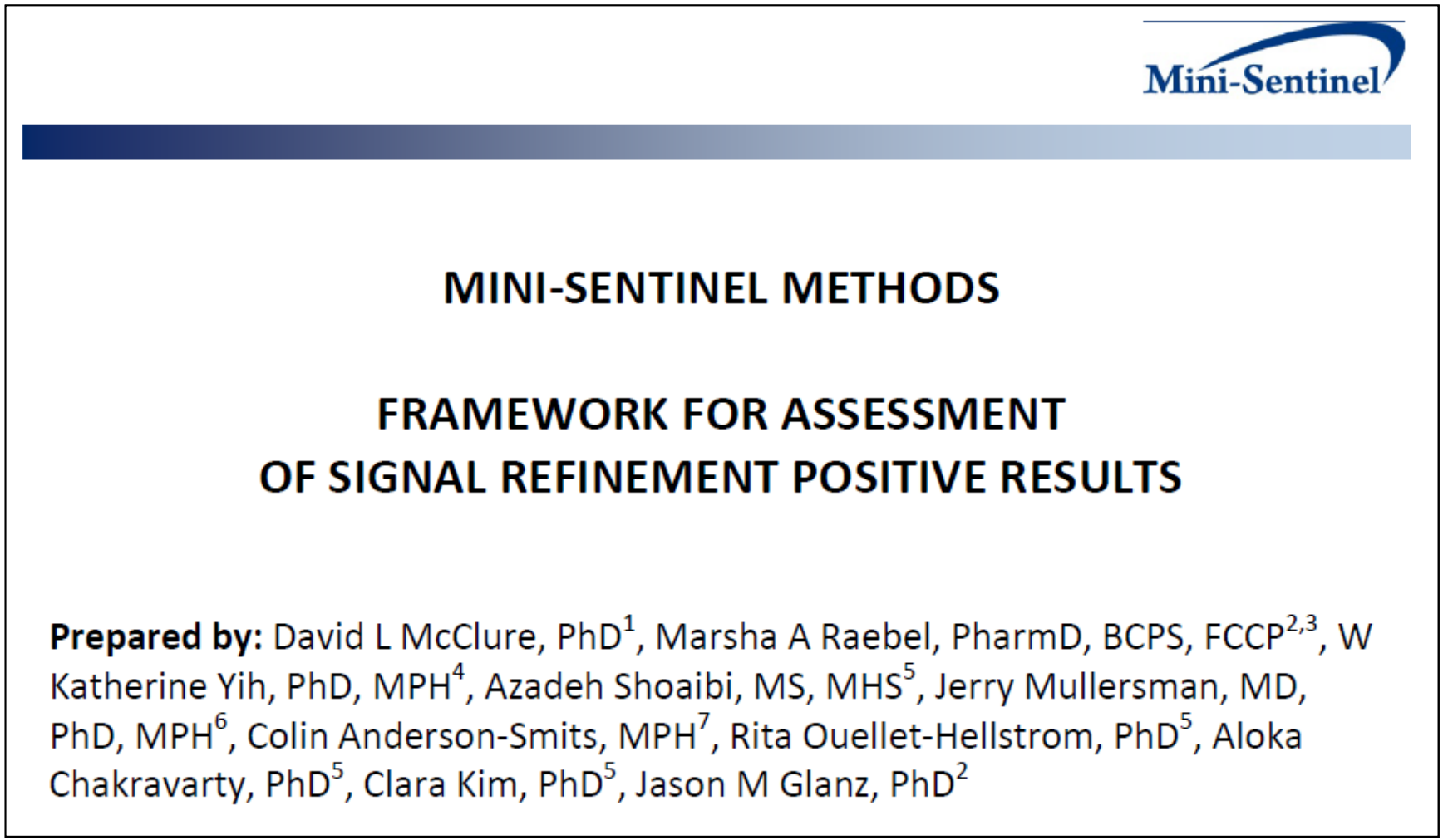
verse effect that can be life-threatening. Using the Food and Drug Administration's Mini-Sentinel program, Toh et al show that all the drugs acting on this system are not associated with the same incidence of angioedema. Specifically, the incidence was significantly higher for angiotensin-converting 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



www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Re-use-of-Mini-Sentinel-Data.pdf



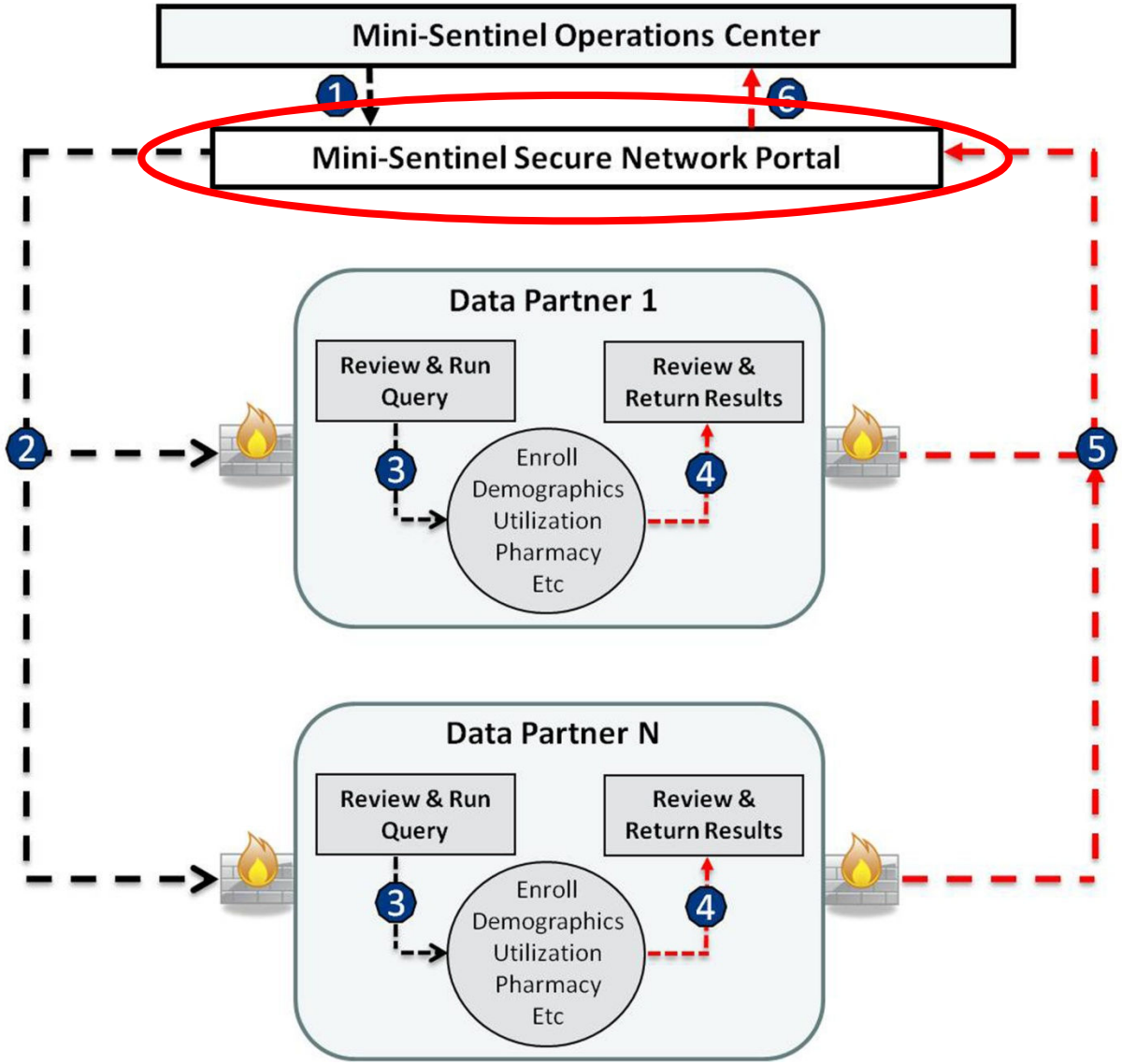
www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Framework-for-Assessment-of-Signal-Refinement-Positive-Results.pdf

In theory there is no difference between theory and practice. In practice there is.

Yogi Berra

www.brainyquote.com/quotes/quotes/y/yogiberra141506.html#gsD0IBx3dytirLPX.99

Mini-Sentinel Distributed Analysis



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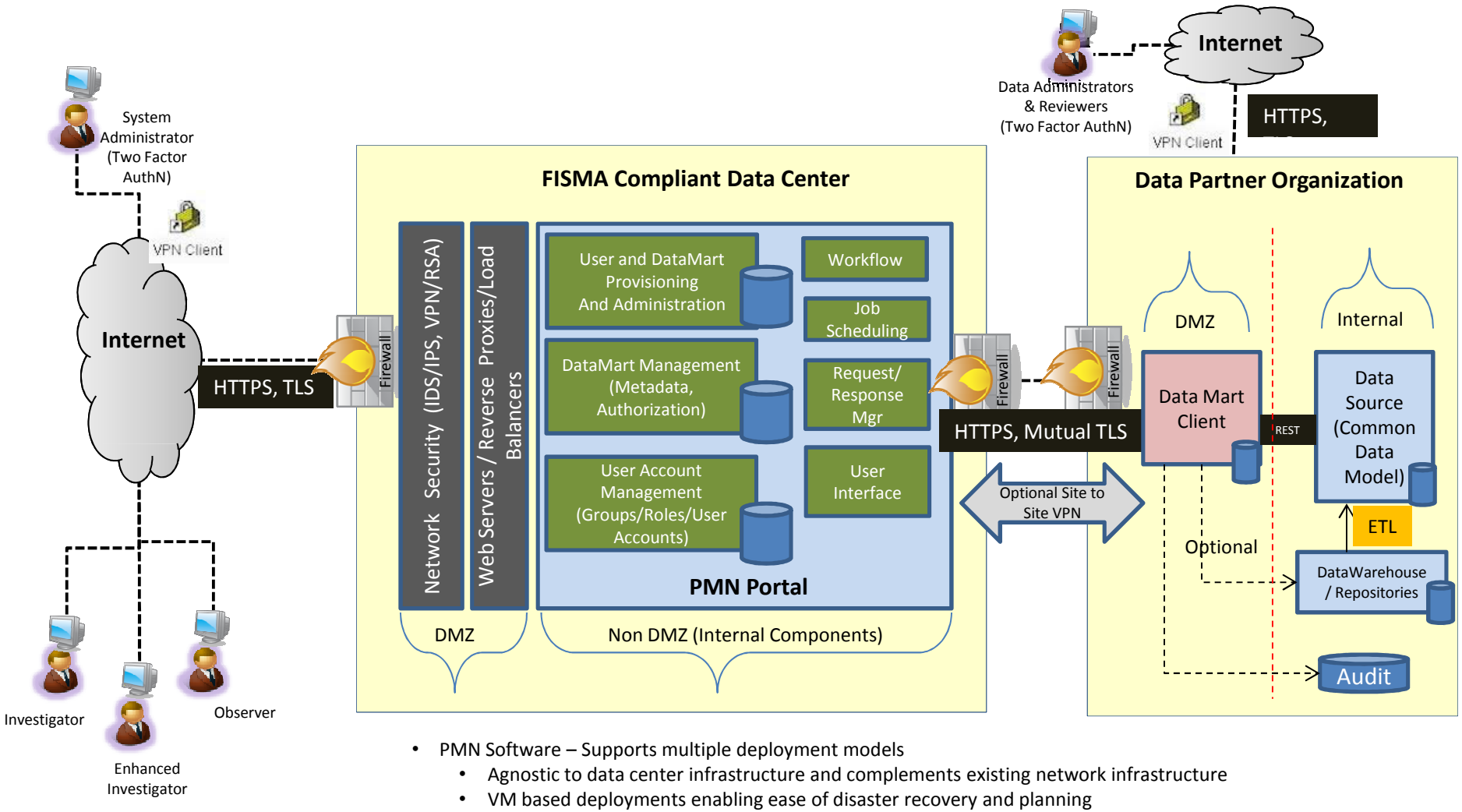
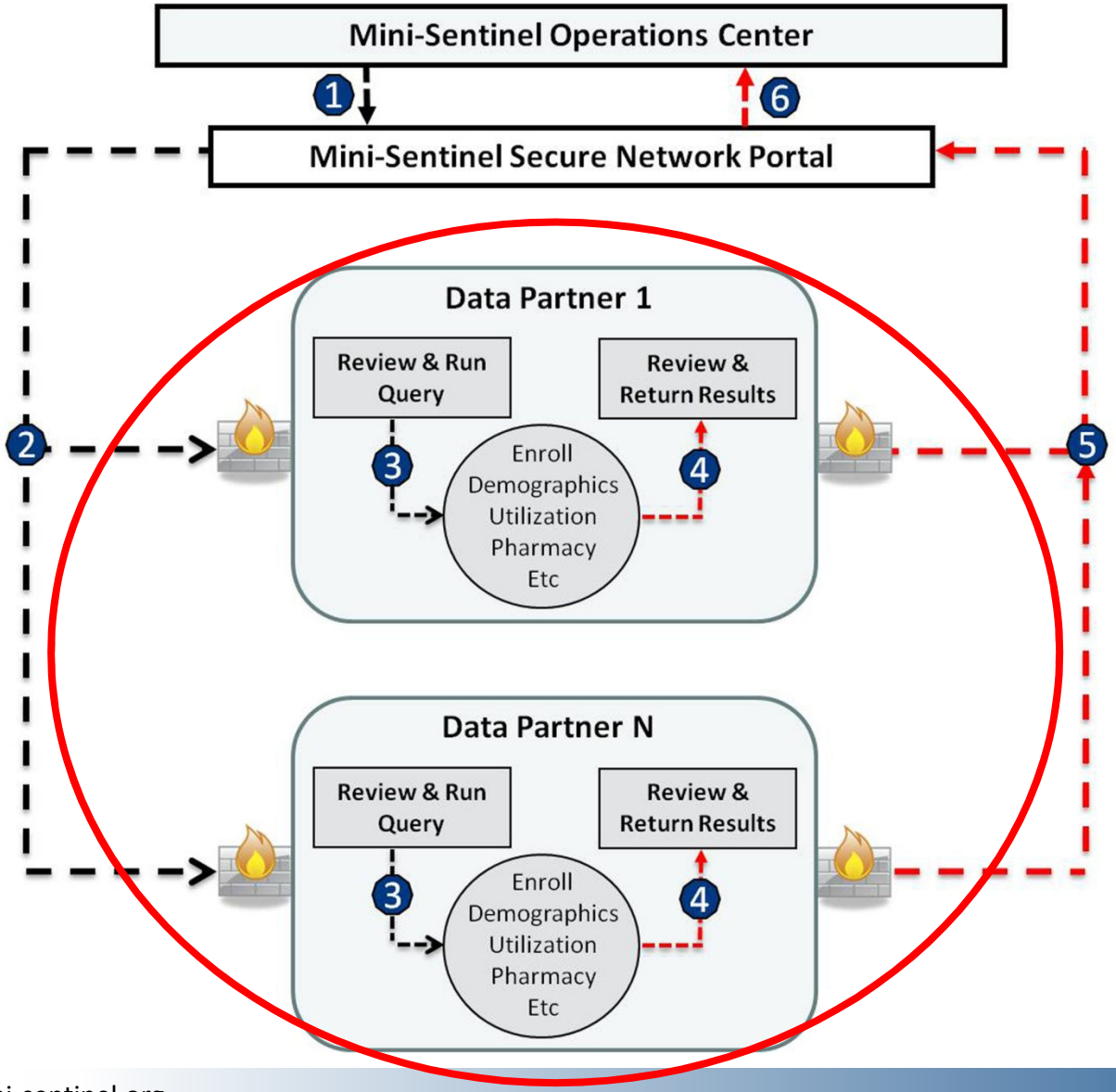
PopMedNet Architecture – Deployment Overview



- PMN Software – Supports multiple deployment models
  - Agnostic to data center infrastructure and complements existing network infrastructure
  - VM based deployments enabling ease of disaster recovery and planning
  - Seamless overlay of VPN Connections (Remote Access, Site to Site, Two Factor User Authentication)
  - Supports consolidation of remote sites into the data center for central management (Data Partner Components can be hosted in a central data center similar to the PMN Portal)
  - Secure End to End connection (Encrypted Transport using X.509 certificates)
  - Supports industry standard RBAC configuration for users
  - Supports Data Source provisioning based on RBAC and additional data source specific metadata
  - Queries distributed using a PULL model instead of PUSH model

LINCOLNPEAK

Mini-Sentinel Distributed Analysis



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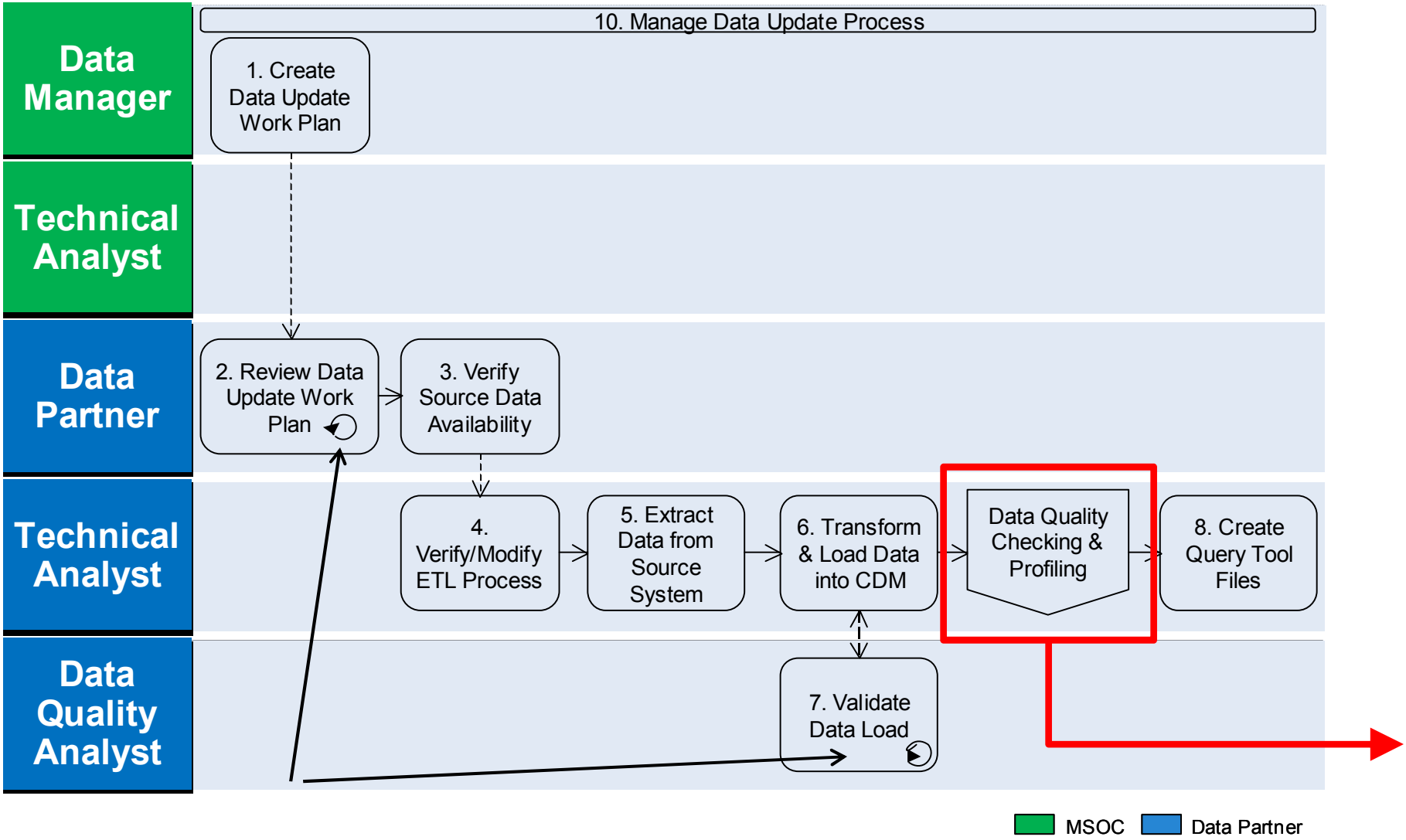
A Mini-Sentinel week

- Distributed dataset development/maintenance
- Query tool development /use
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity
- Contribute to establishing a national resource for evidence development

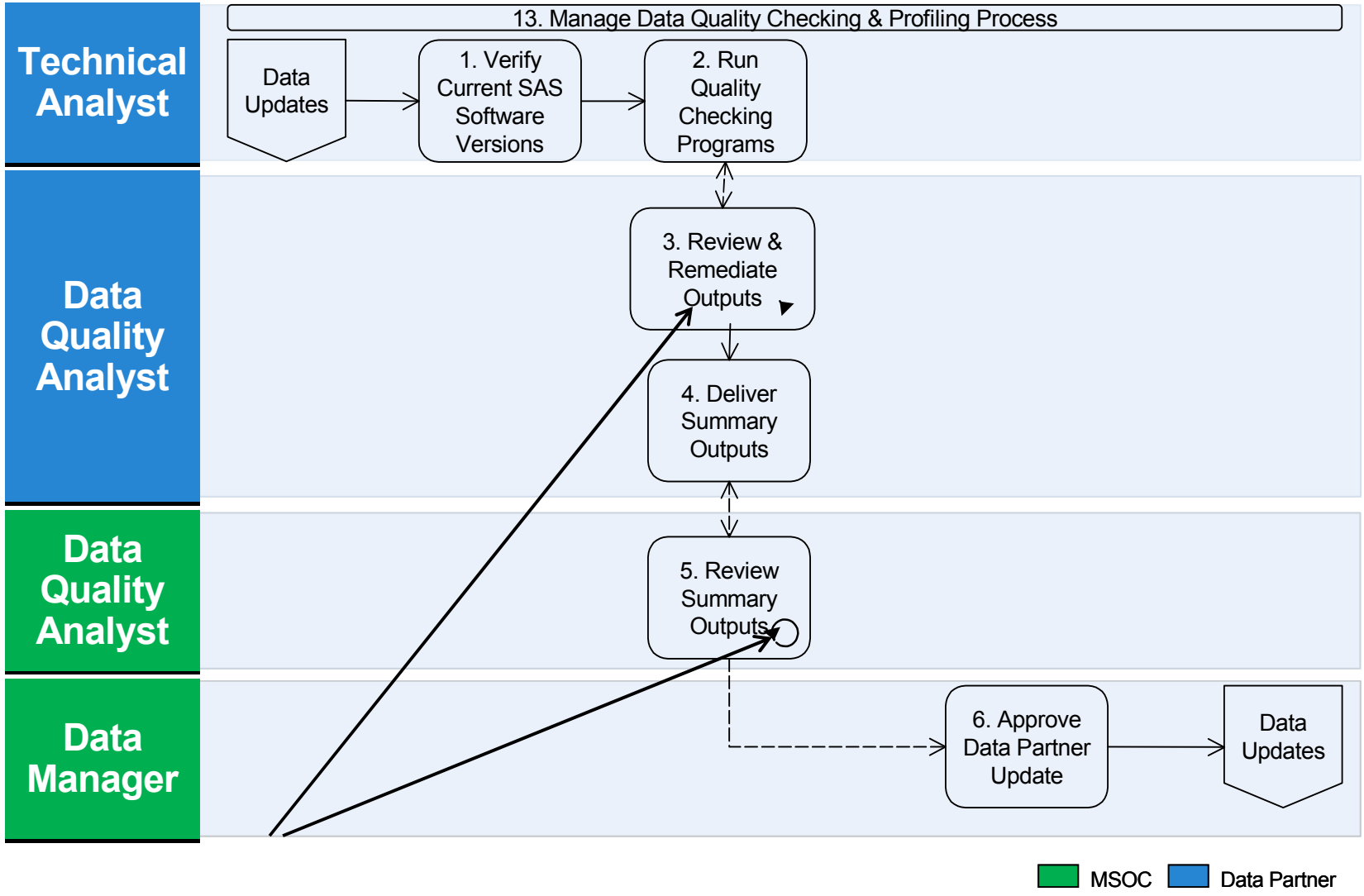
A Mini-Sentinel week

- Distributed dataset development/maintenance

Data Refreshes: Data Partner



Data Refreshes: Operations Center



Data Refreshes

- 120 core data refreshes received since MS began

Standard data checks

- 100+ tables per data partner per refresh

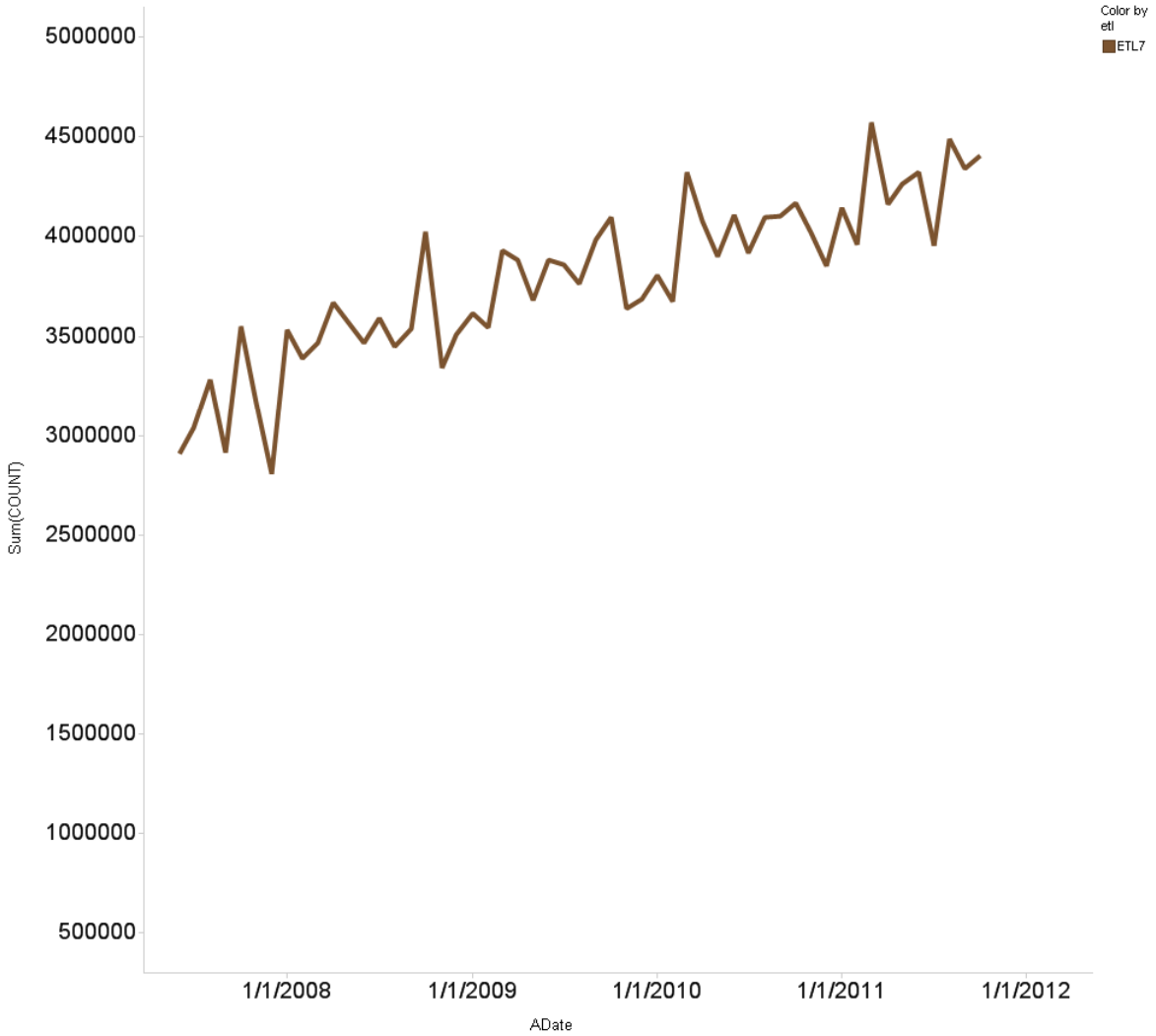
Obs	ENCTYPE	ADATE	COUNT	PERCENT
1	AV	2000	7030952	5.1370
2	AV	2001	7454699	5.4466
3	AV	2002	8014346	5.8555
4	AV	2003	8261199	6.0358
5	AV	2004	8251011	6.0284
6	AV	2005	8857635	6.4716
7	AV	2006	9576674	6.9969
8	AV	2007	10240959	7.4823
9	AV	2008	11831682	8.6445
10	AV	2009	13785025	10.0716
11	AV	2010	14499322	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	0.3302
25	IP	2000	432504	0.3
26	IP	2001	477466	0.3
27	IP	2002	517710	0.3
28	IP	2003	543660	0.3
29	IP	2004	543692	0.3
30	IP	2005	587863	0.4

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
21	2001SEP	251170

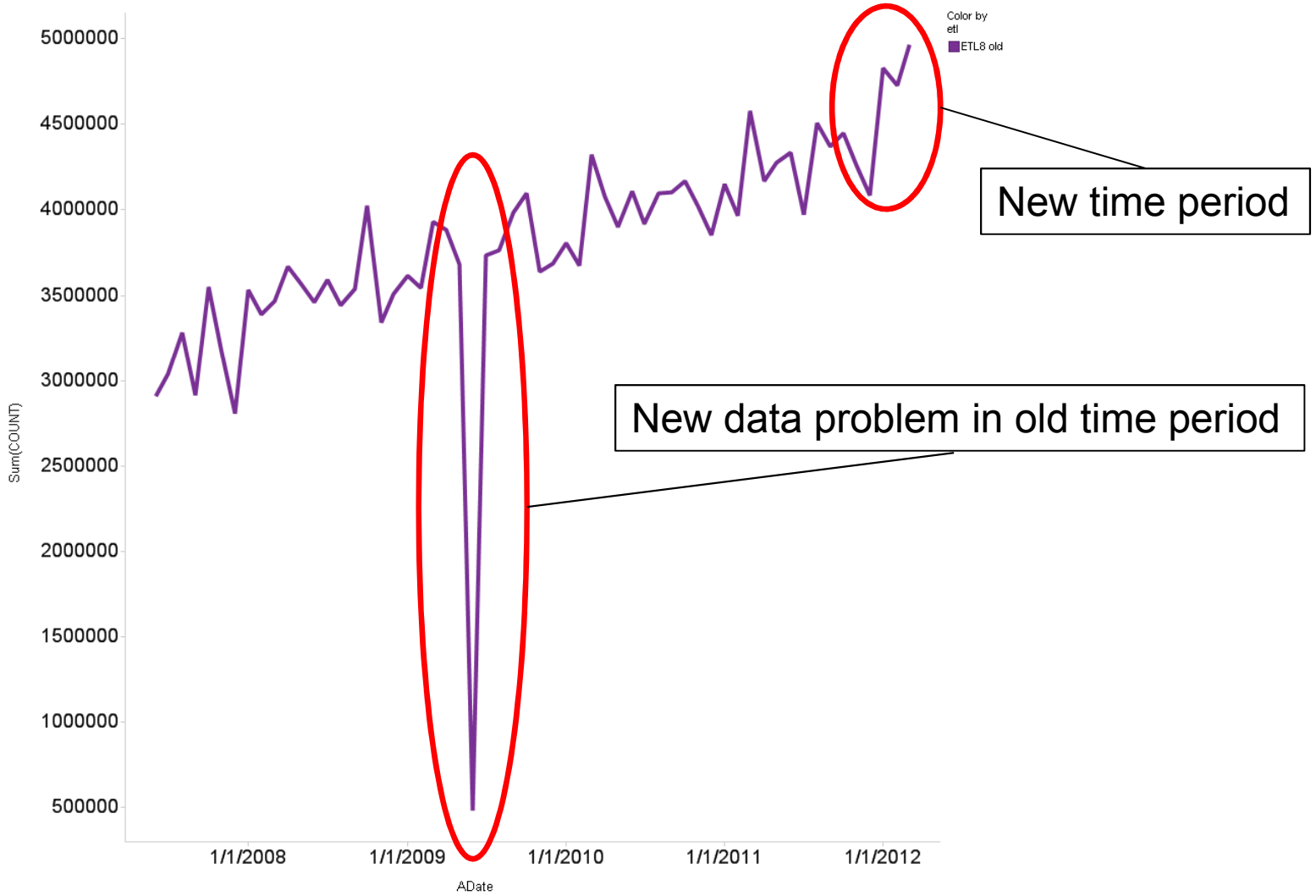
Obs	Age_group	COUNT	PERCENT
1	0.1 0-1 Yrs	602059	1.4996
2	02. 2-4 Yrs	1376997	3.4298
3	03. 5-9 Yrs	2553188	6.3595
4	04. 10-14 Yrs	2638462	6.5719
5	05. 15-18 Yrs	2135457	5.3190
6	06. 19-21 Yrs	1670742	4.1615
7	07. 22-44 Yrs	14770481	36.7906
8	08. 45-64 Yrs	11221814	27.9515
9	09. 65-74 Yrs	1854092	4.6182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

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
24	HC	IS	1600478	0.0848
	HC	OA	31067795	1.6457
	ND	AV	16692216	0.8842
	ND	ED	639229	0.0339
	ND	IP	147970	0.0078
	ND	IS	12924	0.0007
	ND	OA	819916	0.0434
	OT	AV	194765	0.0103
	OT	ED	374	0.0000
	OT	IP	2607	0.0001
	OT	IS	1367	0.0001
	OT	OA	348	0.0000

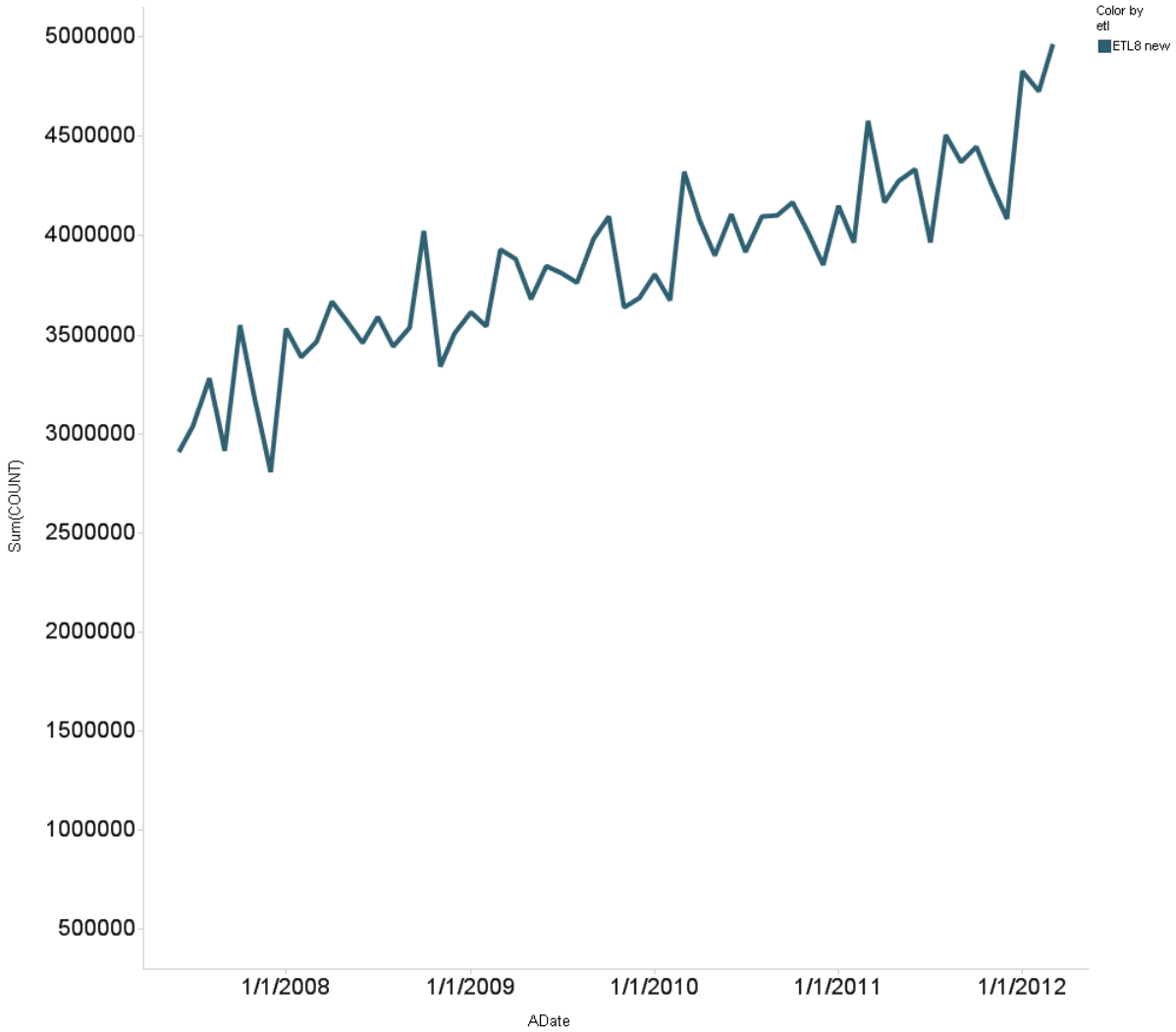
Data Visualization: After 7th refresh, partner A



Data Visualization: After 8th refresh, partner A



Data Visualization: After 8th refresh fixed



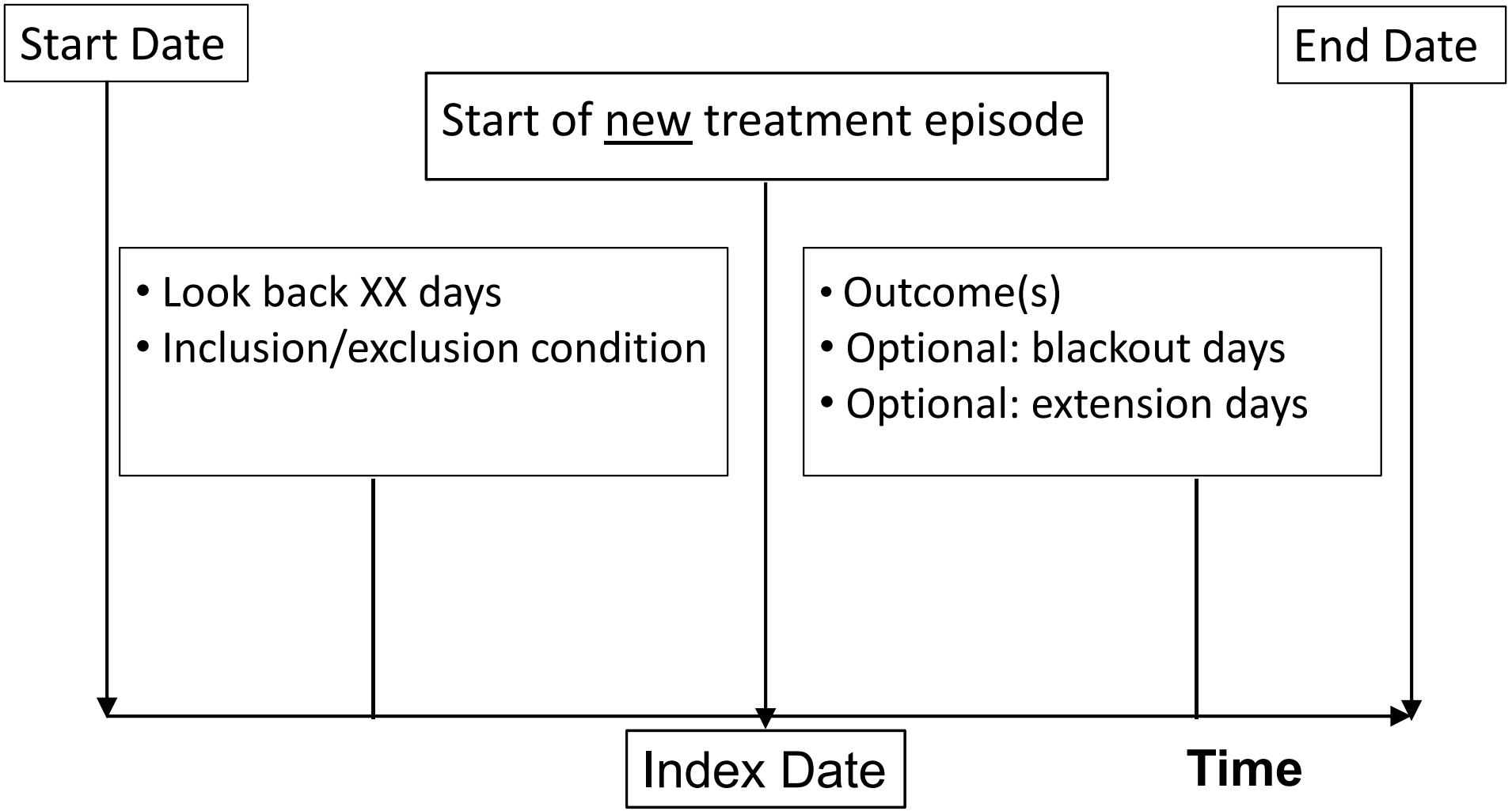
- "Eternal vigilance is the price of liberty"
  -- attributed to Thomas Jefferson

- **"Eternal vigilance is the price of reliable data"**
  -- Mini-Sentinel

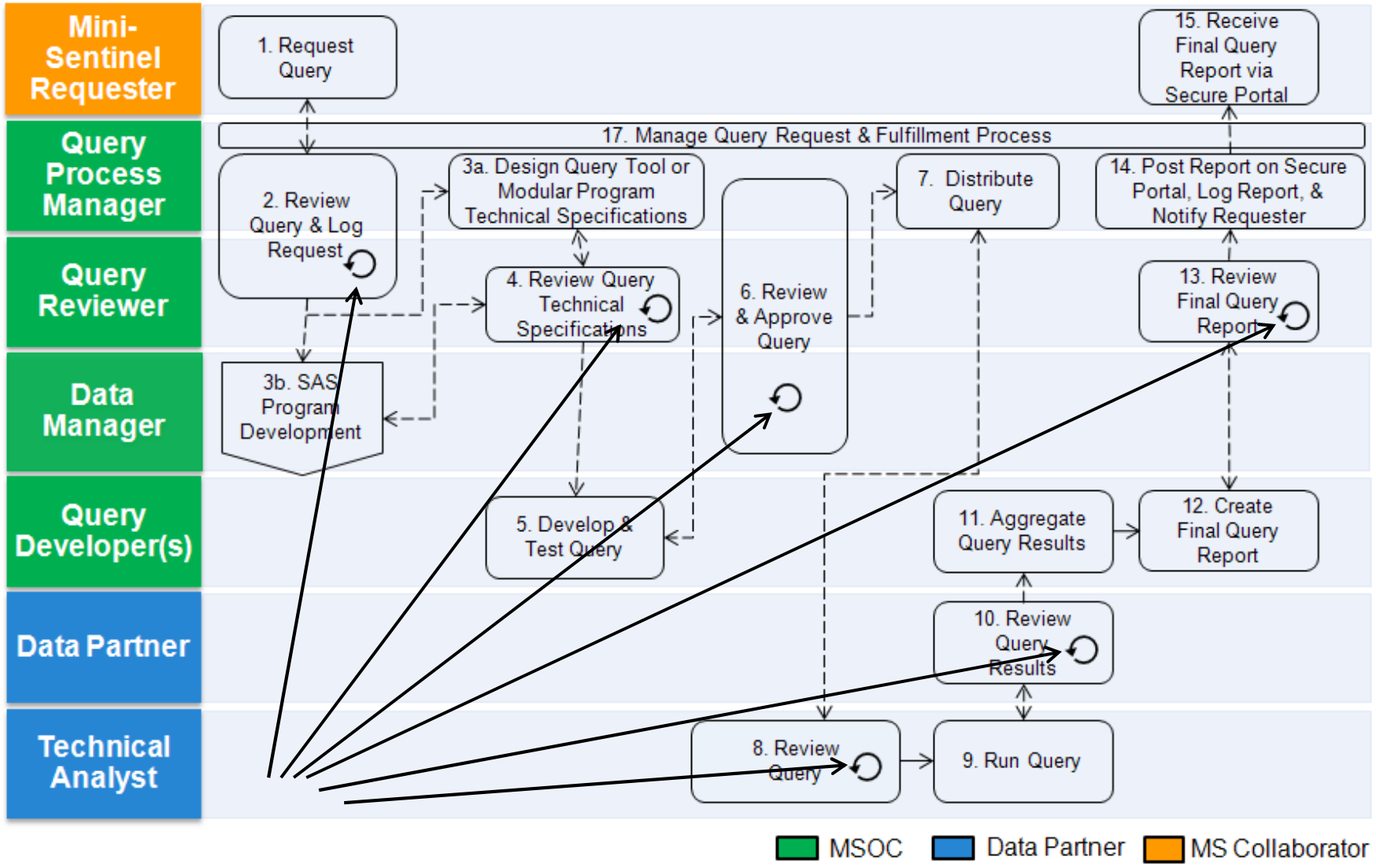
A Mini-Sentinel week

- Distributed dataset development/maintenance
- Query fulfillment tools development /use

Typical Input to Modular Programs



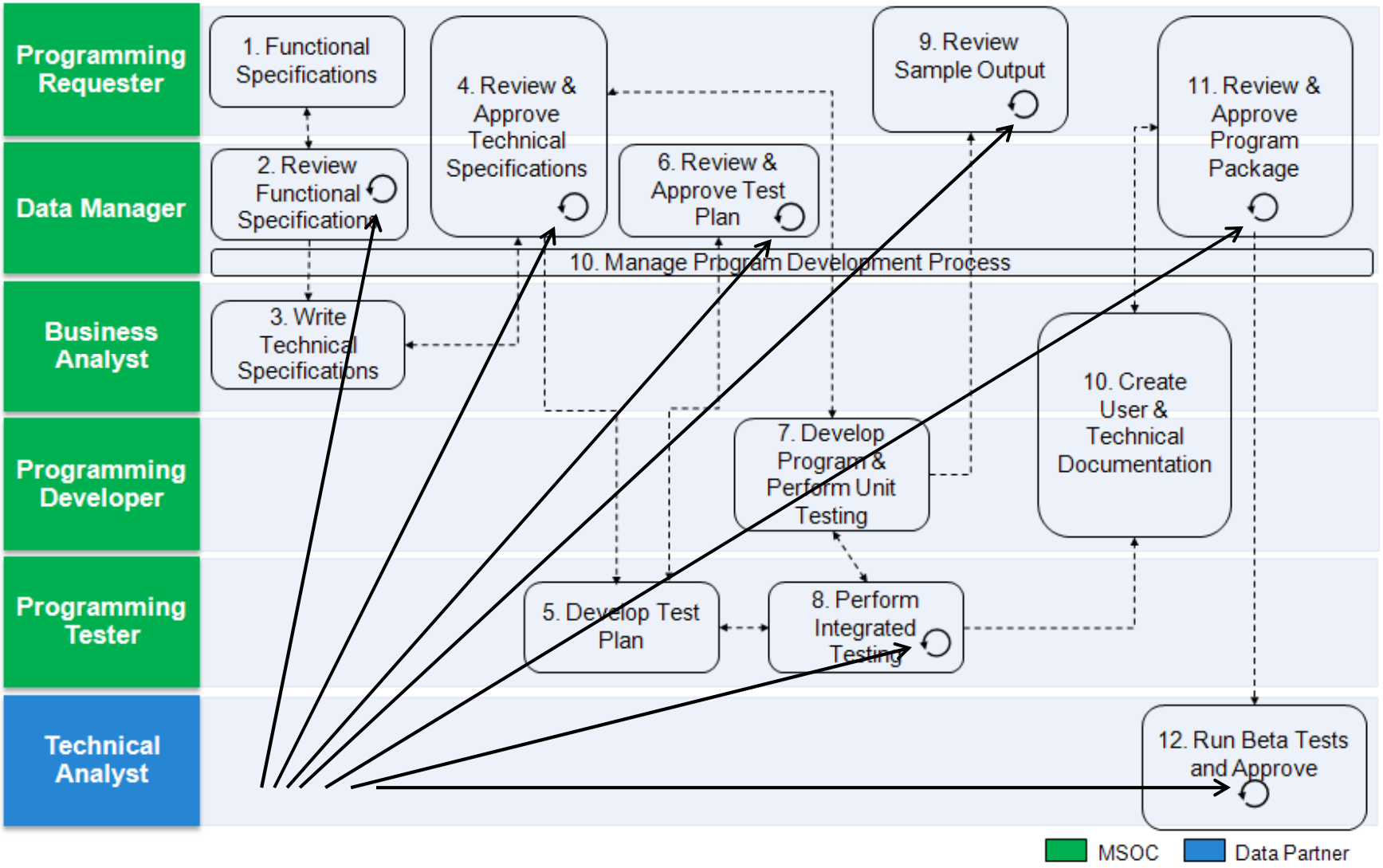
Mini-Sentinel Query Fulfillment Process



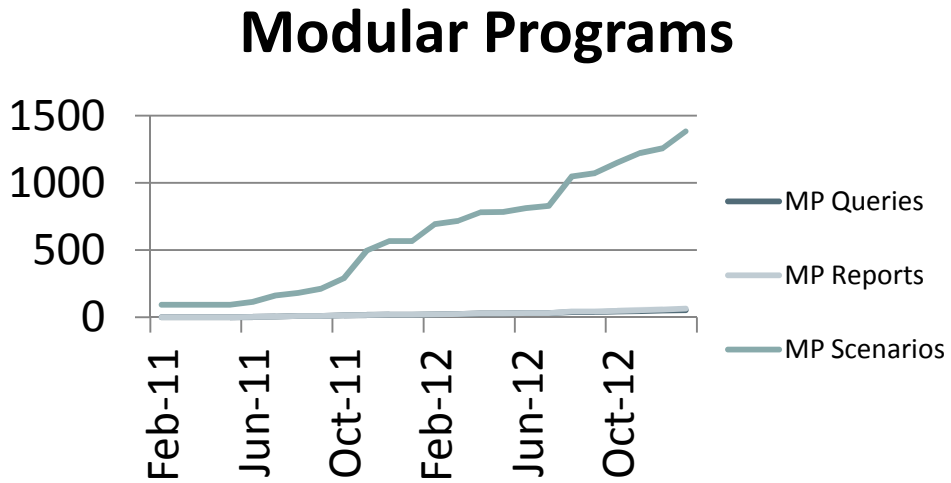
When existing programs aren't enough

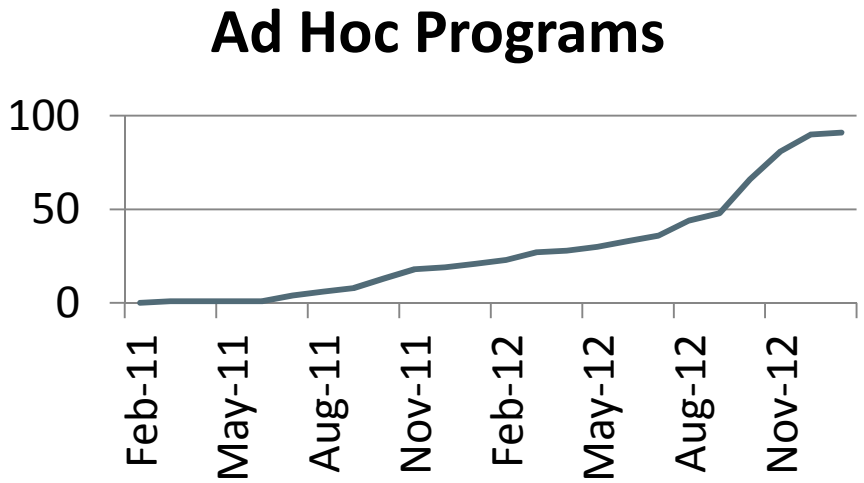
- Modify a modular program, or
- Create a new program

New Program Development



Uses of the distributed database





A Mini-Sentinel week

- Distributed dataset development / maintenance
- Query tool development / use
- Protocol development / implementation

Protocols in the field now

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

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

A Mini-Sentinel week

- Distributed dataset development / maintenance
- Query tool development / use
- Protocol development / implementation
- Methods development / implementation

Methods

- Improving confounder adjustment
- Validation of health outcomes of interest
- Data mining for vaccine adverse events
- **Implementing routine prospective surveillance of new products using sequential methods**

A Mini-Sentinel week

- Distributed dataset development / maintenance
- Query tool development / use
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity

Coming in 2013

- Prospective surveillance of new products
- New query tools
- New bandwidth to respond to more queries
- New data
  - Links to state birth and immunization registries
  - Explore use of inpatient data

A Mini-Sentinel week

- Distributed dataset development/maintenance
- Query tool development /use
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity
- Contribute to establishing a national resource for evidence development

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

Continue external engagements

- NIH Health Care System Collaboratory
- Observational Medical Outcomes Partnership (OMOP)

- Clinical Trials Transformation Initiative
- ONC Standards & Interoperability Framework (Query Health)
- IOM Roundtable on Value and Science-Driven Health Care
- Academy Health EDM Forum
- Other new partners as opportunities present

In conclusion

Key contributors to Mini-Sentinel's progress

- **Close, frequent, coordinated interactions between FDA, data partners, content experts, epidemiologists, and statisticians**
- Distributed data network
- Public health practice
- 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
- Ability to respond quickly to predefined needs

VACCINE SAFETY

DOI: 10.1377/hlthaff.2012.0104
HEALTH AFFAIRS 31,
NO. 11 (2012): 2518–2527

By Daniel Salmon, W. Katherine Yih, Grace Lee, Robert Rosofsky, Jeffrey Brown, Kirsten Vannice, Jerome Tokars, James Roddy, Robert Ball, Bruce Gellin, Nicole Lurie, Howard Koh, Richard Platt, Tracy Lieu, and the PRISM Program Group

Success Of Program Linking Data Sources To Monitor H1N1 Vaccine Safety Points To Potential For Even Broader Safety Surveillance

Daniel Salmon (dsalmon@jhsph.edu) is deputy director of the Institute for Vaccine Safety at the Johns Hopkins Bloomberg School of Public Health, in Baltimore, Maryland.

W. Katherine Yih is an epidemiologist in the Department of Population Medicine at Harvard Medical School, in Boston, Massachusetts.

Grace Lee is an associate professor of population medicine and pediatrics at Harvard Medical School.

Robert Rosofsky is a consultant at Health

ABSTRACT In response to the 2009 H1N1 pandemic and subsequent vaccination program, the Department of Health and Human Services and collaborators developed the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Program as a demonstration project to detect rare

plans and from public immunization registries that had originally not been designed to share data, and on a larger scale than had been previously attempted. The program generated safety data in two weeks rather than three to six monty 10ths—the standard time frame achievable using health plan data. PRISM substantially contributed to the understanding of the safety of H1N1 vaccines. Its use in the case of H1N1 highlights the necessity of proactive planning, scalable infrastructure, and public-private partnerships in t

"…highlights the necessity of proactive planning…"

Salmon Health Affairs 2012; 31:2518

Costs and benefits

- Up to date distributed database + hundreds of rapid response queries
- Protocol based study
- Being prepared for pandemic or other crisis

Expectations confirmed

- Standard programs can help FDA quickly interpret signals from other sources:
  - Dabigatran and bleeding
  - Olmesartan and celiac disease
  - Varenicline and cardiac events
- Many sophisticated analyses do not require exchange of protected health information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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
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

Thank you!