ENGELBERG CENTER for Health Care Reform at BROOKINGS

Highlights from the Fifth Annual Sentinel Initiative Public Workshop

Patrick Archdeacon, Medical Officer, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Richard Platt, Professor and Chair, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute

March 7, 2013

Welcome and Overview

Housekeeping:

- To minimize feedback, please confirm that the microphone on your telephone is muted.
- To mute your phone, press the mute button or '*6'. (To un-mute, press '*7')
- There will be opportunities for questions and discussion at the end of today's presentations. **Please use the Q & A tab on the top of your screen to submit your questions into the queue at any point** and we will call upon you to state your question.
- Call the Level 3 Conferencing at 1-888-447-1119 with technical problems.

Progress and Future Directions of the Sentinel Initiative

Patrick Archdeacon, MD
Medical Officer
Office of Medical Policy/CDER/FDA
March 7, 2013

FDA Amendments Act of 2007

Section 905: Active Postmarket Risk Identification and Analysis

- Establish a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including
  - at least 25,000,000 patients by July 1, 2010
  - at least 100,000,000 patients by July 1, 2012
- Access a variety of sources, including
  - Federal health-related electronic data (such as data from the Medicare program and the health systems of the Department of Veterans Affairs)
  - Private sector health-related electronic data (such as pharmaceutical purchase data and health insurance claims data)

Mini-Sentinel Achievements

- Protocol based one time assessments: RAAS drugs and angioedema; Gardisil and VTE
- Protocol based repeated assessments: Diabetes drugs and AMI
- Modular program based one-time assessments: Dabigatran, warfarin & GI bleed, intracerebral hemorrhage

To date, Mini-Sentinel has focused on analyzing data to test existing hypotheses, either through resource-intensive protocol based studies or rapid (if potentially confounded) modular program assessments.

At Present

- Infrastructure in place to capture product exposures
- Some experience in measuring a few outcomes (AMI, bleeding)
- Sufficient expertise available to develop programming compatible with CDM to apply existing methodologies to specific product:outcome pairs
- More rapid modular programs have limited ability to control for confounding

❖ Highly specialized system that supports important but restricted range of activities

Goal Capacities

- Increase current capabilities

  But also…
- Create semi-automated routine surveillance capability
  - Need vastly expanded menu of measurable outcomes
  - Need adaptable programs that can apply general methodologies to many product:outcome pairs
  - Need improved understanding of appropriate application of statistical and epidemiology tools in this setting to mitigate systematic bias

❖ Comprehensive system capable of full range of safety surveillance

Goal: 1st Iteration of Routine Surveillance System by June 2013

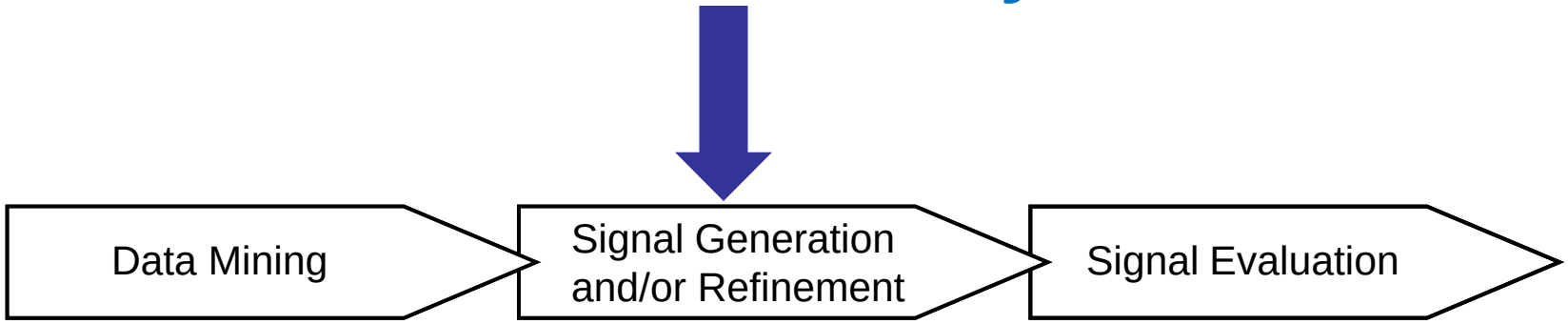
Features

- Ability to select from a menu of HOIs
- Will leverage existing MSDD to evaluate associations between drugs/biologics/vaccines and HOIs
- Employ different methodologies based on product-HOI pair

Gaps

- Not all HOIs will have been validated within MSDD
- Will not have capability to examine associations between most device-HOI pairs
- Methodologies and data use policies will continue to evolve with experience

Focus of 1st Generation Routine Surveillance System



- For newly approved products, the system will look for associations with a restricted set of HOIs through semi-automated queries of the MSDD
- The set of HOIs for a given product will be selected at the Center level from a menu of possible HOIs

Activities Required to Meet Goal

1) Establish algorithms capable of identifying relevant HOIs (and also confounders and cohorts) within the MSDD
2) Create new modules capable of replicating features of basic epidemiologic study designs
3) Develop data use strategies, refine policies, and create implementation tools

HOIs with Algorithms under Development

- Pulmonary Fibrosis
- Severe Acute Liver Injury
- Anaphylaxis
- Acute Kidney Injury
- Acute Myocardial Infarction
- GI Bleed
- Hypertensive Emergency
- Premature Delivery
- Neutropenia
- Agranulocytosis
- VTE
- Asthma Exacerbation
- Sepsis
- Tuberculosis
- EMM/SJS/TENs
- Guillain Barre Syndrome
- Aplastic Anemia
- Bell's Palsy
- Stillbirth/Spontaneous Abortion
- Acute Pancreatitis
- Ischemic Stroke
- Hemorrhagic Stroke
- Acute Respiratory Failure
- Juvenile Rheumatoid Arthritis
- Deafness
- Systemic Lupus Erythematosis
- Thrombocytopenia
- TTP
- Inflammatory Bowel Disease
- Peripheral Neuropathy
- Pulmonary Hypertension
- Hip Fracture
- Rhabdomyolysis
- Sudden Cardiac Death
- Tendon Rupture
- Type 1 Diabetes
- Seizure, febrile
- Suicide, including attempted suicide
- Valvulopathy
- ITP

Mini-Sentinel also Developing Algorithms to Identify Cohorts

- Nursing home residents
- Pregnant women
- Live births
- Babies born prematurely
- Immunocompromised patients
- Patients who received fluoroquinolones for PEP
- Asthmatics
- Smokers
- Patients with CAD
- First Responders
- Patients with Obesity
- Patients with ESRD
- Patients with dementia
- Patients with mood disorder
- Diabetics

Activities to Develop Analytic Modular Programs for Routine Surveillance

Module 1

Self-controlled case series

Parameters:

- Exposure time trend adjustment
- …

Maclure et al. PDS 2012
Whitaker et al. Stat Med 2006
Wang et al. Epidemiology 2011
Musonda et al. Vaccine 2008

Module 2

Cohort approach 1

Parameters:

- Score-based matching (PS, DRS)
- fixed/variable ratio
- …

Rassen et al AJE 2011, PDS 2012; Schneeweiss et al. Epidemiol 2009; Glynn et al PDS 2012; Austin et al Stat Med 2011

Module 3

Cohort approach 2

Parameters:

- Regression
- Weighted or unweighted
- …

Cook et al. PDS 2012
Austin et al. Stat Med 2007, 2010
Robins et al. Epid 2000
Cole et al. AJE 2008

For each epidemiologic design, a modular program will be built and tested using example datasets for selected positive and negative controls. The selection of these three designs was informed by the prior work of the Taxonomy workgroup.

Additional Tasks Required to Support Routine Surveillance

- Determine appropriate uses of preliminary vs finalized administrative data for optimizing “near real time” surveillance
- Determine appropriate policies regarding data use and re-use in the context of routine surveillance
- Develop operations manual to guide end-user application of routine surveillance tools

Protocol-Based Evaluations vs Semi-Automated Surveillance

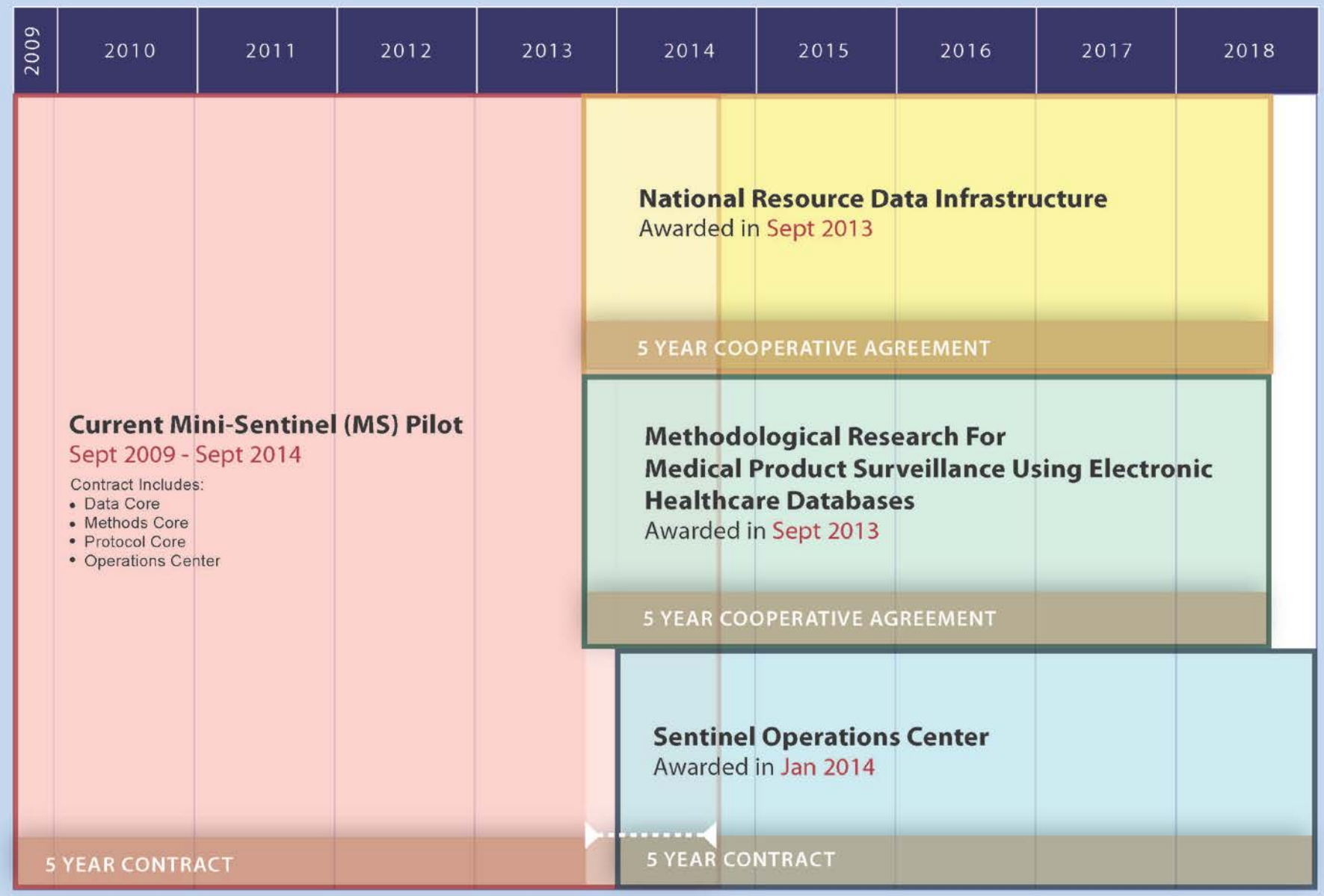
Protocol-Based

- More resource intensive
- Greater control of systematic biases
- Typically one time analysis
- Ability to test hypotheses

Semi-Automated

- Less resource intensive
- Less control of systematic biases
- Sequential analyses
- Ability to generate hypotheses

SENTINEL INTIATIVE TIMELINE
(PROPOSED)



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

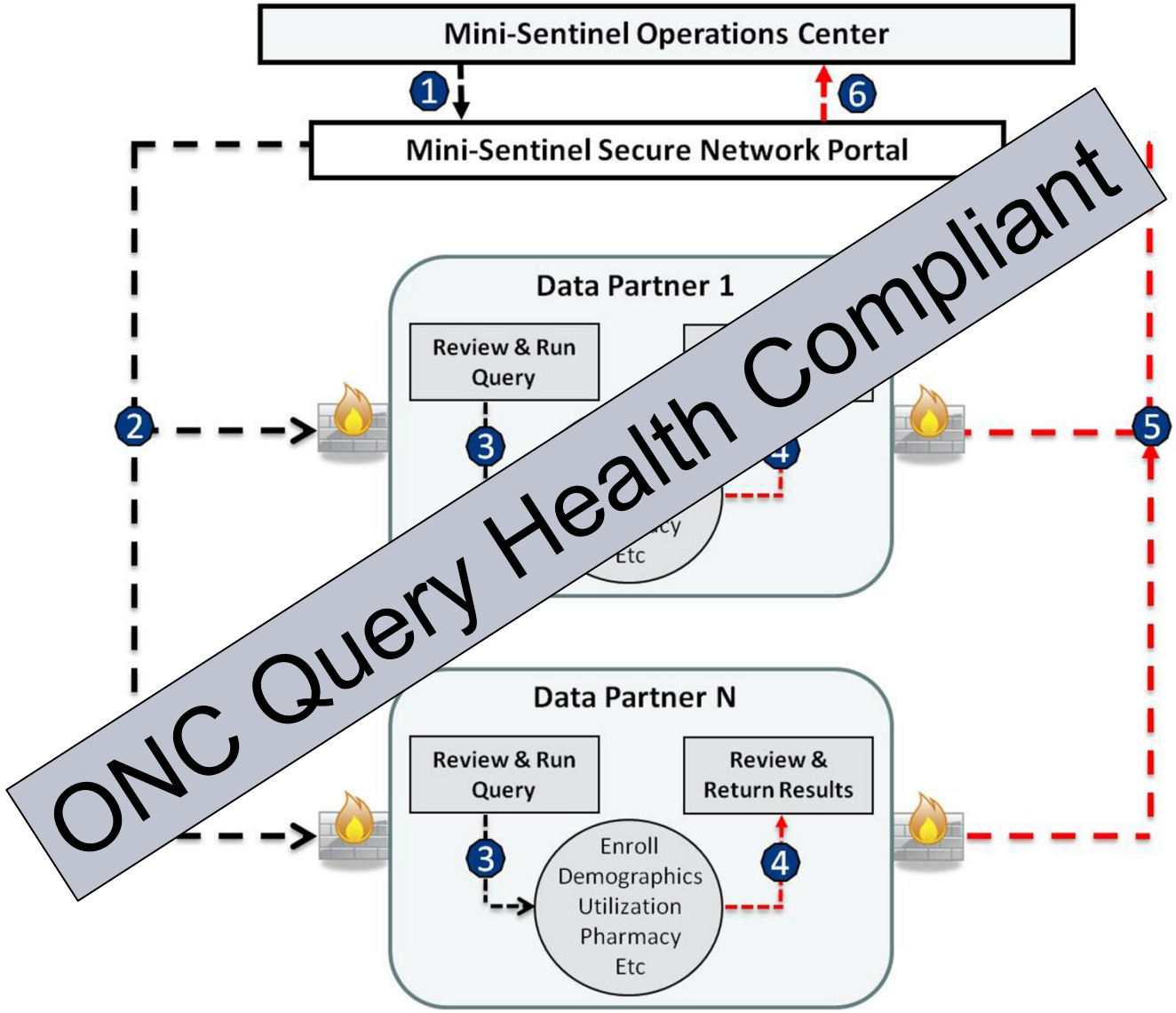
March 7, 2013

Mini-Sentinel in brief

- Congress mandated FDA develop a safety surveillance system based on electronic health data
- Mini-Sentinel is a five year pilot program. Its goals:
  - Develop capacity for active medical product safety surveillance using existing automated healthcare data
  - Develop and evaluate scientific methods
  - Allow FDA to evaluate safety issues
  - Assess barriers and challenges
- Mini-Sentinel recently entered its fourth year

Mini-Sentinel partner organizations

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

"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

A Mini-Sentinel week

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

A Mini-Sentinel week

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Data Refreshes and Standard Data Checks

- 120+ core data refreshes received to date
- 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

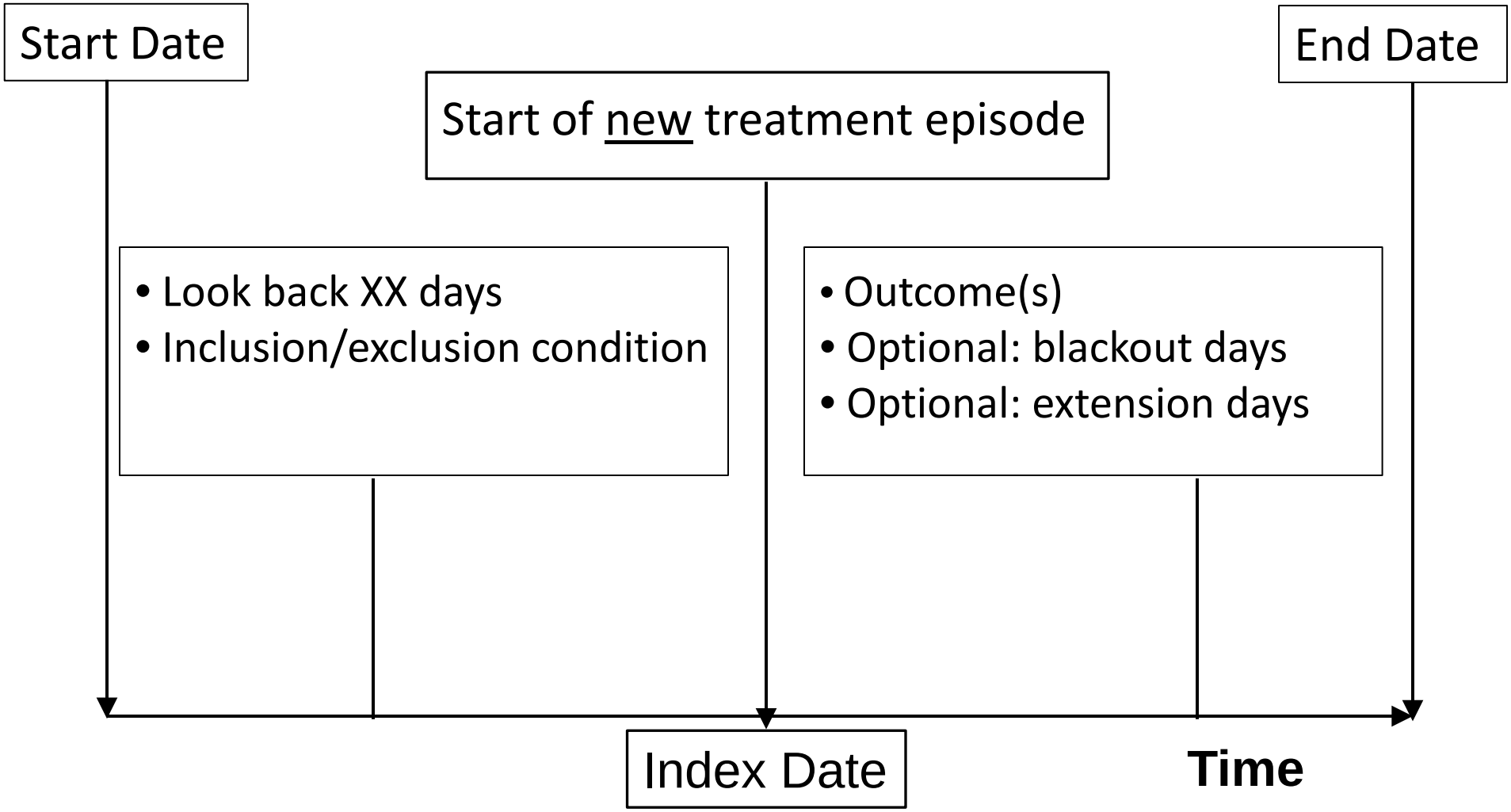
Obs	Age_group	COUNT	PERCENT
1	0.1 0-1 Yrs	602059	1.4996
2	02. 2-4 Yrs	1376997	3.4298
3	03. 5-9 Yrs	2553188	6.3595
4	04. 10-14 Yrs	2638462	6.5719
5	05. 15-18 Yrs	2135457	5.3190
6	06. 19-21 Yrs	1670742	4.1615
7	07. 22-44 Yrs	14770481	36.7906
8	08. 45-64 Yrs	11221814	27.9515
9	09. 65-74 Yrs	1854092	4.6182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

A Mini-Sentinel week

- Distributed dataset development/maintenance
- **Modular programs development / use to address "standard" questions**
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity
- Contribute to establishing a national resource for evidence development

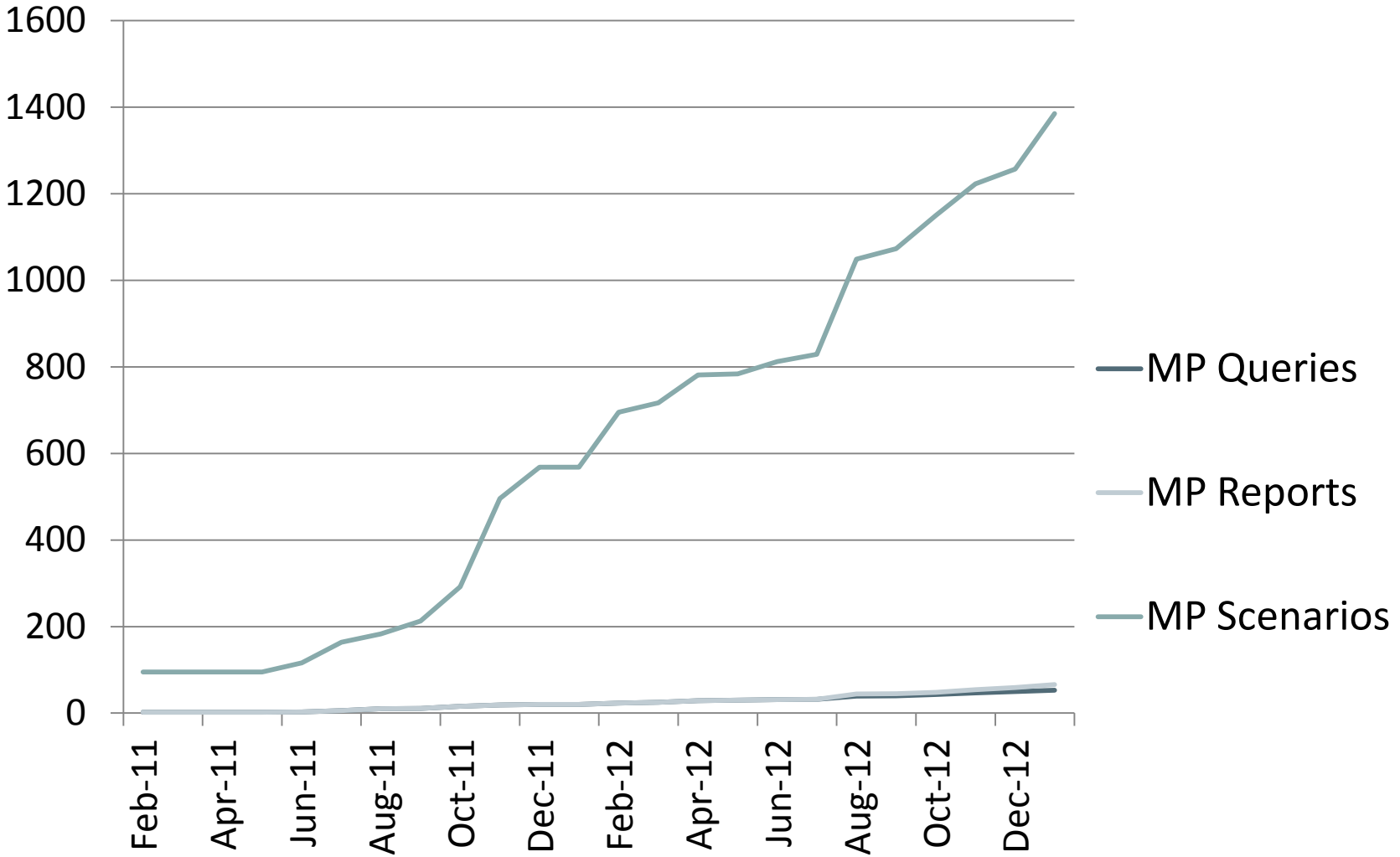
Typical input to modular programs



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

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

Use of modular programs



A Mini-Sentinel week

- Distributed dataset development/maintenance
- Modular program development /use
- **Protocol development / implementation to address unique types of questions**
- Methods development / implementation
- Develop new capacity
- Contribute to establishing a national resource for evidence development

ORIGINAL INVESTIGATION

ONLINE FIRST

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

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

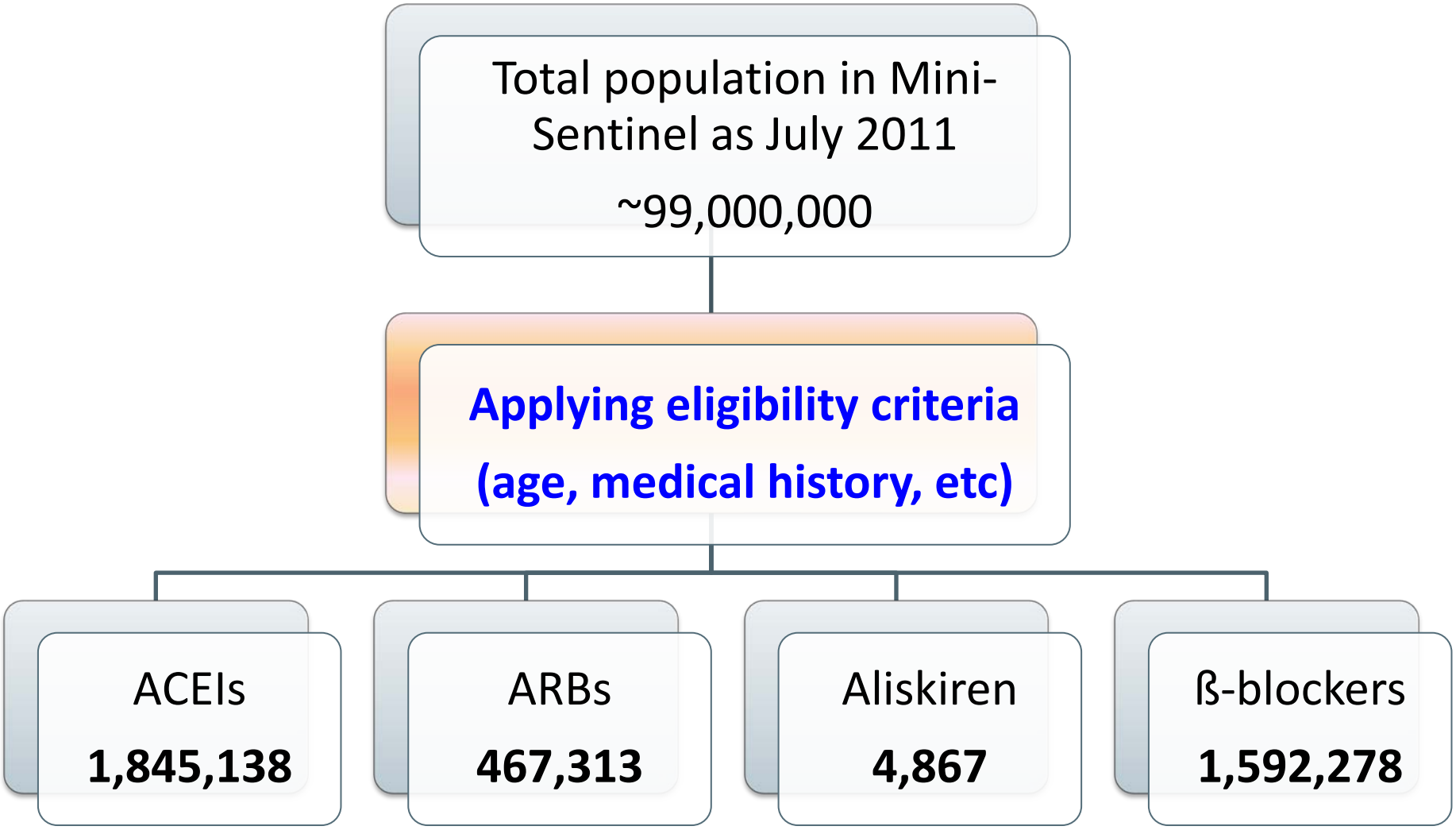
Overarching goals of the project

- Assess selected drug-event associations
  - Drugs targeting renin-angiotensin-aldosterone system & angioedema
- Build general strategies for safety assessments of medical products on the market for >2 years
- NOT designed to provide definitive evidence of a causal relation

Process to conducting a MS protocol-based assessment

FDA identifies topic

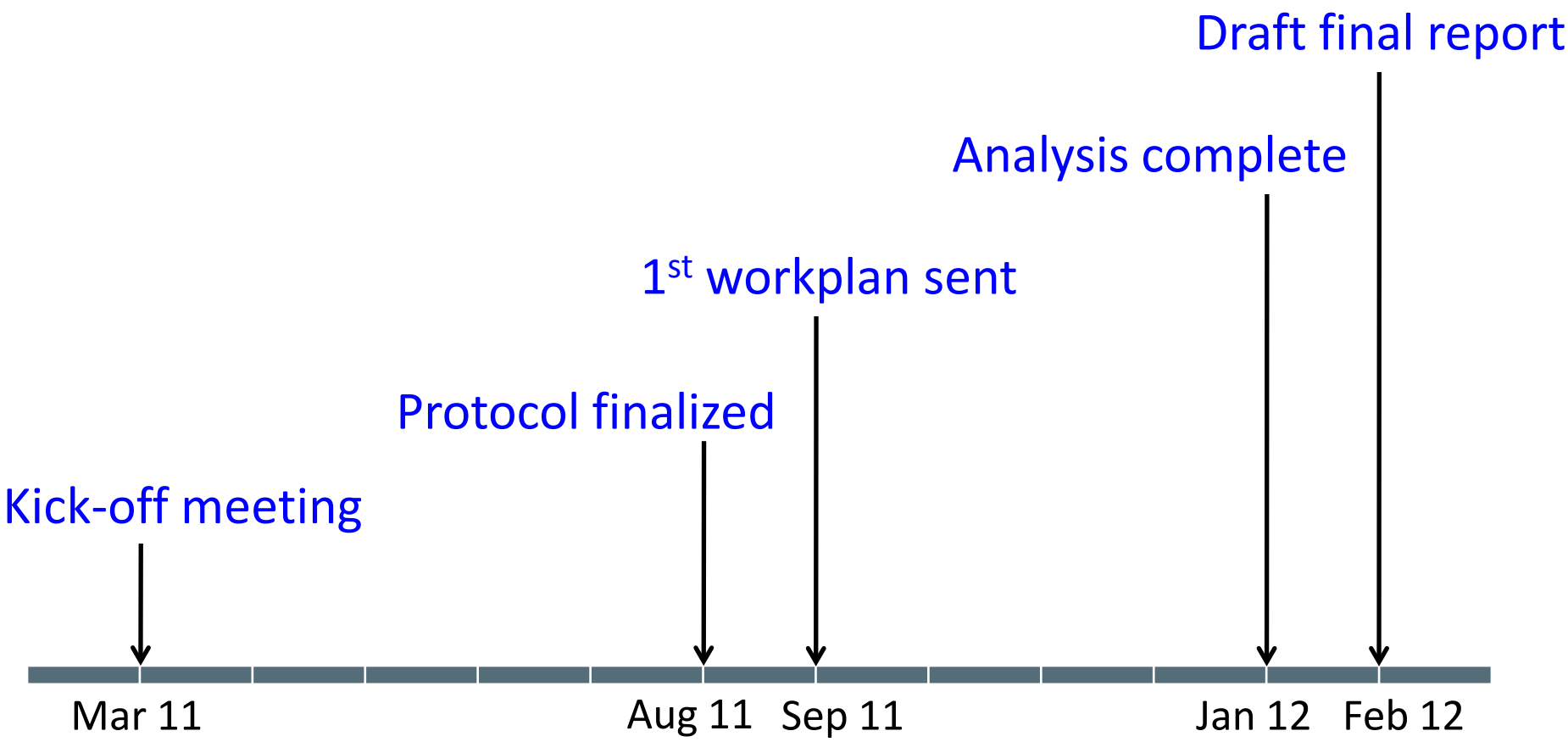
Cohort creation



Statistical analysis

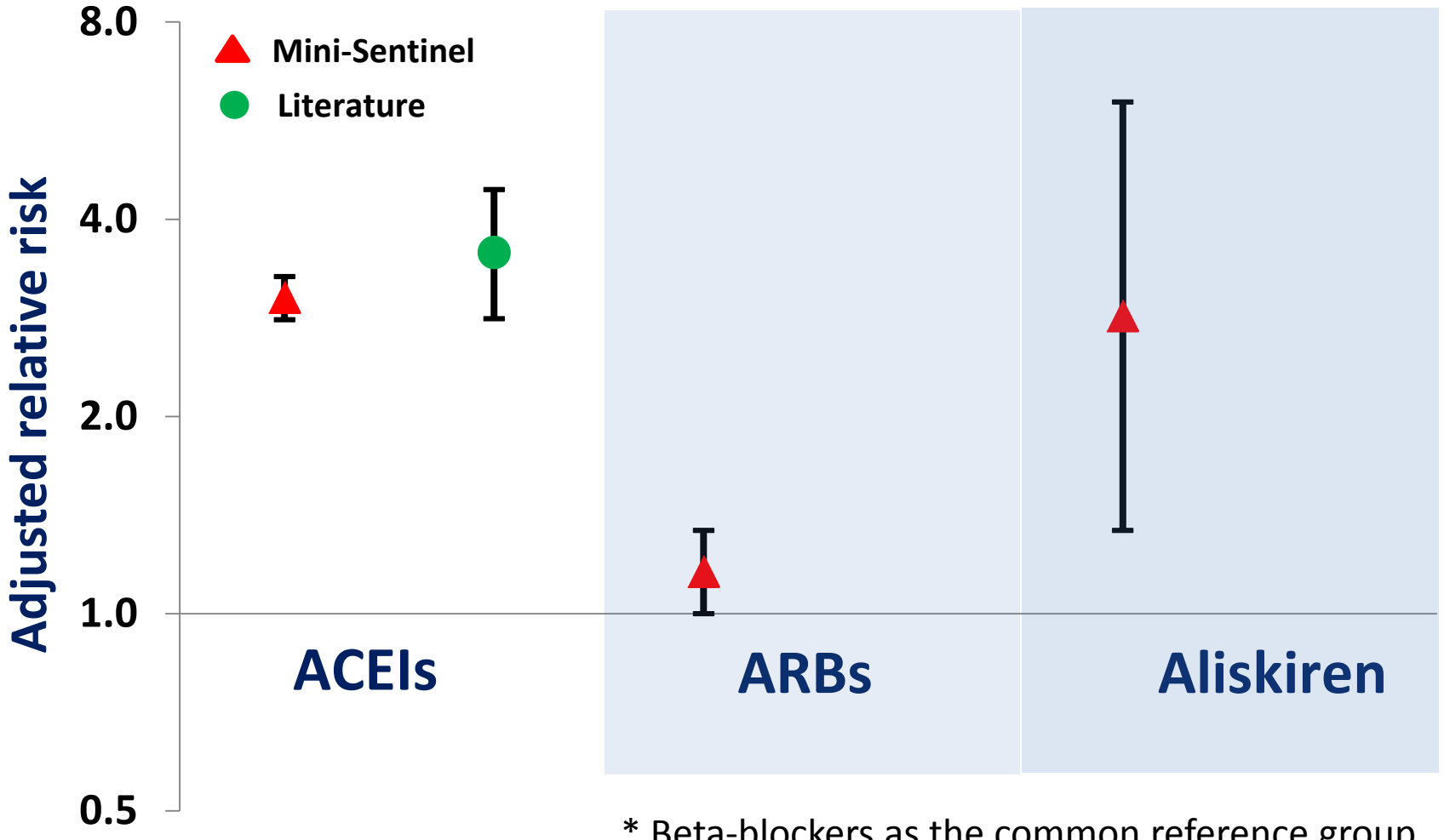
- Propensity score approach
  - Condensing information from a large number of variables into a non-identifiable measure
- Case-centered approach and meta-analysis
  - Needing only aggregated data to complete the analysis

Timeline



Total time from start to completion: ~11 months

Results



* Beta-blockers as the common reference group

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

Summary of overarching goal #1

- 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

Summary of overarching goal #2

- Developed a time and cost efficient process to perform medical product safety assessments within a large distributed data system

- Developed analytic strategies to perform robust statistical analysis without sharing identifiable information

Reviewing medical records

- Claims data are reliable for some diagnoses and many exposures
- Medical records are sometimes needed to
  - Adjudicate case status
  - Confirm exposure to product of interest
- Mini-Sentinel can obtain relevant parts of selected records
  - Data partners obtain relevant sections of records, redact identifying information, forward de-identified material to expert adjudicating panel
  - Expert panel applies standard definitions to classify case status, assesses accuracy of exposure data

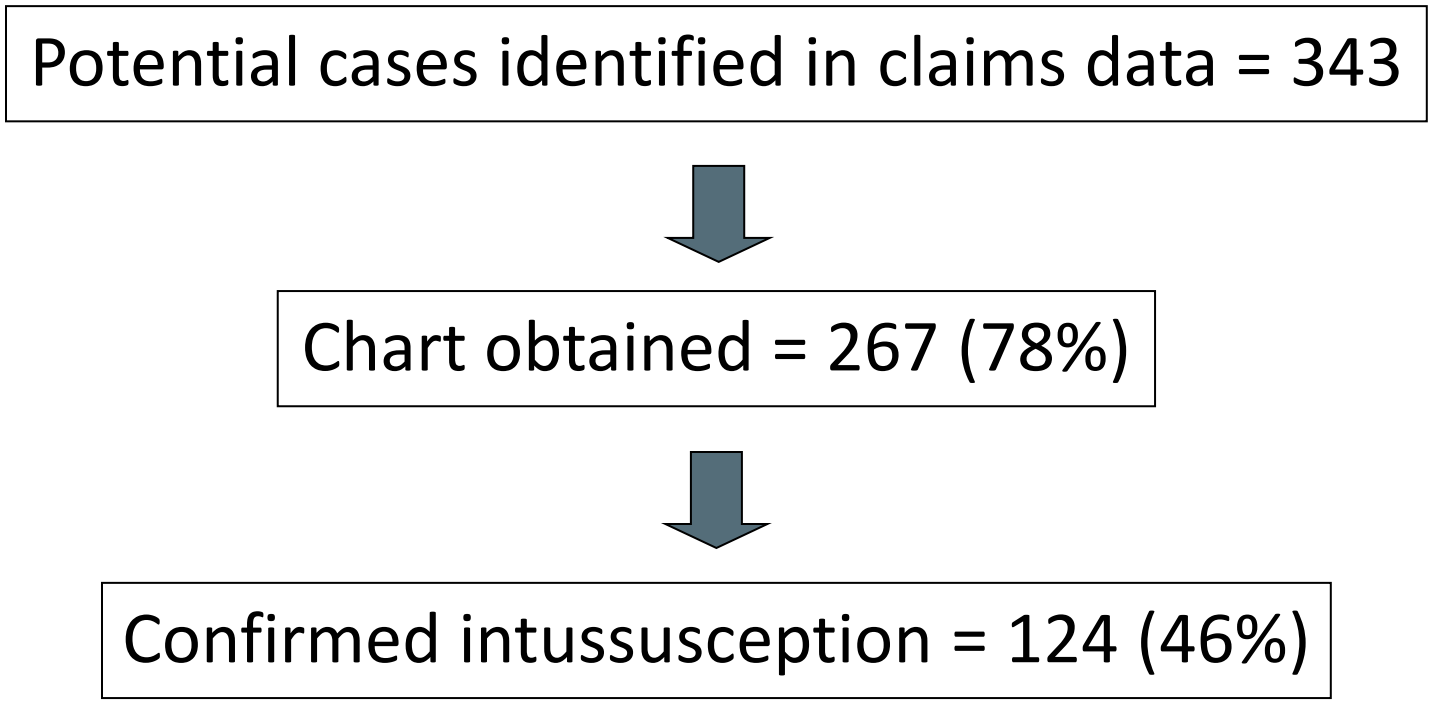
Rotavirus vaccines and intussusception

- Rotavirus vaccines are live, attenuated, oral vaccines
- Rotashield
  - Licensed in August 1998
  - In 1999, Rotashield voluntarily withdrawn due to increased risk of intussusception
  - Excess risk: 1-2 cases/10,000 vaccine recipients
- RotaTeq (2006) and Rotarix (2008) licensed after clinical trials with >60,000 infants
- Need to confirm both intussusception case status and vaccine exposure

Rotavirus vaccine doses through 6/2011

	1st doses	All doses
RotaTeq	507,874	1,277,556
Rotarix	53,638	103,098

Case identification



Cases are from whole infant population and include unexposed

Protocols in the field now

- Rotavirus vaccine and intussusception
- Impact of labeling change on use of long acting beta agonists
- 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
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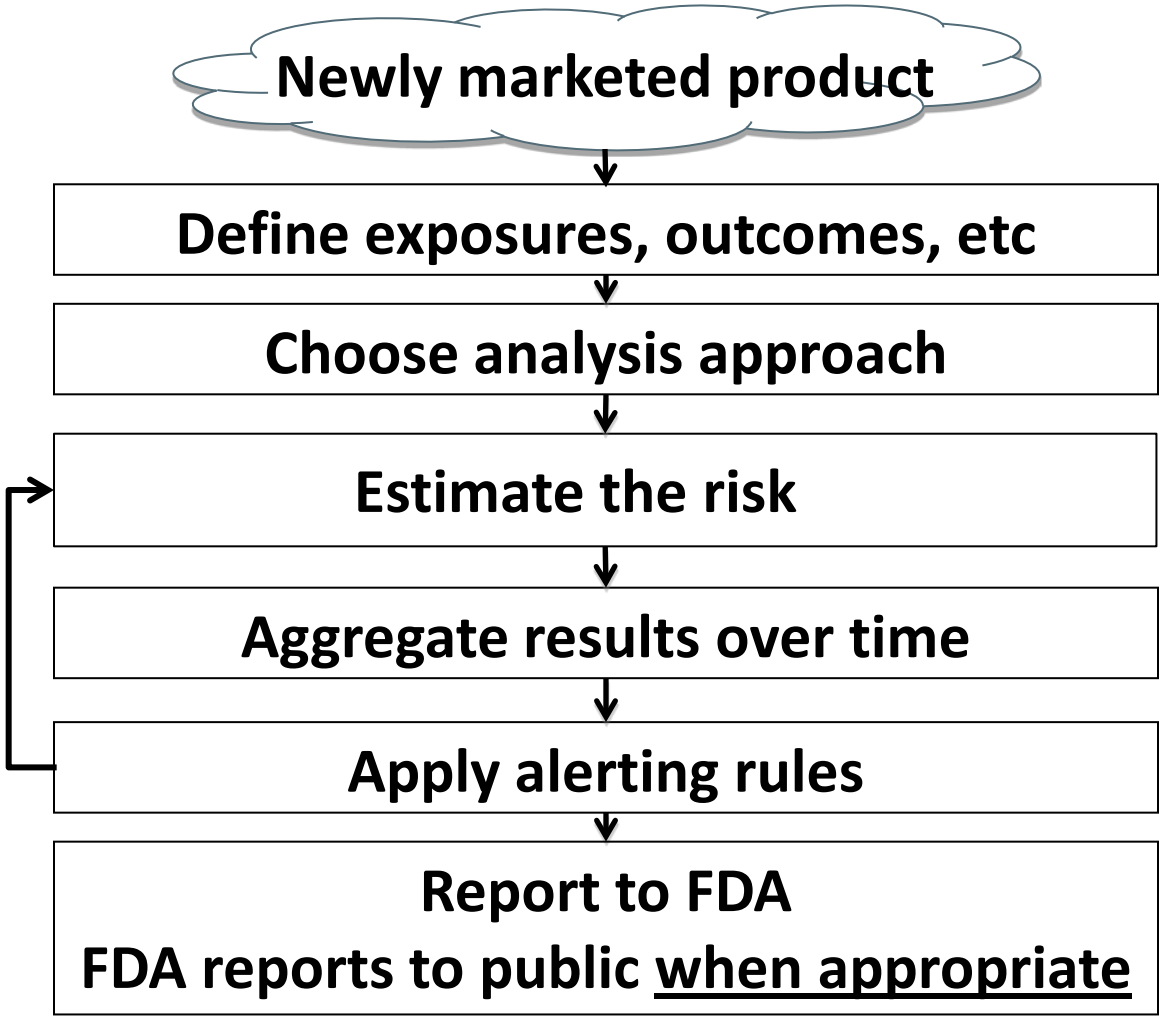
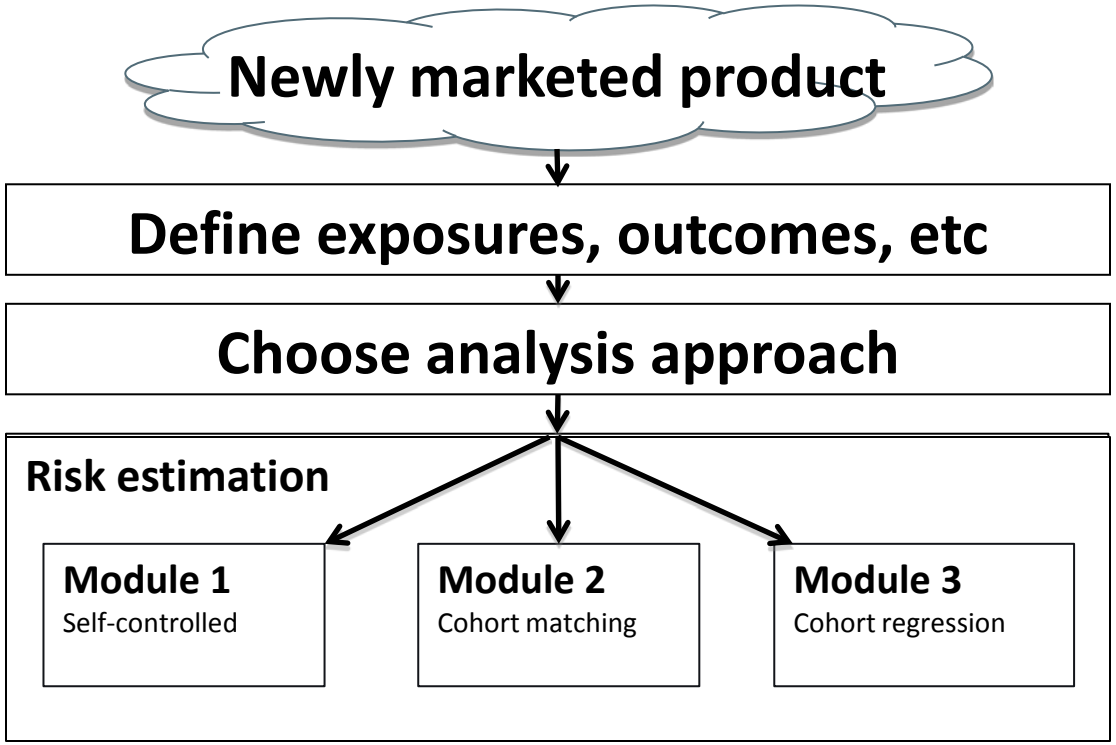
Methods

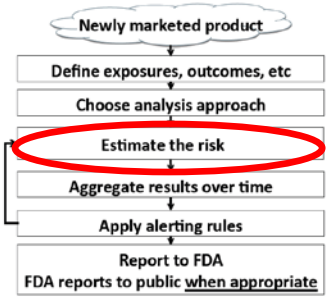
- **Implementing routine prospective surveillance of new products using sequential methods**
- Improving confounder adjustment
- Validation of health outcomes of interest
- Data mining for vaccine adverse events

Prospective surveillance at a glance



Prospective surveillance: estimate risk





A Mini-Sentinel week

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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
- Modular program development /use
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity
- **Contribute to establishing a national resource for evidence development**

External engagements

- Observational Medical Outcomes Partnership
- NIH Health Care System Research Collaboratory
- 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

NIH Health Care Systems Research Collaboratory

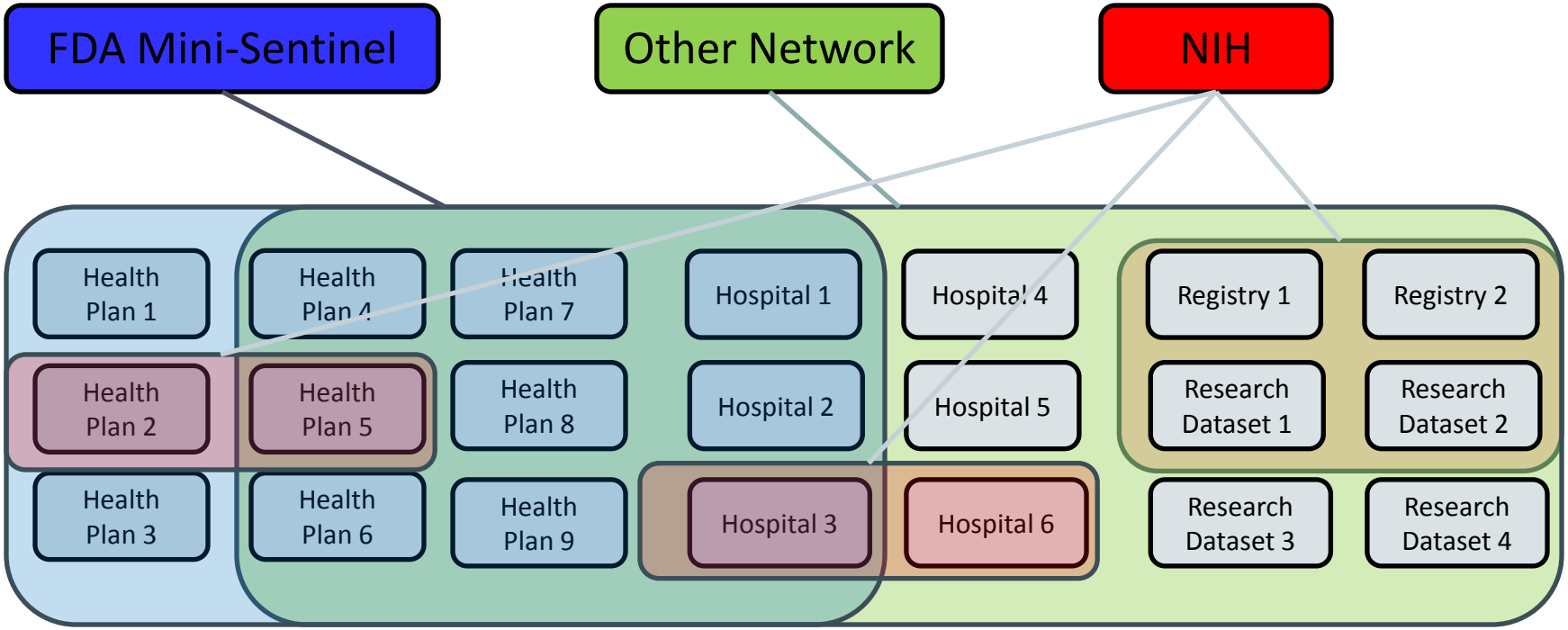
Home of the NIH Distributed Research Network

Millions of people. Strong collaborations. Privacy first.

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

The Collaboratory

Multiple networks sharing infrastructure



- **Partner Organizations** can choose to participate in multiple networks
- **Networks** can leverage existing data, query tools, program libraries

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

Costs and benefits

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

Thank you!

ENGELBERG CENTER for Health Care Reform at BROOKINGS

Roundtable Discussion and Questions

View this and past Active Medical Product Surveillance webinars at:

http://www.brookings.edu/health/Projects/surveillance/roundtables.aspx