Sentinel Initiative

Building the National Evaluation System for Medical Devices: Using Real-World Evidence to Improve Device Safety and Effectiveness

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Background

- **2007**: FDA Amendments Act
  - A mandate to create an active surveillance system
  - Access data from **25 million** individuals by July 2010
  - Access data from **100 million** individuals by July 2012
- 2008: FDA launched the Sentinel Initiative
- 2009: Mini-Sentinel funded under Sentinel Initiative
- 2014: Funding awarded for Sentinel

Mini-Sentinel

- An FDA-funded pilot project
- Develop scientific operations for an active medical product safety surveillance
- Continuous access to electronic healthcare databases
- Operate under FDA's public health authority

Mini-Sentinel Partner Organizations

Lead – HPHC Institute

Data and scientific partners

Scientific partners

Impact / Dissemination

- 4 FDA drug safety communications
  - Tri-valent inactivated flu vaccine and febrile seizures (no increased risk)
  - Rotarix and intussusception (label change)
  - Dabigatran and bleeding (no increased risk)
  - Olmesartan and sprue-like enteropathy (label change)
- 70 peer-reviewed articles
- 48 methods reports / white papers
- Thousands of unique queries and comparisons contributing to over 140 formal assessments

www.mini-sentinel.org

Sentinel

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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- **Safety & Availability (Biologics)**
- Biologics Product Shortages Q&A
- Recalls (Biologics)
- Biologic Product Shortages
- Report a Problem to the Center for Biologics Evaluation & Research
- Biologic Product Security
- Pandemics
- Blood Safety & Availability
- Tissue Safety & Availability
- Vaccine Safety & Availability
- HIV Home Test Kits

Resources for You

- 2013 Safety and Availability Communications

FDA Releases Final Study Results of a Mini-Sentinel Postlicensure Observational Study of Rotavirus Vaccines and Intussusception

FDA Safety Communication — June 13, 2013

FDA Releases Final Study Results of a Mini-Sentinel Postlicensure Observational Study of Rotavirus Vaccines and Intussusception

FDA Approves Required Revised Labeling for RotaTeq Based on the Study Results

Purpose: To inform the public and healthcare providers that FDA is releasing final study results from a Mini-Sentinel postlicensure observational study of intussusception (a form of bowel obstruction) after vaccination with RotaTeq (Merck and Co., Inc.) and Rotarix (GlaxoSmithKline Biologicals).

RotaTeq and Rotarix are vaccines for the prevention of rotavirus gastroenteritis in infants 6 weeks to 32 weeks of age (RotaTeq) and infants 6 weeks to 24 weeks of age (Rotarix). The study was conducted in Mini-Sentinel's Postlicensure Rapid Immunization Safety Monitoring (PRISM) program, the largest vaccine safety surveillance program in the Unit

Label change

FDA has approved n and Patient Information for RotaTeq as a result of the new safety d information was added to the Highlights, the existing intussusception subsection of the Warnings and Precautions section, and the Post-Marketing Experience section of the Full Prescribing Information, as well as to the Patient Information. The Mini-Sentinel PRISM study is the largest study of intussusception after rotavirus vaccines to date and identified an increased risk of intussusception in the 21 day time period after the first dose of RotaTeq, with most cases occurring in the first 7 days after vaccination. No increased risk was found after the second or third doses. These findings translate into 1 to 1.5 additional cases of intussusception per 100,000 first doses of RotaTeq.

The data from the Mini-Sentinel PRISM study regarding the risk of intussusception following the use of Rotarix were inconclusive. Based on this study, no changes were made to the Prescribing Information or to the Patient Information for Rotarix. However, based on data from an observational study previously conducted in Mexico, it is estimated that 1 to 3 additional cases of intussusception would occur per 100,000 vaccinated infants in the United States within 7 days following the first dose of Rotarix. In September 2012, FDA announced that it had approved revisions to the Prescribing Information and to the Patient Information for Rotarix to include these results from the study in Mexico.

http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm356758.htm

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intussusception Risk after Rotavirus Vaccination in U.S. Infants

W. Katherine Yih, Ph.D., M.P.H., Tracy A. Lieu, M.D., M.P.H., Martin Kulldorff, Ph.D., David Martin, M.D., M.P.H., Cheryl N. McMahill-Walraven, M.S.W., Ph.D., Richard Platt, M.D., Nandini Selvam, Ph.D., M.P.H., Mano Selvan, Ph.D., Grace M. Lee, M.D., M.P.H., and Michael Nguyen, M.D.

Yih, N Engl J Med. 2014;370:503

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

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

The NEW ENGLAND JOURNAL of MEDICINE

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

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

In medicine, "big data" come in many forms. With the financial incentives provided by Medicare and Medicaid for the "meaningful

functions of billing and clinical care. If, as Nate Silver suggests in *The Signal and the Noise*, "Most of

tional Heart, Lung, and Blood Institute have produced data sets with millions of genetic variants for each participant, encouraged the development of consortia with hundreds of thousands of study participants, and resulted in discoveries about the genetic origins

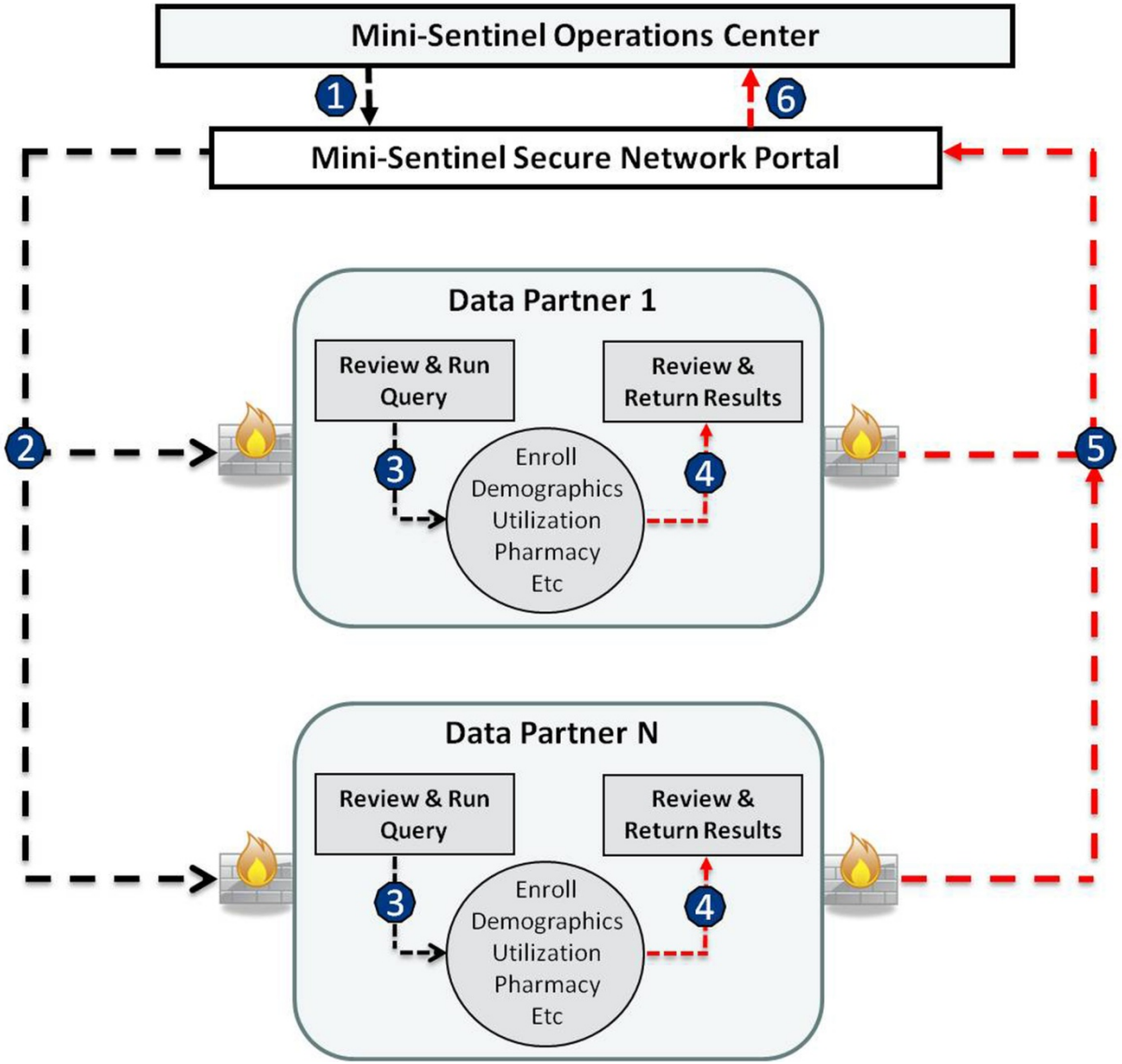
that can contribute meaningfully to the health of the public.

One model is the Mini-Sentinel. A pilot project of the Sentinel Initiative of the Food and Drug Administration (FDA), the Mini-Sentinel has created a nationwide system that uses electronic data

"The Mini-Sentinel ' provides an essential public health service. The current configuration — the data model, the methods development, and the investigative team — represents an impressive achievement..

Psaty. N Engl J Med 2014;370:2165

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

Common Data Model (CDM)

Administrative

Enrollment
Person ID
Enrollment start & end dates
Drug coverage
Medical coverage
Medical record availability

Demographic
Person ID
Birth date
Sex
Race
ZIP code

Dispensing
Person ID
Dispensing date
National drug code (NDC)
Days supply
Amount dispensed

Encounter
Person ID
Dates of service
Provider seen
Type of encounter
Facility
Etc.

Diagnosis
Person ID
Date
Principal diagnosis flag
Encounter type & provider
Diagnosis code & type
Etc.

Procedure
Person ID
Dates of service
Procedure code & type
Encounter type & provider
Encounter ID
Etc.

Clinical Data Elements

Lab Result
Person ID
Dates of order, collection & result
Test type, immediacy & location
Procedure code & type
Test result & unit
Etc.

Vital Signs
Person ID
Date & time of measurement
Height and weight
Diastolic & systolic BP
Tobacco use & type
Etc.

Death Information

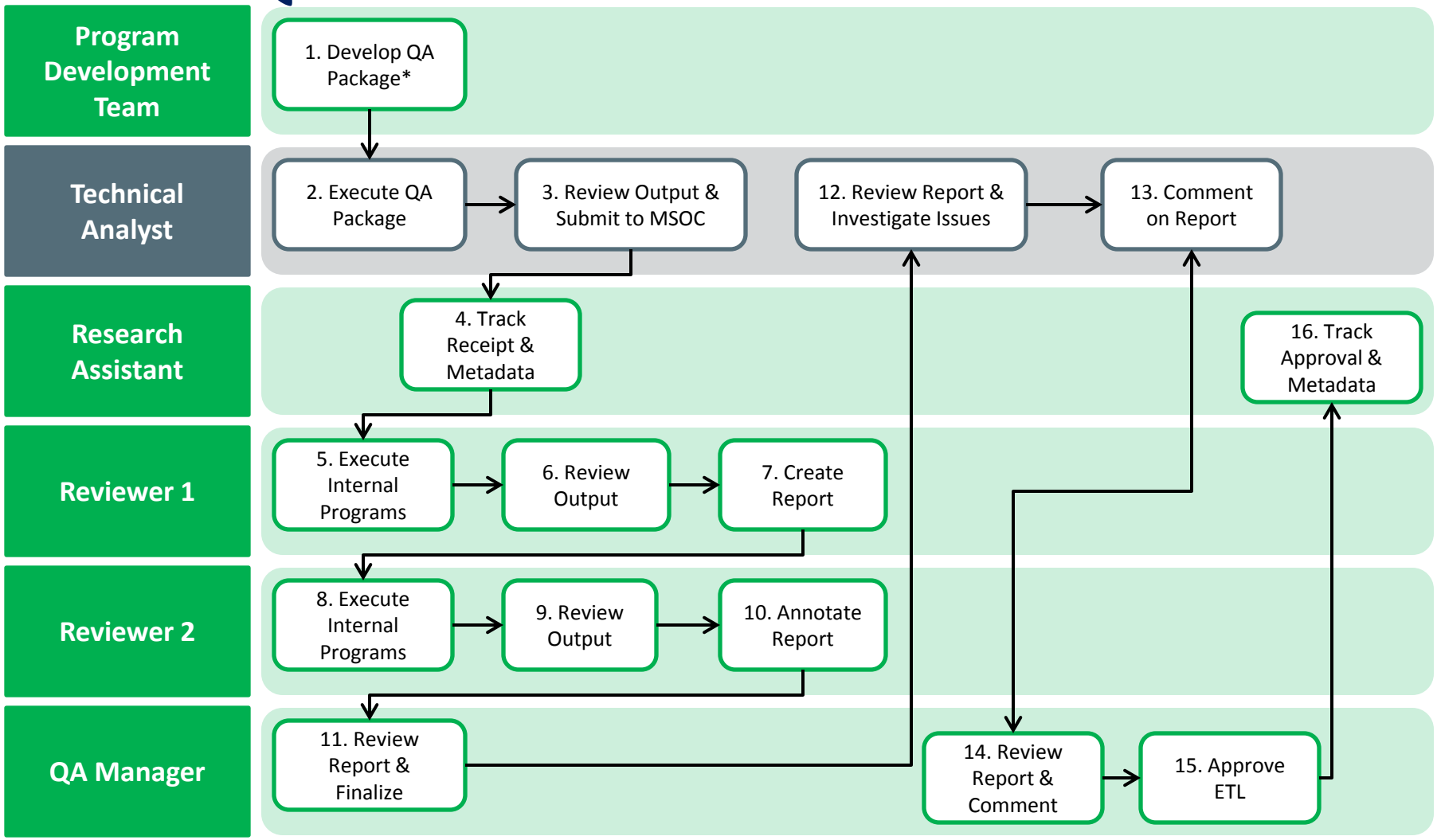
Death
Person ID
Death date
Source
Confidence
Etc.

Cause of Death
Person ID
Cause of death
Source
Confidence
Etc.

Registry

State Vaccine
Person ID
Provider
Admission Type
Vaccine Code
Vaccine Code Type
Etc.

Data QA and Characterization



*Program Development Team Follows MS SAS Program Development SOP to Create QA Package

Data Partner MSOC

Data Checking and Characterization

- Hundreds of tables per data partner per refresh
- 4 levels of data checks
- > 1500 checks

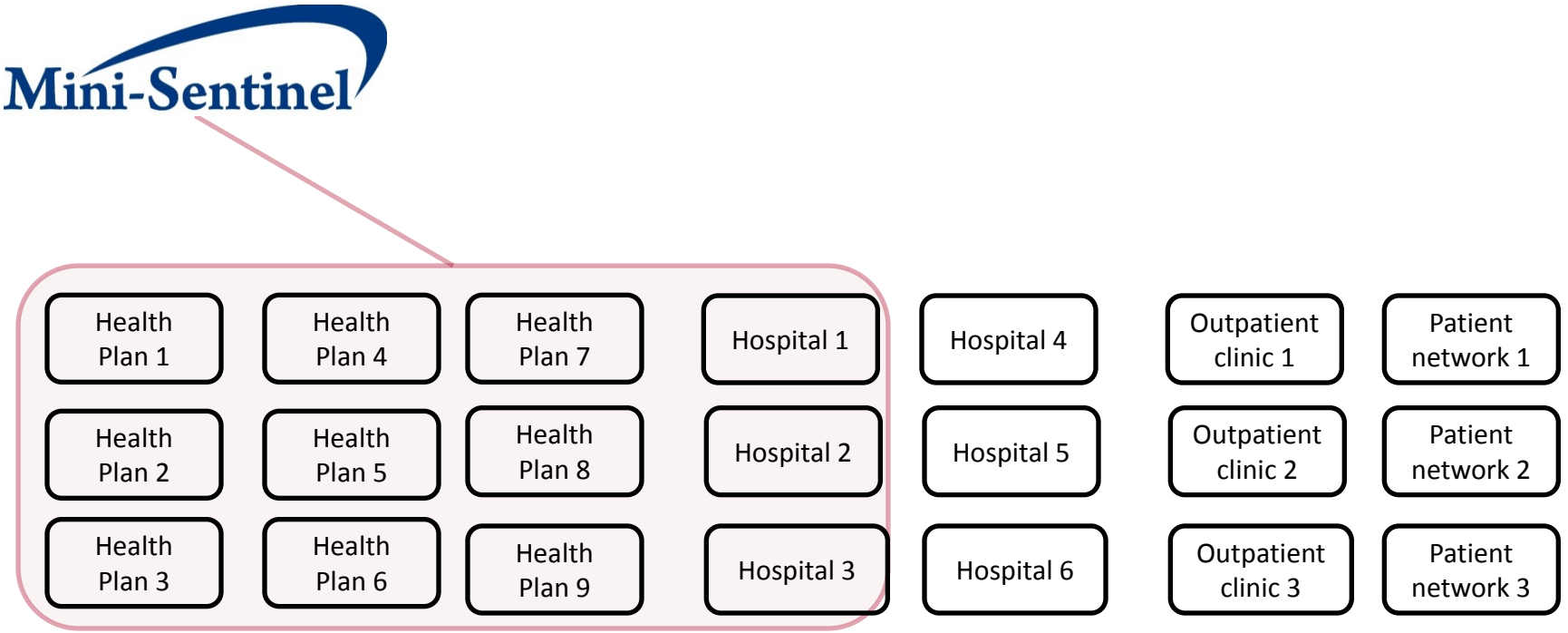
Obs	ENCTYPE	ADATE	COUNT	PERCENT
1	AV	2000	7030952	5.1370
2	AV	2001	7454699	5.4466
3	AV	2002	8014346	5.8555
4	AV	2003	8261199	6.0358
5	AV	2004	8251011	6.0284
6	AV	2005	8857635	6.4716
7	AV	2006	9576674	6.9969
8	AV	2007	10240959	7.4823
9	AV	2008	11831682	8.6445
10	AV	2009	13785025	10.0716
11	AV	2010	14499322	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

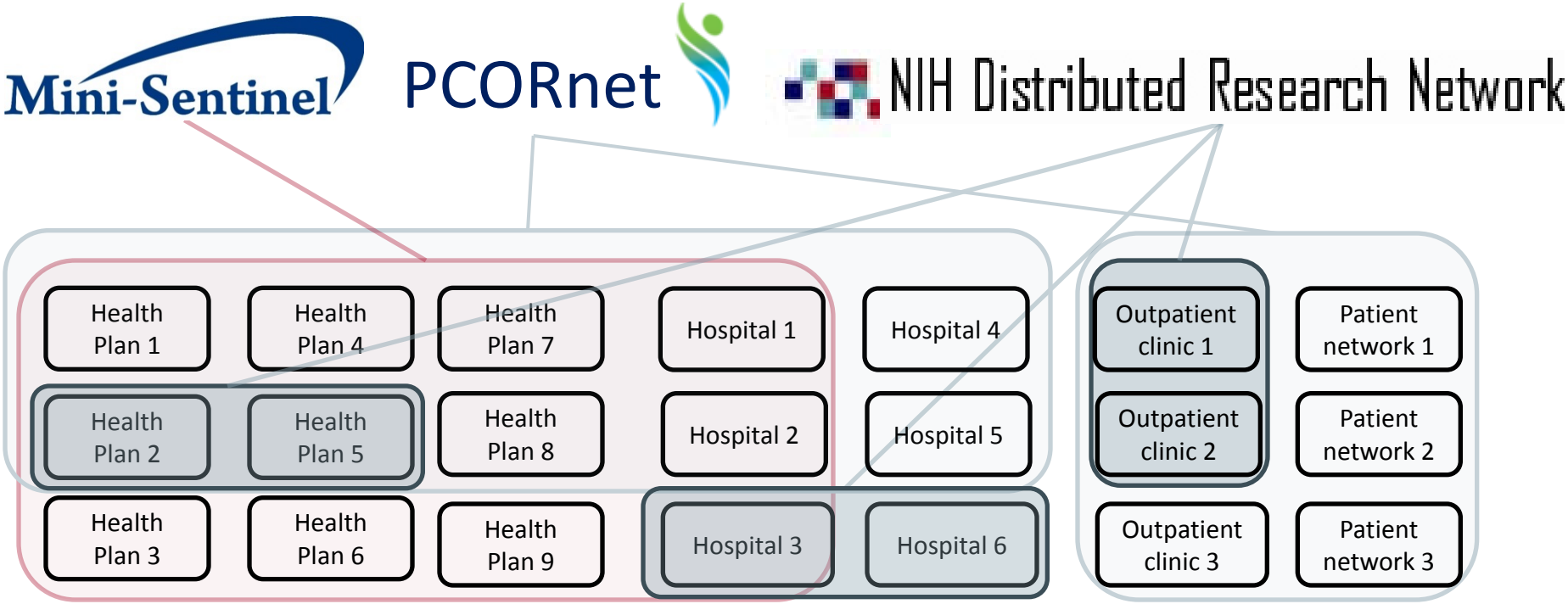
Obs	Age_group	COUNT	PERCENT
1	0.1 0-1 Yrs	602059	1.4996
2	02. 2-4 Yrs	1376997	3.4298
3	03. 5-9 Yrs	2553188	6.3595
4	04. 10-14 Yrs	2638462	6.5719
5	05. 15-18 Yrs	2135457	5.3190
6	06. 19-21 Yrs	1670742	4.1615
7	07. 22-44 Yrs	14770481	36.7906
8	08. 45-64 Yrs	11221814	27.9515
9	09. 65-74 Yrs	1854092	4.6182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

Multiple networks sharing infrastructure



Multiple networks sharing infrastructure



- Each organization can participate in multiple networks
- Each network controls its governance and coordination
- Networks share infrastructure, data curation, analytics, lessons, security, software development

Key Contributors to Mini-Sentinel's Progress

- **Tightly Coupled** network
- **Frequent and coordinated interactions between FDA, data partners, content experts, epidemiologists, and statisticians**
- Clear ownership and goals
- Established agreements and contracts
- Distributed data network (no central repository)
- Public health practice
- Focused on best understood and useful data for purpose
  - First: Claims and administrative data, plus access to full text records
    - Syntax and semantics are clear and understood
  - Then: electronic medical records, registries, …
    - Much more complex to understand, standardize, and use for research
- Rapid cycle development of capabilities

UDI in Sentinel

- UDI not routinely captured in administrative claims data
- Algorithms could be explored in both available CDM data and data held by data partners
  - Cost data is routinely available with data partners but not mapped into CDM
- Linkage to device registries, PCORNet