ENGELBERG CENTER for
Health Care Reform
at BROOKINGS

Sentinel Initiative Public Workshop

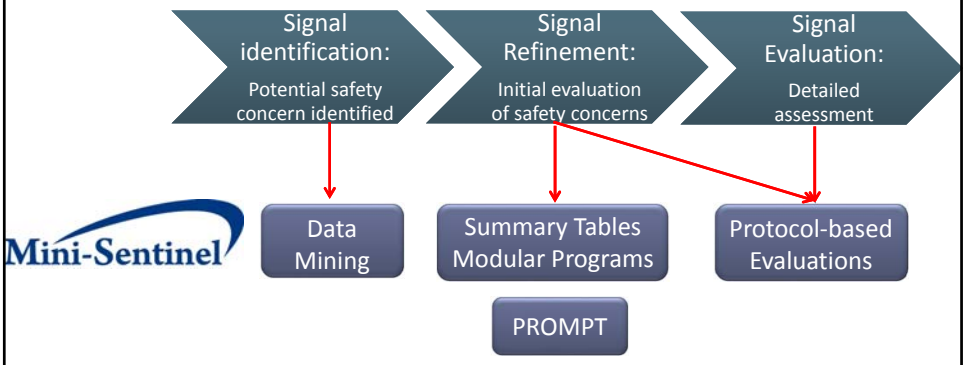
Washington Plaza Hotel • Washington, DC
Thursday, February 5, 2015

Mini-Sentinel

Richard Platt

February 5, 2015

Post-Market Safety Surveillance



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Impact / Dissemination

- 4 FDA drug safety communications
  - Tri-valent inactivated flu vaccine and febrile seizures (no increased risk)
  - RotaTeq, Rotarix and intussusception (label change for RotaTeq, no label change for Rotarix)
  - Dabigatran and bleeding (no increased risk)
  - Olmesartan and sprue-like enteropathy (label change)
- 26 Presentations by FDA
- 48 Methods reports / white papers
- 70 Peer-reviewed articles
- 137 Assessments of products, conditions, product-outcome pairs

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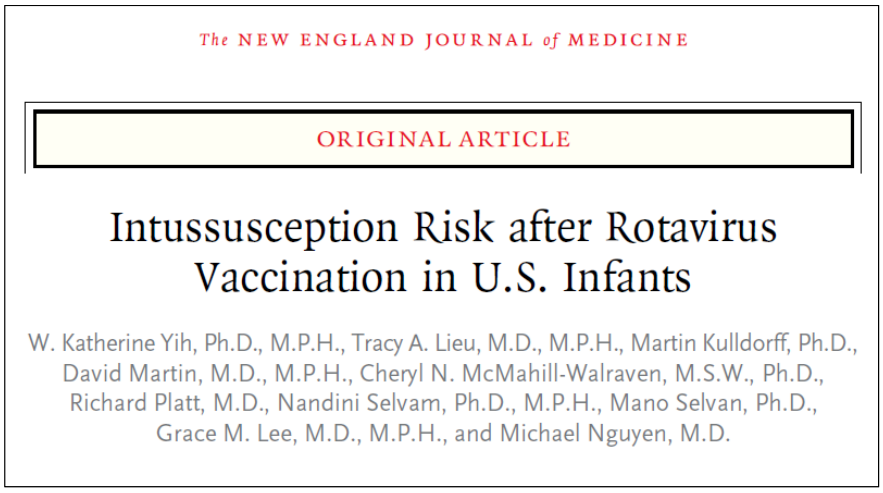


Yih, N Engl J Med. 2014;370:503

Mini-Sentinel

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.

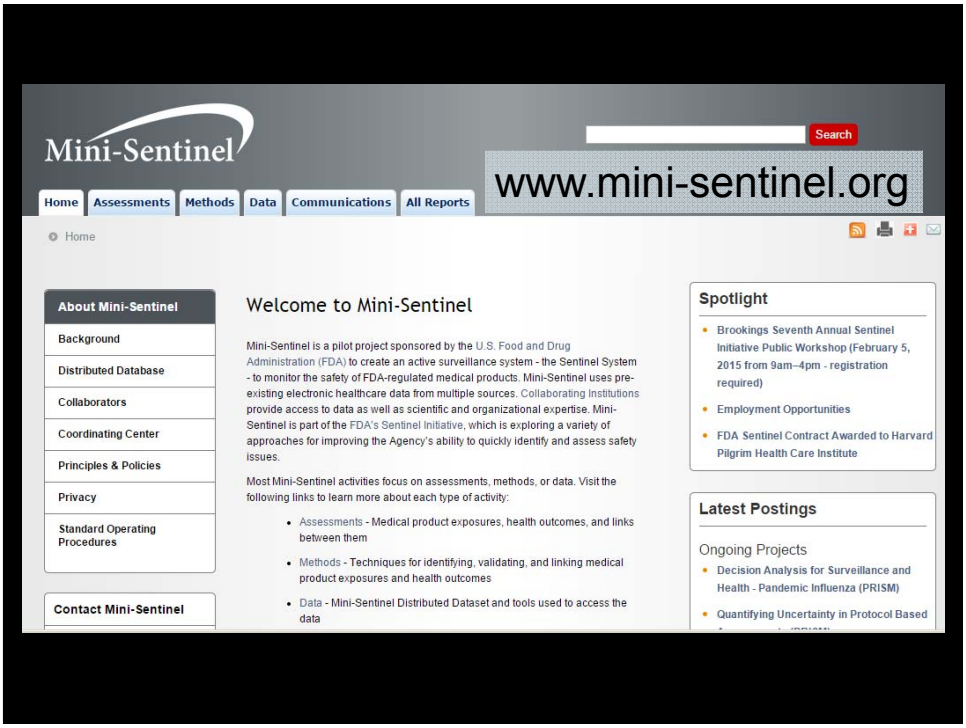
In medicine, "big data" come in many forms. With the financial incentives provided by Medicare and Medicaid for the "meaningful [illegible] functions of billing and clinical care. If, as Nate Silver suggests in *The Signal and the Noise*, "Most of [the increasing quantity of infor[illegible] tional Heart, 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 [illegible] create systems of study settings 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

info@mini-sentinel.org 5



Mini-Sentinel

Mini-Sentinel Partner Organizations

Lead – HPHC Institute

Data and scientific partners

Scientific partners

Mini-Sentinel

Three major domains

- Data
- Methods
- Active surveillance

Three major domains

- **Data**
- Methods
- Active surveillance

Mini-Sentinel Distributed Database*

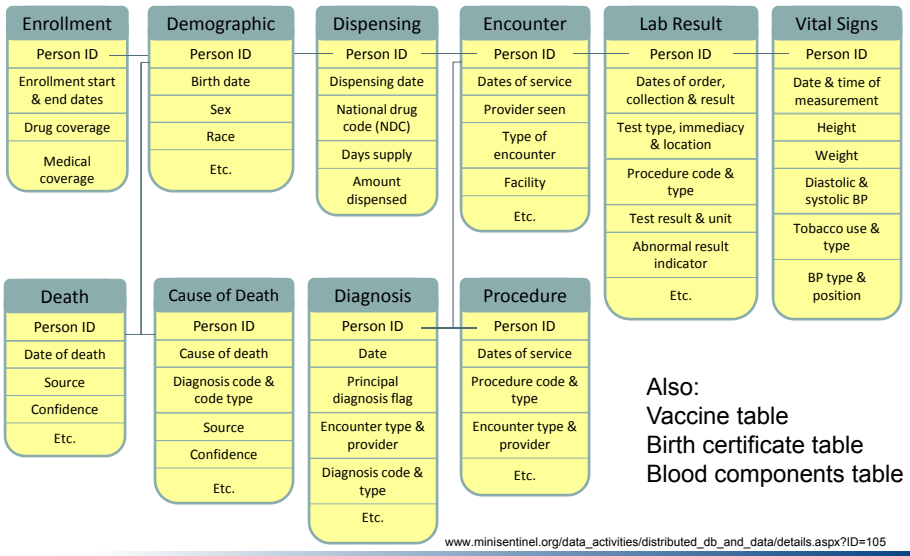
- Populations with well-defined person-time for which most medically-attended events are known
- 178 million members**
- 358 million person-years of observation time
- 48 million people currently accruing new data
- 4 billion dispensings
- 4.1 billion unique encounters
  - 42 million acute inpatient stays
- 30 million people with ≥1 laboratory test result

*As of July 2014
** Double counting exists for individuals who change health plans

Mini-Sentinel's Data Sources

- Administrative data
  - Enrollment
  - Demographics
  - Outpatient pharmacy dispensing
  - Utilization (encounters, diagnoses, procedures)
- EHR and laboratory test result data for 10%
  - Height, weight, blood pressure, temperature
  - Laboratory test results (selected tests)
- Registries
  - Immunization
  - Birth certificates
- **Full text records** (small number to confirm selected exposures and outcomes – names, etc. redacted)

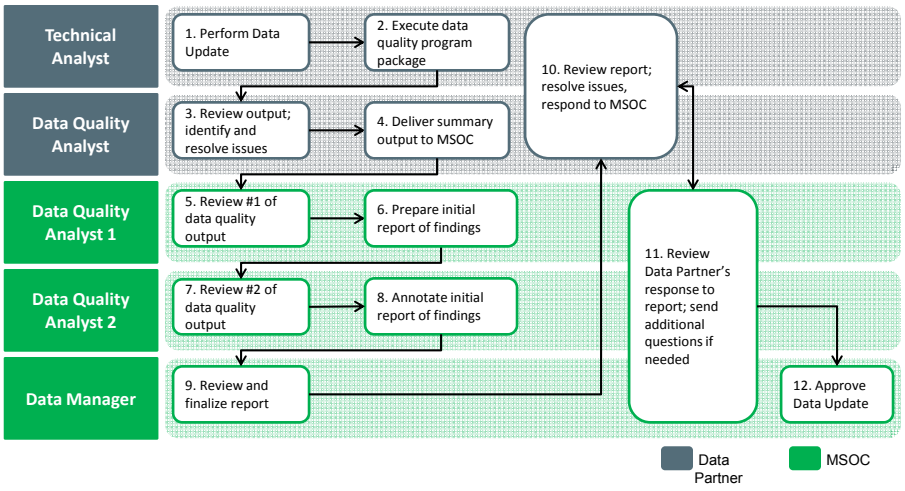
Mini-Sentinel's Common Data Model



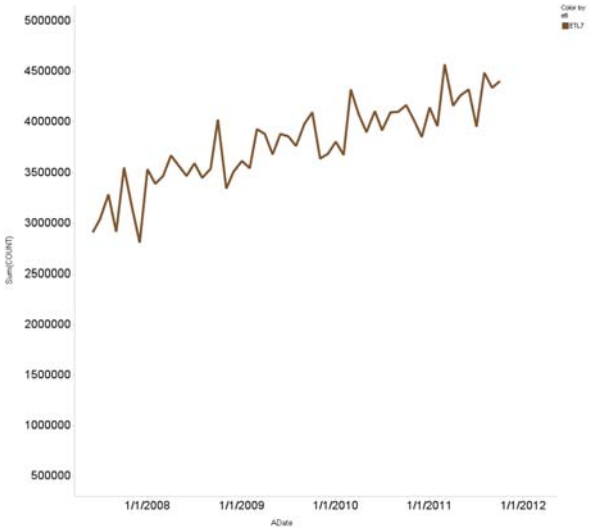
Also:
Vaccine table
Birth certificate table
Blood components table

www.minisentinel.org/data_activities/distributed_db_and_data/details.aspx?ID=105

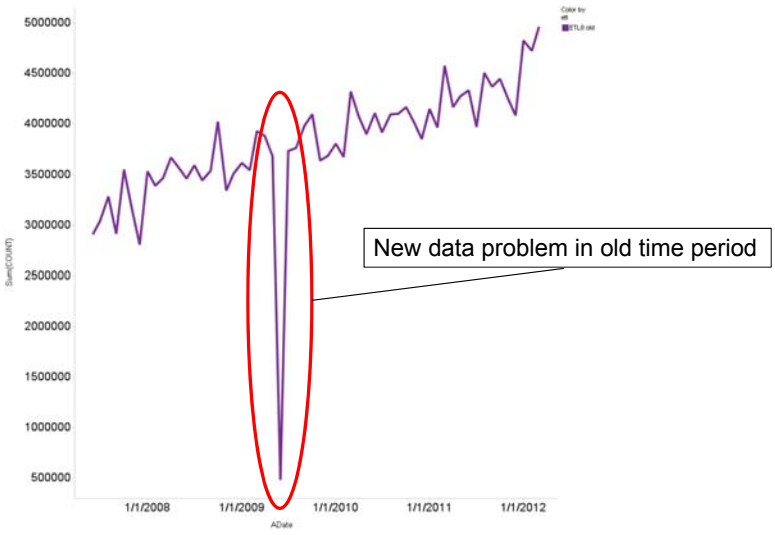
Data Quality Assurance review process



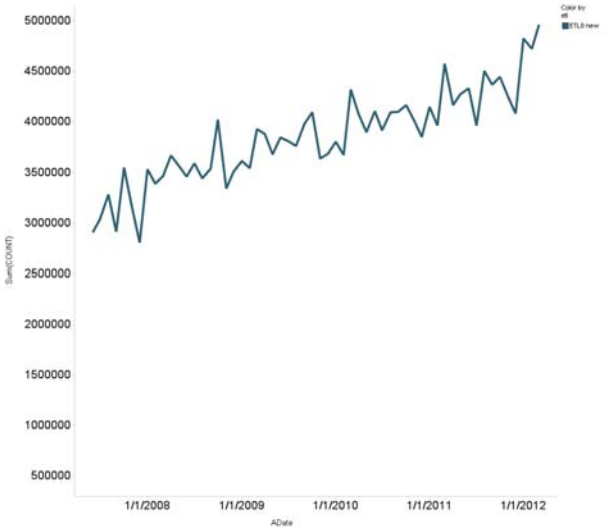
Data Visualization: After 7th refresh, partner A



Data Visualization: After 8th refresh, partner A



Data Visualization: After 8th refresh fixed



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A word about EHR data

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Variation in platelet count result units

Blank	FL	TH/UL	X10(3)
%	K/CMM	THOU/CMM	1000/UL
/100 W	k/cmm	thou/cmm	X10(3)/MCL
/CMM	K/CU MM	thou/mm3	X10(3)/UL
CMM	K/CUMM	THOU/UL	X10(6)/MCL
10 3 L	K/MCL	THOUS/CU.MM	X10*9/L
10X3UL	K/mcL	THOUS/MCL	X10E3/UL
10^3/UL	K/UL	THOU/mcL	X1000
10*3/uL	k/uL	THOUS/UL	X10X3
10?3/uL	KU/L	Thou/uL	X10^3/UL
10E3/uL	K/MM3	THOUSA	x10
10e3/uL	K/mm3	THOUSAND	X10?3/ul
10e9/L	LB	THOUSAND/UL	X10E3/UL
E9/L	PLATELET CO	U	X10E3
BIL/L	T/CMM	X 10-3/UL	K/A?L
bil/L	TH/MM3	X 10(3)/UL	K/B5L
CU MM	th/mm3	X10 3	

Raebel. Pharmacoepi and Drug Safety, 2014 DOI: 10.1002/pds

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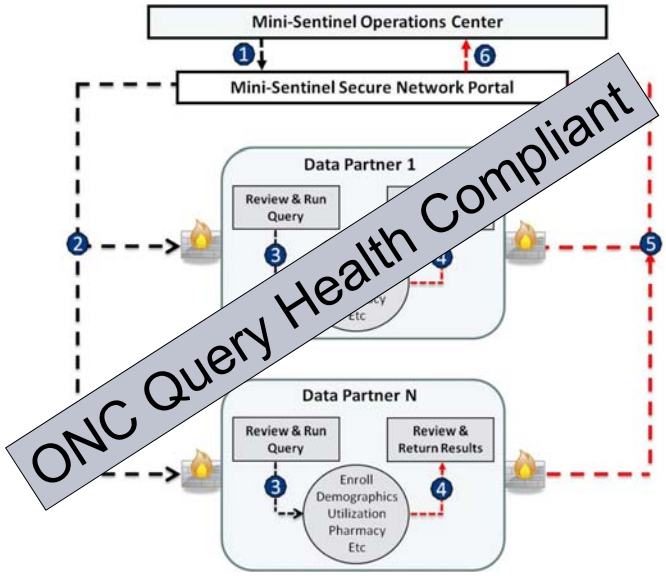
Mini-Sentinel Distributed Analysis



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

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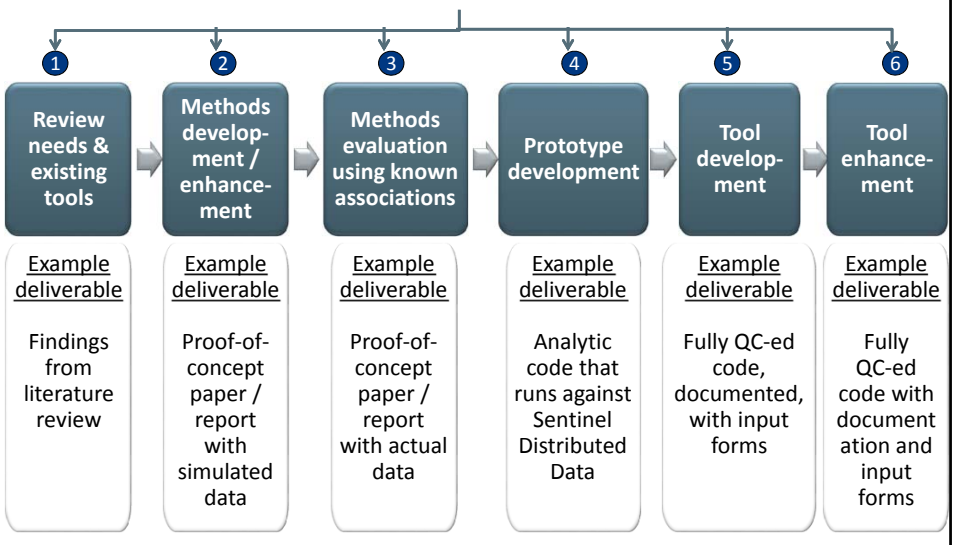
Three major domains

- Data
- **Methods**
- Active surveillance

Domains of methods development / examples

Data Fitness and Capacity	Evaluating Methods	Target Monitoring
• Integrity (validity, completeness) • Environments – *Claims, EHR, registries* – *Outpatient, inpatient* • Anonymous linkage • Enriching the CDM – *Lab results* • Data sharing	• Validity, power/ robustness, time-to-signal detection • Empirical, simulation • Heterogeneity across databases • In collaboration with IMEDS	• Preparedness Design – *Systematic selection* – *Self-controlled* – *Cohort methods* • Analysis – *Confounder adjustment* – *Distributed methods* – *Quantifying uncertainty* • Sequential Analysis
Signal Generation	**Signal Follow-up**	**Decision Making**
• Data mining (untargeted) • Sample size tools	• Data/code quality • Sensitivity analyses • Timing of signals • 2-phase designs	• Decision analysis framework

Tool development steps



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Health Outcome and Confounder Libraries

- Need standardized operational definitions for health outcomes and confounding conditions
- Summarize literature sources
- Document definitions used in protocol-based assessments

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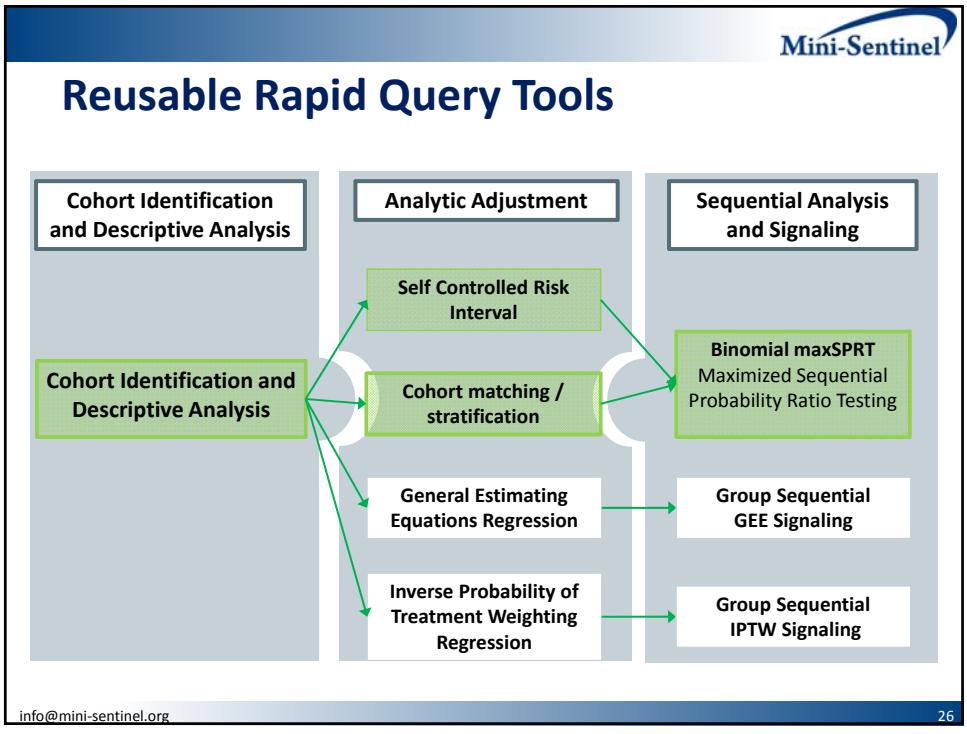
Taxonomy

Structured decision table to facilitate methods selection for particular active medical product monitoring scenarios

Monitoring scenario characteristics with implication for design choice[a]							Monitoring scenario characteristics with implication for analytic choice[a]		
	Characteristics of the (potential) exposure-HOI link								
			Strength of confounding						
Exposure persistence *(transient, sustained)*	**Onset of exposure risk window** *(Immediate, delayed)*	**Duration of exposure risk window** *(short, long)*	**Within-person** *(negligible, needs to be addressed)*	**Between-person** *(negligible, needs to be addressed)*	**HOI onset** *(abrupt, insidious)*	**Design choice[b]** *(self-controlled, cohort)*	**Background frequency of exposure** *(infrequent, rare)*	**Background frequency of HOI** *(infrequent, rare)*	**Analytic choice**
Transient (e.g. vaccine, *initiation* of a drug; including episodic drug use [e.g. triptans] to the extent that the question pertains to its transient nature)	Immediate	Short	Negligible	Needs to be addressed	Abrupt	3 self-controlled (or cohort)	Infrequent	Infrequent	9
								Rare	10
							Rare	Infrequent	11
								Rare	12
					Insidious	4 self-controlled or cohort	Infrequent	Infrequent	13
								Rare	14
							Rare	Infrequent	15
								Rare	16
			Needs to be addressed	Negligible	Abrupt	5	Infrequent	Infrequent	17

Exposure-outcome scenarios linked to design strategies

www.mini-sentinel.org/data_activities/modular_programs/details.aspx?ID=166



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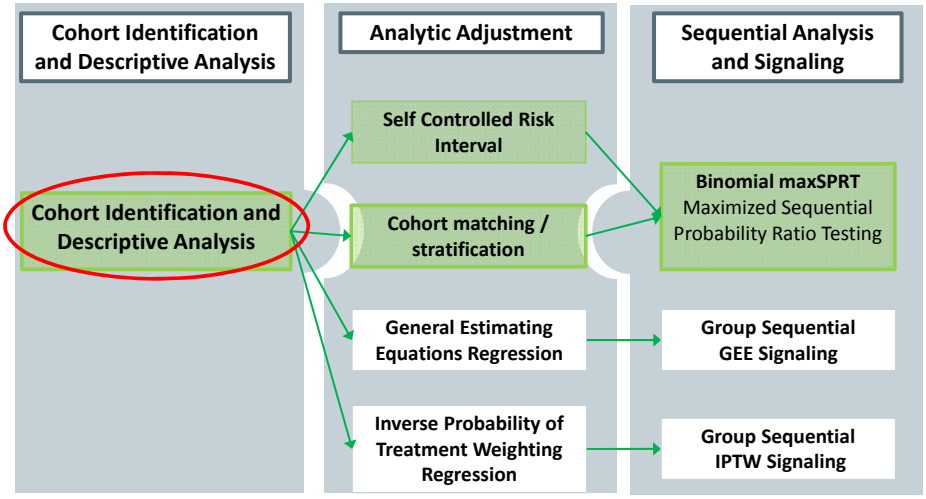
Reusable Rapid Query Tools



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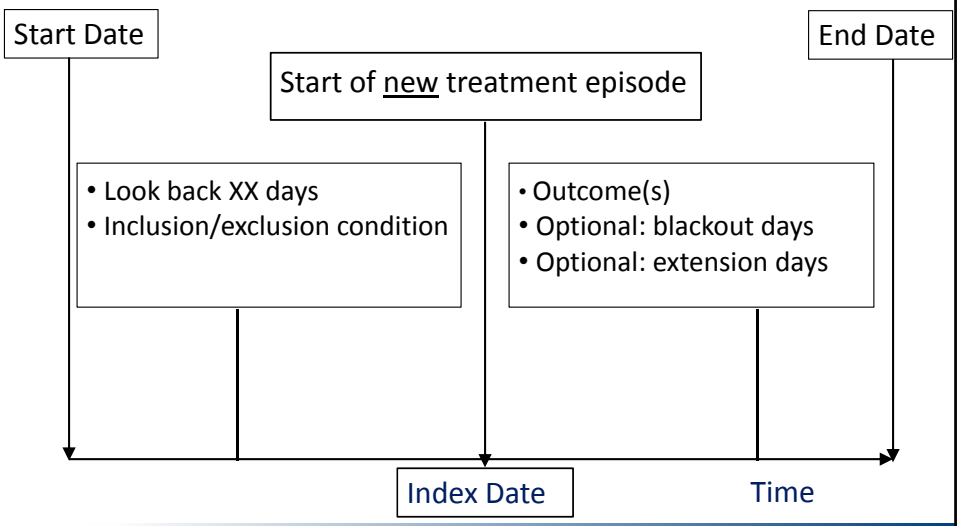
New User Cohort Design



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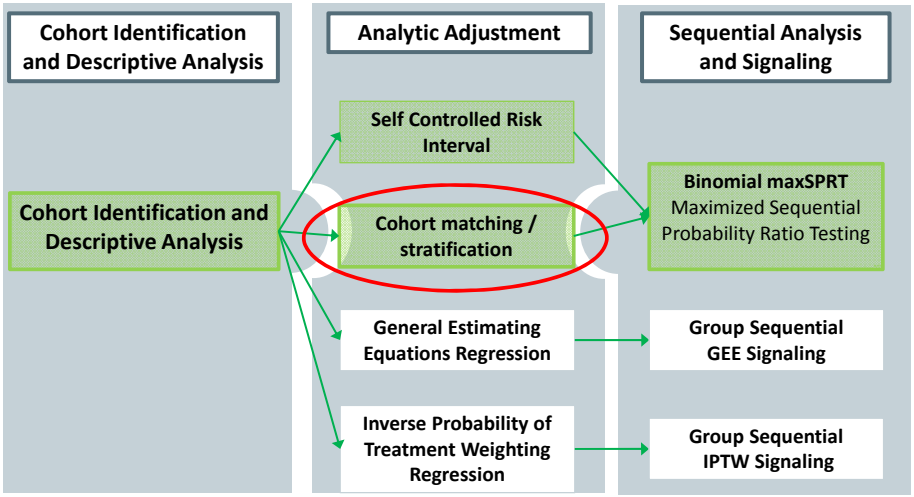
Reusable Rapid Query Tools



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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

- Used data for 3.9 million new users of anti-hypertensives in 18 organizations
- Propensity score matched stratified analysis
- No person-level data was shared
- **Five months and $250,000 required for programming and analysis – compared to 1-2 years and $2 million without analysis-ready distributed dataset**

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

Query Request Form: Study Design

1. Select the Query Type (Level):	Level 2: Cohort Selection and Analytic Adjustment
2. Select the Analysis Tool:	Propensity Score Matching Tool
3. Describe Study Objectives:	*To assess the ability of Mini-Sentinel comparative assessment modular programs to reproduce the known association between ACEIs and angioedema*
4. Define Study Period:	01/01/2008 - 09/30/2013
If multiple looks are planned (PROMPT), enter the time period for the first look. Look frequency and time period covered should be included in the surveillance plan.	
5. List the age group(s) of interest:	*18 +*
6. Specify enrollment requirements:	
Coverage type:	Medical and drug coverage
Maximum enrollment gap (days):	45
Continuous enrollment before exposure (days):	183

www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Known-Positives-ACEI-Angioedema.pdf

Query Request Form: Exposures

	Exposure of Interest	Comparator of Interest (1)
1. Define exposures (generic/brand names):	ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, perindopril, ramipril, or tranolapril)	Beta-blockers (acebutolol, atenolol, bisoprolol, carvedilol, labetalol, metoprolol, nebivolol, pindolol, propranolol, or timolol)
2. Define exposure incidence:		
Washout period (days):	183	183
Other exposures: *Incidence defined with respect to additional exposures*	Beta-blockers, aliskiren, ARBs (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, or valsartan)	ACE inhibitors, aliskiren, ARBs (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, or valsartan)
3. Specify exposed time assessment (AT or ITT):	As Treated (AT)	As Treated (AT)
4. Specify follow-up duration (for ITT assessments; in days): *Leave blank for AT assessments*		

www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Known-Positives-ACEI-Angioedema.pdf

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Query Request Form: Exposures

5. Allow one or multiple exposure episodes? *For propensity score matched analyses, select "One"*	One	One
6. Specify treatment episode creation details (in days): *Relevant for AT assessments only; leave blank for ITT*		
Episode allowable gap:	14	14
Episode extension period:	14	14
Minimum episode duration:	0	0
Minimum days supply:	0	0
7. Specify exposure episode censoring rules:		
Truncate episode(s) at death?	Yes	Yes
Truncate episode(s) at occurrence of incidence defining exposures (defined in Question #2)?	Yes	Yes
8. Specify induction period (days): *If an outcome is observed during the induction period, the exposure episode is discarded*	0	0

www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Known-Positives-ACEI-Angioedema.pdf

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Query request: Additional Inputs

- Outcomes
  - ICD-9-CM code 995.1 in any position during outpatient, inpatient, or emergency department encounter
  - Washout period (days before first dispensing): 183 days
- Inclusion criteria
- Exclusion criteria
- Covariates
- Propensity score matching options
  - Comorbidity, utilization, high dimensional propensity score
  - Matching ratio
  - Caliper size

Angioedema: Table 1. Unmatched Cohort

Table 1. Cohort of New Initiators of ACE Inhibitors and Beta Blockers (Unmatched)

Characteristic	Primary Analysis: ACE Inhibitors N	%	Beta Blockers N	%	Covariate Balance: Absolute Difference	Standardized Difference
3.9 million new users						
Patients	2,211,215	100%	1,673,682	100%	0.0	-
Events while on therapy	5,158	0.2%	1,292	0.1%	0.1	0.0
Person-time at risk (days)	186.9	266.6	149.2	235.1	37.7	0.2
Patient Characteristics						
Gender (F)	997,962	45.10%	946,344	56.50%	-11.4	-0.2
Mean age (std dev)	54.6	12.7	53.7	15.6	0.9	0.1
Recorded History of:						
Allergic reactions	207,344	9.4%	190,387	11.4%	-2.0	-0.1
Diabetes	471,661	21.3%	173,083	10.3%	11.0	0.3
Heart failure	41,060	1.9%	74,897	4.5%	-2.6	-0.1
Ischemic heart diseases	109,948	5.0%	224,681	13.4%	-8.4	-0.3
NSAID use	318,298	[illegible]%	250,697	15.0%	-0.6	0.0
Health Service Utilization Intensity:	**Mean**	**Std D**				
Number of generics	3.4	3.5				
Number of filled prescriptions	7.5	9.6				
Number of inpatient hospital encounters (IP)	0.1	0.4				
Number of non-acute institutional encounters (IS)	0.0	0.6	0.1	0.9	-0.1	-0.1
Number of emergency room encounters (ED)	0.2	0.7	0.4	1.0	-0.2	-0.2
Number of ambulatory encounters (AV)	4.8	6.3	6.9	8.4	-2.1	-0.3
Number of other ambulatory encounters (OA)	1.1	2.6	1.5	3.6	-0.4	-0.1

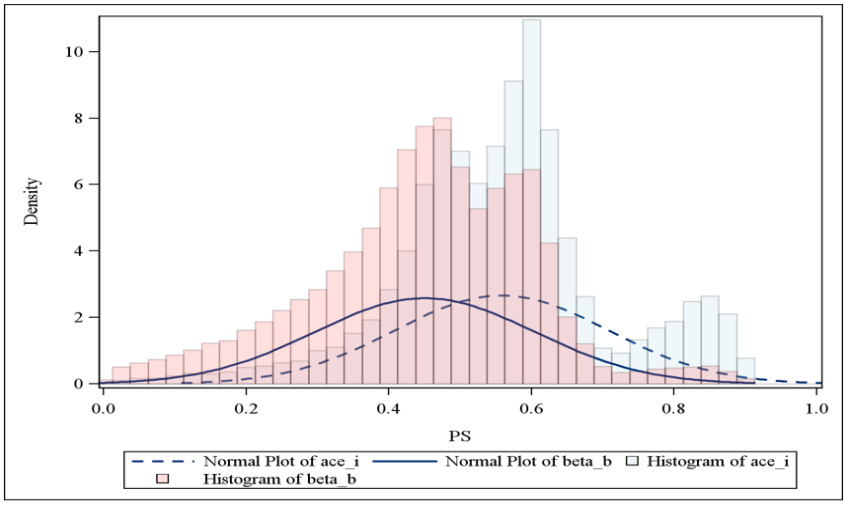
Diabetes 21% vs 10%
Heart failure 2% vs 4%
Ischemic heart disease 5% vs 13%

www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Known-Positives-ACEI-Angioedema.pdf

Propensity Scores Before Match

Histograms of PS distribution by DP (masked)

Histogram of Predefined PS, Unmatched Cohort C-Stat for Predefined: 0.695



DP3 www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Known-Positives-ACEI-Angioedema.pdf

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Angioedema: Table 2. Matched Cohort

Table 2. Cohort of New Initiators of ACE Inhibitors and Beta Blockers (Matched Predefined PS, Caliper = .025)

	Primary Analysis				Covariate Balance	
	ACE Inhibitors		Beta Blockers			
	N	%	N	%	Absolute Difference	Standardized Difference
Patients	1,309,104	59.2%	1,309,104	78.2%	0.0	-0.4
Events while on therapy	3,311	0.3%	988	0.1%	0.2	0.0
Person-time at risk (days)	183.8	263.7	151.8	238.9	31.9	0.1
Patient Characteristics						
Gender (F)	723,955	55.3%	689,617	52.7%	2.6	0.1
Mean age (std dev)	54.1	13.1	54.4	14.9	-0.3	0.0
Recorded History of:						
Allergic reactions	137,920	10.5%	134,933	10.3%	0.2	0.0
Diabetes	150,036	11.5%	150,551	11.5%	0.0	0.0
Heart failure	35,302	2.7%	38,966	3.0%	-0.3	0.0
Ischemic heart diseases	102,200	7.8%	106,786	8.2%	-0.4	0.0
NSAID use	191,798	[illegible]%	189,612	14.5%	0.2	0.0
Health Service Utilization Intensity:	**Mean**	**Std**				
Number of generics	3.7	3.7%				
Number of filled prescriptions	8.1	10.2%				
Number of inpatient hospital encounters (IP)	0.1	0.5%				
Number of non-acute institutional encounters (IS)	0.1	0.7%	0.1	0.7%	0.0	0.0
Number of emergency room encounters (ED)	0.3	0.8%	0.3	0.8%	0.0	0.0
Number of ambulatory encounters (AV)	5.6	7.3%	5.6	6.6%	0.0	0.0
Number of other ambulatory encounters (OA)	1.2	2.9%	1.3	3.0%	0.0	0.0

2.6 million new users

Diabetes 10% vs 10%
Heart failure 3% vs 3%
Ischemic heart disease 8% vs 8%

www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Known-Positives-ACEI-Angioedema.pdf

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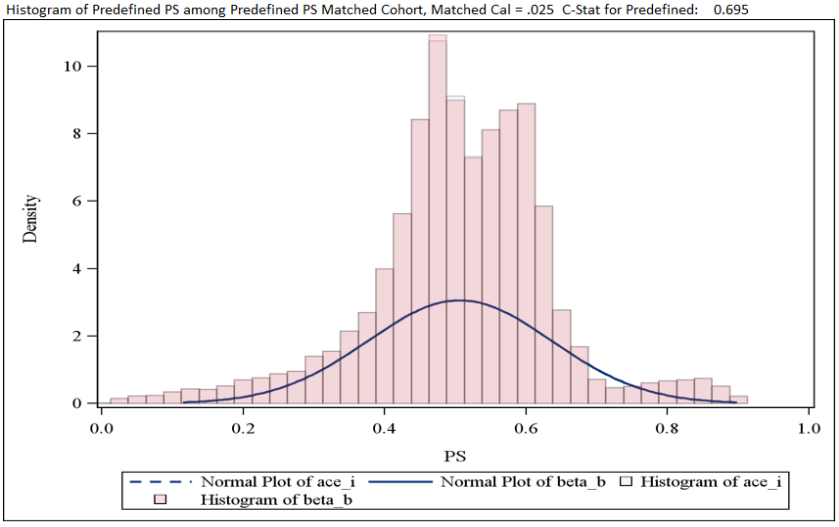
Propensity Scores After Match

Histograms of PS distribution by DP (masked)

Histogram of Predefined PS among Predefined PS Matched Cohort, Matched Cal = .025 C-Stat for Predefined: 0.695



DP3 www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Known-Positives-ACEI-Angioedema.pdf

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Angioedema: Table 3. Results

ACEI vs β-blocker 1:1 matched analysis:

- **HR = 3.1** (95% CI, 2.9-3.4)

Toh *et al* findings:

- **HR = 3.0** (95% CI, 2.8-3.3)

Table 3: Sequential Estimates for Angioedema Events by Analysis Type, and Drug Pair

Exposure Definition	Monitoring Period	New Users	Person Years at Risk	Average Person Years at Risk	Number of Events
Unmatched Analysis (Site-adjusted only)					
ACE Inhibitors	1	2,211,215	1,131,526	0.51	5,158
Beta Blockers		1,673,682	683,614	0.41	1,292
1:1 Matched Analysis; Caliper=0.025					
ACE Inhibitors	1	1,309,104	658,700	0.50	3,311
Beta Blockers		1,309,104	544,285	0.42	988

Incidence Rate per 1000 Person Years	Risk [illegible] New Users	Difference per 1000 Person Years	Difference in Risk per 1000 New Users	Hazard Ratio (95% CI)	Wald P-Value
4.558	2.33	2.67	1.56	2.55 (2.40, 2.71)	<.0001
1.890	0.77				
5.027	2.53	3.21	1.77	3.14 (2.86, 3.44)	<.0001
1.815	0.75				

www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Known-Positives-ACEI-Angioedema.pdf

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Additional workgroups (selected)

Data activities

- Feasibility of blood product safety surveillance
- Clinical data elements, including lab test results
- National Death Index linkage
- Birth certificate linkage
- Diabetes registry linkage (SUPREME-DM)
- Medical Counter Measures
- Sequential analysis of influenza vaccine safety
- Linkage with PCORnet

Statistical and analysis tools

- Prospective monitoring tools (PROMPT) enhancements
- Robustness of surveillance
- Quantifying uncertainty in protocol-based assessments
- Expansion of data mining (TreeScan Pilot and TreeScan power)
- Scan statistics and pregnancy
- Practical guidance for signal follow-up

Three major domains

- Data
- Methods
- **Active surveillance**

Query Fulfillment

- Year 5 Activities
  - 48 Summary Table Requests
  - 63 Modular Program Requests
    - Over 2000 “scenarios”
    - Over 90 reports to FDA
- To Date
  - ~350 Summary Table Requests
  - ~175 Modular Program Requests

Selected Protocol Based Assessments Planned or Under Way

- CDER
  - Mirabegron and several outcomes (prospective monitoring)
  - Rivaroxaban and several outcomes (prospective monitoring)
  - Dabigatran and several outcomes
  - Metabolic effects of 2nd generation antipsychotics in youth
  - Diabetes drugs and acute myocardial infarction
  - IV Iron and anaphylaxis
- CBER
  - IV Immune Globulin and thromboembolic events
  - Gardasil and venous thromboembolism
  - Influenza vaccines and pregnancy outcomes
  - Gardasil 9 and Pregnancy Outcomes
  - Prevnar 13 and Kawasaki disease
  - Blood components and Transfusion-Related Lung Injury (TRALI)

Plans for Sentinel

Mini-Sentinel

New Populations

- Part of Sentinel contract
  - BCBS Massachusetts
  - Hospital Corporation of America
  - PCORnet Clinical Data Research Networks

11 Clinical Data Research Networks

Lead Organization
Oregon Community Health Information Network
The Chicago Community Trust
University of Kansas Medical Center
Louisiana Public Health Institute
Vanderbilt University
Weill Medical College of Cornell University
The Children's Hospital of Philadelphia
Kaiser Foundation Research Institute
University of California, San Diego
University of Pittsburgh
Harvard University

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Potential future populations

- CMS data
- Veterans Health Administration
- Department of Defense

New academic partners

- Harvard School of Public Health
- University of Florida
- University of North Carolina

Patient advocates

- Steve Mikita* – Utah Asst Attorney General
- Bray Patrick-Lake** – Clinical Trials Transformation Initiative Director of Stakeholder Engagement
- Sharon Terry – President/CEO Genetic Alliance

* Current
** Former, returning

Data

- Expand the Common Data Model
  - New EHR variables
  - Link to external sources
- Inpatient/outpatient EHR
  - Hospital Corporation of America
  - Current data partners
  - PCORnet Clinical Data Research Networks

Preparing for ICD-10

- The data model is ready for ICD-10!
- Need to learn to use the codes:
  - In-depth literature review
  - Discussion of potential algorithms
  - Documentation of rationale
  - Completed: AMI, acute kidney injury, angioedema, , intussusception, stroke
    e.g., proposed algorithm for AMI: ICD-10 = I21.X
    - Expected PPV ~ 74% – 100%*
  - Ongoing: anaphylaxis, GI bleed

* Coloma et al. BMJ Open 2013 20;3(6)

Methods priorities

- Data linkage: National death index (NDI)
- Method evaluation: Comprehensive evaluation of Sentinel programs' operational and statistical performance
- Targeted prospective surveillance (enhancing PROMPT)
  - Historical comparison groups (vaccines, rare outcomes)
  - More flexible survival data estimation/signaling methods
  - Improving sequential design selection processes
  - Prospective temporal scans in self-controlled & cohort designs
- Signal follow-up from prospective surveillance
  - Practical guidance for follow-up of safety signal
  - Electronic claims profile retrieval tool to review HOIs
- Signal generation: extending tree scan data mining

Mini-Sentinel

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 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 information to answer additional

Mini-Sentinel

Linking Data from Public Health Medical Countermeasure Campaigns with Electronic Health Records

The Mini-Sentinel Medical Countermeasure Post-marketing Surveillance Project

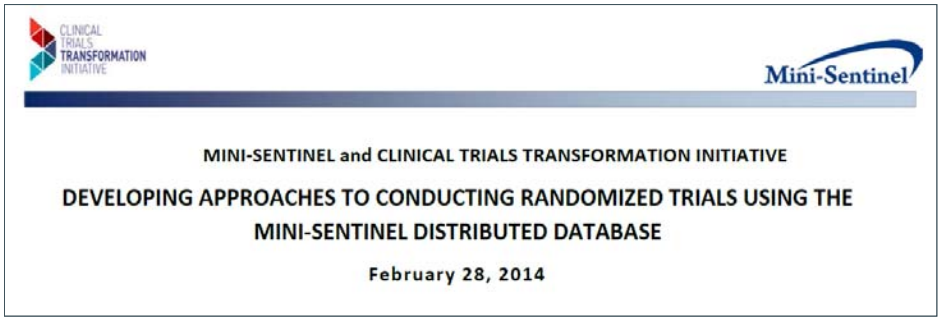
Rationale

Marsha E Reichman, PhD
Senior Advisor & Scientific Lead for Surveillance Programs
CDER Sentinel Initiative Lead
OPE/OSE/CDER/FDA

KAISER PERMANENTE® DENVER HEALTH Level One Care for ALL Denver Public Health NACCHO National Association of County & City Health Officials

External engagements

- Clinical Trials Transformation Initiative
- PCORnet – Nat'l Patient Centered Research Network
- NIH Health Care System Collaboratory
- Reagan Udall Foundation – IMEDS
- ONC Standards & Interoperability Framework (Query Health)
- IOM Roundtable on Value & Science-Driven Health Care
- Academy Health EDM Forum


MINI-SENTINEL and CLINICAL TRIALS TRANSFORMATION INITIATIVE

DEVELOPING APPROACHES TO CONDUCTING RANDOMIZED TRIALS USING THE MINI-SENTINEL DISTRIBUTED DATABASE

February 28, 2014

www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_CTTI_Developing-Approaches-to-Conducting-Randomized-Trials-Using-MSDD.pdf

pcornet The National Patient-Centered Clinical Research Network

www.pcornet.org

Home | About PCORnet | Member Networks | Task Forces | Events | PCORnet News | References & Resources

PCORnet: The National Patient-Centered Clinical Research Network

The Patient-Centered Outcomes Research Institute (PCORI) is supporting the development of PCORnet, the National Patient-Centered Clinical Research Network, to create a large, highly representative, national network for conducting clinical outcomes research.

PCORnet will transform clinical research by engaging patients, care providers, and health systems in collaborative partnerships to improve healthcare and advance medical knowledge. By bringing research and patient care together, this innovative health data network will be able to explore the questions that matter most to patients and their families. Read more ….

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Resource Center

Contact Us

Office Hours

Questions?

(844) 275-6276 / 844-ASK-NCRN
Local: (919) 668-2286

Member Log-in [Central Desktop]

Resources

FAQs

FDA Mini-Sentinel Assessments

PCORnet's Goal

Improve the nation's capacity to conduct rapid, efficient, and economical [multi-center] comparative effectiveness research

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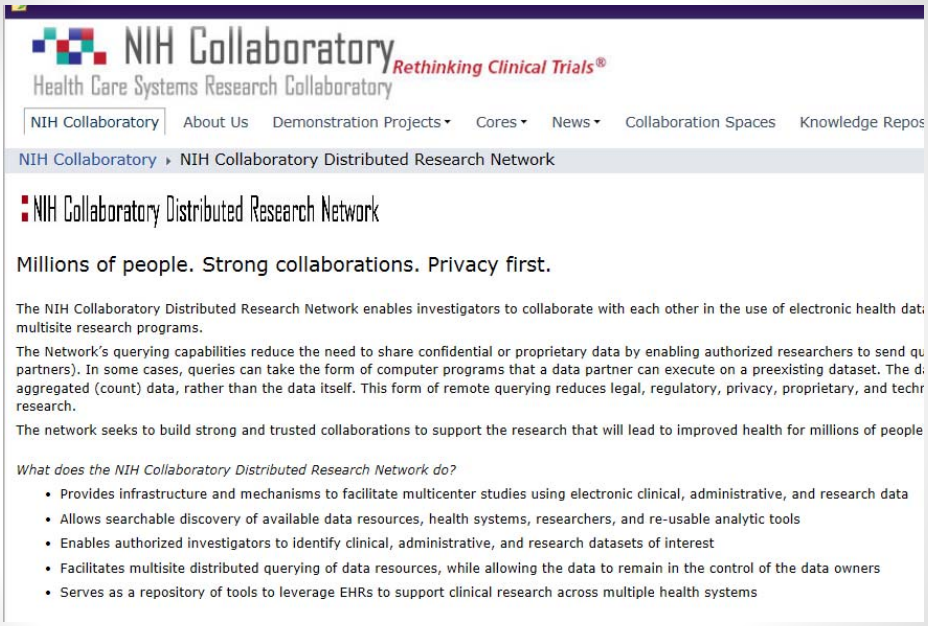

www.nihcollaboratory.org/Pages/distributed-research-network.aspx

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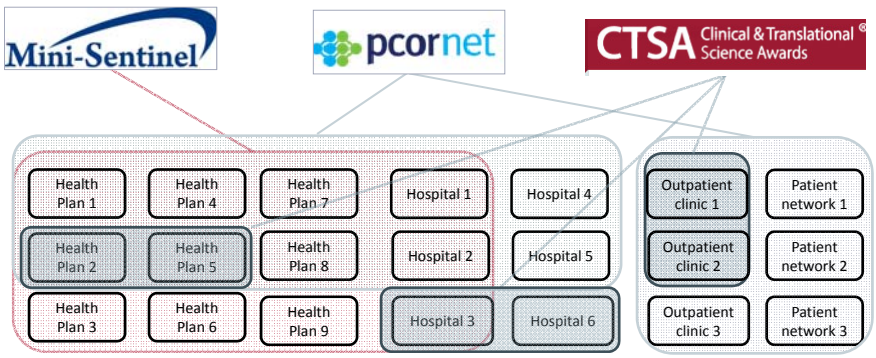
NIH Collaboratory DRN organizations

- ➢Aetna
- ✓Group Health Research Institute
- ➢Harvard Pilgrim Health Care Institute
- ➢HealthCore, Inc. (Anthem – 14 Blue Cross plans)
- ✓HealthPartners Institute for Education and Research
- ➢Humana: Comprehensive Health Insights, Inc.
- The MURDOCK Study
- ➢OptumInsight, Inc.

✓ Indicates current PCORnet and Sentinel site
➢ Sentinel site

NIH Collaboratory NIH Distributed Research Network

Critical Partners in a National 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
- Other potential partners: disease or treatment-specific networks; :

Key contributors to Mini-Sentinel's progress

- **Close, frequent, coordinated interactions between FDA, data partners, clinical 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


Mini-Sentinel
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???
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Mini-Sentinel

Thank you!

Mini-Sentinel Review: CDER Use of Mini-Sentinel Tools / Resources

Marsha E. Reichman, Ph.D.
Scientific Lead for Surveillance Programs
CDER Sentinel Initiative Lead
OPE/OSE/CDER/FDA
February 5, 2015

Goals / Outline

- Overview of the spectrum of assessments under Mini-Sentinel
- How the resulting data is being used
- Specific assessments
  - NDI+ Linkage to ascertain out of hospital death and cause of death
    - Sudden Cardiac Death Outcome – expanding data sources
  - Evaluation of Medication Use During Pregnancy
    - Rationale – assessment topic selection
    - Tool development – development of a reusable tool

Mini-Sentinel Pilot Program Summary

Total Program Years	5 Years
Total Data Items (drugs, diagnoses, procedures) Queried by Summary Tables	200 requests to date for >650 data items
Total Drugs Queried by Modular Programs	150 requests to date for >250 data items
PROMPT Assessments	3
Total Protocol Based Assessments	9 ongoing or successfully completed

Enhancements Over Time: "Modular Programs"

- Complexity of Safety Scenarios
  - Pre-existing conditions
  - Concomitant treatments
  - Complex outcomes and exposures
- Analytics
  - Adjustment for confounding
  - Sequential analyses
- PROMPT
  - Semi-automated design (new user cohort, self-controlled)
  - Secondary and sensitivity analyses

Mini-Sentinel – Complex Modular Program (MP) Assessments

Selected complex assessments use multiple, or enhanced, MPs:

- Switching between generic and brand drugs
- Characterization of uptake and persistency for NMEs
- Topiramate/other AEDs – kidney stones
- Long term bisphosphonate use
- Rehospitalization for C. diff with outpatient treatment w vancomycin, fidaxomicin, or metronidazole
- Dabigatran/Warfarin – ICH, GIH
- Anti-diabetics and hypoglycemia
- Genetic testing associated with drug use
- Concomitant use of ACEIs and DPP IV inhibitors – angioedema
- Off label drug use in pediatric patients
- Switching between brand and generic warfarin
- Alosetron and ischemic colitis
- Levetiracetam and comparators – agranulocytosis
- Multiple MPs assessing testosterone use with different diagnoses, laboratory tests and persistency
- Statin use and rhabdomyolysis

Results of completed queries on www.minisentinel.org

Mini-Sentinel Drug Safety Studies
PROMPT
Prospective Routine Observational Monitoring Program Tools

- Rivaroxaban/Warfarin – severe bleeding/stroke*
- Mirabegron/Other Over Active Bladder (OAB) drugs – AMI*
- Niacin – severe bleeding*
- Additional analyses in planning, or early implementation stage

*Data analysis underway

Mini-Sentinel Drug Safety Studies Protocol Based Assessments

- Saxagliptin/Sitagliptin - AMI**
- Dabigatran / Warfarin – Severe Bleeds **
- ACEI/ARBS/Aliskiren/β-blockers – Angioedema -completed *
- Evaluation of FDA Regulatory Actions – LABAs*
- Use of Drugs during Pregnancy****
- Pediatric Anti-Psychotics / Metabolic Syndrome, Diabetes**
- IV Iron / Anaphylaxis**
- Identification of Sudden Cardiac Death through Linkage with NDI+***
- Identification and Safety Follow-up of Individuals Receiving a Medical Counter Measures Medical Product*

* Complete or manuscripts in preparation

** Data analysis underway

***Protocol development

****Initial analysis complete and manuscripts in preparation/submitted; reusable tool developed is being used for additional assessments

Mini Sentinel – Selected Use of Results

- FDA Drug Safety Communications (DSC):
  - Dabigatran/severe bleeding; olmesartan/sprue like enteropathy
- Safety reviews mandated under section 915 of FDAAA, AC presentations, TSI reviews:
  - Saxagliptin & sitagliptin/MI, ketoconazole /SALI, use of epidural injections of corticosteroids, isotretinoin and multiple sclerosis, niacin/bleeding, etc
- Evaluation of FDA regulatory actions (labeling, etc):
  - Lower use of prasugrel than clopidogrel in patients with prior TIA/stroke, LABAs
- Drug use:
  - Comparison with nationally projected databases presented at DIA 2012, uptake of NMEs; use of various drugs and drug classes during pregnancy

Identification of Sudden Cardiac Death (SCD) through Linkage with NDI+

NDI+ Linkage Workgroup

- Susan Andrade
- Denise Boudreau
- Rajat Deo
- Sascha Dublin
- James Floyd
- Candace Fuller
- Monica Fuji
- Margie Goulding
- David Graham
- Sean Hennessey
- Stephine Keeton
- Todd Lee
- Charles Leonard
- Mark Levenson
- Nancy Lin
- Katrina Mott
- Jennifer Nelson
- Rita Ouellet-Hellstrom
- Simone Pinheiro
- Bruce Psaty
- Marsha Reichman
- Robert Rosofsky
- David Siscovick
- Mary Ross Southworth
- Darren Toh
- Robert Wellman

Death and Mini-Sentinel

- MS obtains death information only if a medical claim/administrative data is generated
- Standardized information on out of hospital death/cause of death is highly desirable – sudden cardiac death, suicide, etc.
- Potential linkage with National Death Index (NDI+) – National Center for Health Statistics / CDC
  - Centralized database of state-based death record information
  - Retrieval of an NDI death record requires a match on various combinations of data including:
    - SSN, first /last name, month/day/year of birth, sex

Example – Sudden Cardiac Death

- In drug development, QT studies may be required as part of an NDA application to assess risk for proarrhythmia
  - QT prolongation is a marker for risk
- Approach successful but
  - Expensive
  - Unacceptable QT findings lead to halted development, but these findings don't always signify important effects on pertinent cardiac ion channels
  - Not all proarrhythmic risk is associated with QT prolongation
- Could this be done reliably in the post-marketing period?

- Algorithms exist (and could be developed/enhanced) to investigate cause specific death
  - Ray's Algorithm for sudden cardiac death (SCD)[1]
    - Uses Death certificate data, inpatient diagnosis and treatment codes

•[1]Chung CP et al, A computer case definition for sudden cardiac death, PDS 2010.

NDI+ Linkage Project: Outcomes of Death and SCD

Objectives:

- Create standard process for matching to NDI+ by linking selected cases to NDI data
- Identify cases of possible death* in 4 cohorts to submit to NDI+, retrieve cause of death

Cohorts:

- Cohort 1: Antiarrhythmic medication users ↑ risk SCD
- Cohort 2: General Population ↓risk SCD
- Cohort 3: Users of select Antibiotics
- Cohort 4: Users of select Antidepressants

*Possible death algorithm being defined. Broadly including those without evidence of continued enrollment or medical care for a specific time period.

NDI+ Linkage Project: Outcomes of Death and SCD

Status

- Protocols are being reviewed and finalized
- Survey of data partners complete – availability of data needed for linkage
- Defining the process and the programming specifications
- Application to NCHS for linkage w NDI+ is under development

Evaluation of Medication Use During Pregnancy in the MSDD

Evaluation of Medication Use During Pregnancy in the MSDD Workgroup

- Susan Andrade
- Carrie Ceresa
- Susan Forrow
- Katie Haffenreffer
- Monica Houstoun
- Caren Kieswetter
- Katrina Mott
- Marilyn Pitts
- Marsha Reichman
- Darren Toh

Background

- The need for routine postmarketing surveillance on medication use during pregnancy is well-recognized
- Prior studies in the U.S. have reported that the majority of women use at least one prescription medication during pregnancy
- At this time, there is no comparable size population with current data on drugs used by pregnant women delivering a live infant
- Request from Advisory Committee for drug use during pregnancy for several classes of drugs

Objective

- To **assess medication use** among pregnant women delivering a live born infant and a comparison group of non-pregnant women in the Mini-Sentinel pilot data
- To **develop a reusable tool** to monitor drug use among pregnant women delivering a live born infant over time
- Enable examination of drug use among **pregnant women** delivering a live born infant **who have pre-existing conditions** defined by diagnosis, procedure or drug codes

Study population

- Women aged 10-54 years who delivered a liveborn infant between 2001 and 2012
- Pregnancy episodes for which the women were continuously enrolled in the health plan with pharmacy benefits at least 480 days before the admit date for delivery
- Comparison group of non-pregnant women with similar eligibility criteria
  - randomly matched 1:1

Analysis

- Pregnancy start and end dates (and trimesters) were based upon an algorithm using diagnosis codes to determine gestational age at birth
- Characteristics of pregnant and non-pregnant cohort
- Prevalence of medication use by
  - Gestational period
  - Year of delivery
  - Maternal age
- The SAS code was developed to be re-usable
- Additional capabilities
  - Stratification by gestational age category – pre-term, post-term
  - Restriction to those with a pre-existing condition or prior medication use

Maternal age at delivery (years)

Mini-Sentinel, 2001-2012 (n=1,678,410)	%	U.S. live birth, 2012 * (n=3,952,841)	%
	--	<15	0.1%
<20	6.7%	15-19	7.7%
20-24	14.2%	20-24	23.2%
25-29	26.2%	25-29	28.4%
30-34	31.4%	30-34	25.6%
35-39	17.1%	35-39	12.0%
40-44	4.0%	40-44	2.8%
45-54	0.4%	45-49	0.2%
--	--	50-54	0.0%
Preterm birth code	132,859 (7.9%)		11.6%
Postterm birth code	223,901 (13.3%)		14.2%

- * CDC/NCHS, National Vital Statistics Reports, Births: Final Data for 2012

Medication exposure during pregnancy

Drug	Use in the 90 days before pregnancy		Any use during pregnancy		Any use, first trimester		Any use, second trimester		Any use, third trimester	
	P	NP	P	NP	P	NP	P	NP	P	NP
ACEIs	**0.43%**	1.03%	**0.38%**	1.46%	**0.36%**	1.08%	**0.12%**	1.12%	**0.06%**	1.16%
Anticonvulsants	**2.47%**	3.59%	**2.06%**	5.64%	**1.84%**	3.72%	**0.80%**	3.84%	**0.67%**	3.96%
Anti-diabetics	**1.96%**	1.52%	**4.26%**	2.09%	**2.07%**	1.60%	**1.85%**	1.65%	**3.28%**	1.70%
SSRIs	**5.65%**	7.10%	**6.05%**	9.80%	**4.87%**	7.27%	**3.32%**	7.35%	**3.27%**	7.46%
Statins	**0.26%**	0.71%	**0.22%**	1.05%	**0.21%**	0.75%	**0.07%**	0.79%	**0.04%**	0.83%

- **P:** pregnant cohort; **NP:** non-pregnant cohort

Medication exposure during pregnancy

Drug	Use in the 90 days before pregnancy		Any use during pregnancy		Any use, first trimester		Any use, second trimester		Any use, third trimester	
	P	NP	P	NP	P	NP	P	NP	P	NP
Methotrexate	**0.03%**	0.12%	**0.01%**	0.17%	**0.01%**	0.12%	**0.00%**	0.13%	**0.00%**	0.13%
Mycophenolate	**0.01%**	0.05%	**0.00%**	0.06%	**0.00%**	0.05%	**0.00%**	0.05%	**0.00%**	0.05%
Ribavirin	**0.00%**	0.01%	**0.00%**	0.01%	**0.00%**	0.01%	**0.00%**	0.01%	**0.00%**	0.01%
Ribavirin/interferon	**0.00%**	0.00%	**0.00%**	0.00%	**0.00%**	0.00%	**0.00%**	0.00%	**0.00%**	0.00%
Warfarin	**0.06%**	0.14%	**0.05%**	0.19%	**0.05%**	0.14%	**0.02%**	0.15%	**0.02%**	0.15%

- **P:** pregnant cohort; **NP:** non-pregnant cohort

Strengths

- Large, geographically and demographically diverse populations
- Avoids recall bias for information on medication exposures
- Analytic tool is readily adaptable to provide timely information on the use of medications during pregnancy

Limitations

- Inability to ascertain whether medications dispensed were actually taken by the women
- Lack of data on the length of gestation in the MSDD
- Currently no information on pregnancies that did not result in a live birth
- Not linked to infant records

Thank you

Marsha.Reichman@fda.hhs.gov

CBER's Sentinel Program Update

Sentinel Initiative Public Workshop

February 5, 2015

Michael Nguyen, MD
Division of Epidemiology, Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research

Plan for Talk

- Role of Sentinel within product lifecycle at CBER
  - Map key Sentinel studies launched to date onto the regulatory lifecycle

- Illustrate Sentinel's impact on each major phase
  - Current impact
  - Future impact

*Regulatory decision making frameworks presented here were simplified for illustration purposes and do not necessarily reflect all possible product safety scenarios or imply that future decisions will have similar outcomes.

Key Time Points

* Signifies 2 post-approval safety reviews: (a) postmarket safety evaluation mandated by Section 915, FDA Amendments Act (FDAAA) 2007, and (b) post-approval safety review to the Pediatric Advisory Committee

Sentinel Impact on Pre-Approval Planning

Level of concern	Pre-Sentinel Options	Post-Sentinel Options
Routine	-Passive surveillance	
Desire to further describe safety profile	-Postmarket commitment (PMC) study (e.g., pregnancy registry, general safety studies)	
Safety signal	-Required postmarket study (PMR)*	

* Since FDAAA 2007

Sentinel Impact on Pre-Approval Planning

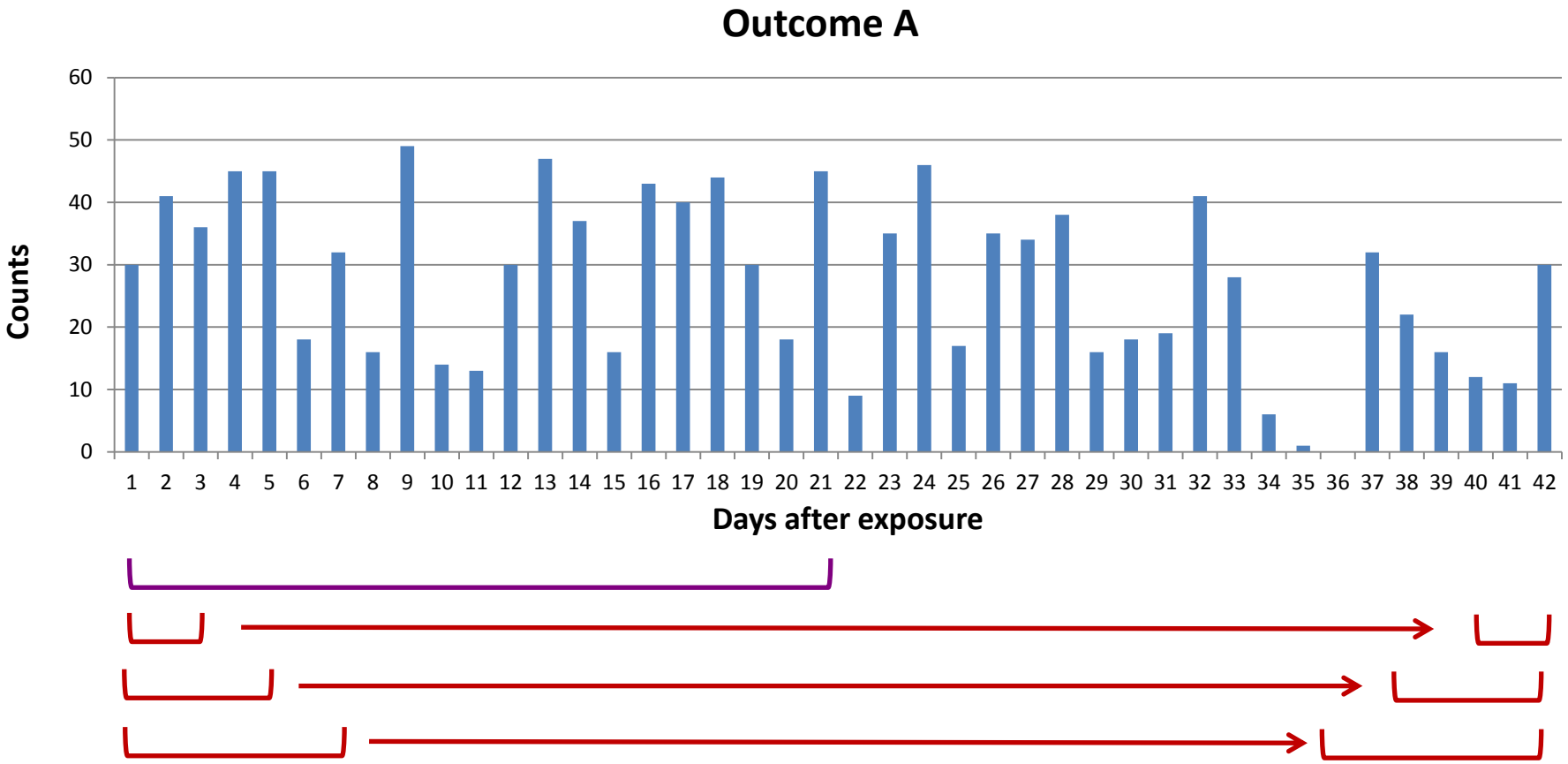
Level of concern	Pre-Sentinel Options	Post-Sentinel Options
Routine	-Passive surveillance	**+ Modular programs**
Desire to further describe safety profile	-Postmarket commitment (PMC) study (e.g., pregnancy registry, general safety studies)	**+ TreeScan** **+ PROMPT** **+ Pregnancy safety study** **+ Autoimmune study**
Safety signal	-Required postmarket study (PMR)*	**+ Targeted outcome study**

* Since FDAAA 2007

Sentinel substantially expands postmarket safety monitoring options to allow more strategic and tailored surveillance of new drugs and biologics

PROMPT: Prospective Routine Observational Monitoring Program Tools

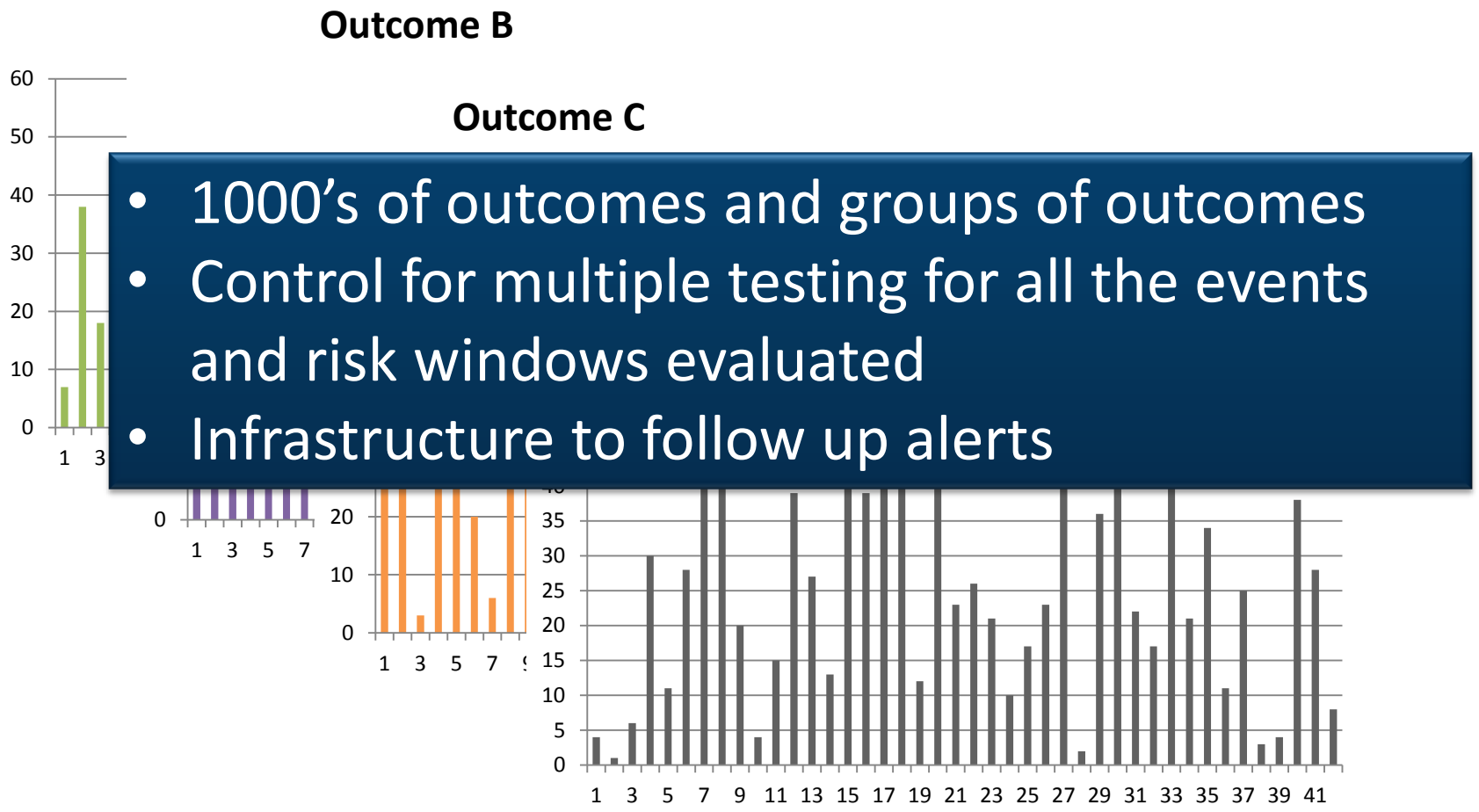
Signal Detection with TreeScan



Identifies unusual clusters after exposure using a variably sized, scanning risk window

* All data were randomly generated and for illustration purposes only

Signal Detection with TreeScan



- 1000's of outcomes and groups of outcomes
- Control for multiple testing for all the events and risk windows evaluated
- Infrastructure to follow up alerts

* All data were randomly generated and for illustration purposes only

Welcome to Mini-Sentinel

www.fda.gov

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to create an active surveillance system - the Sentinel System - to monitor the safety of FDA-regulated medical products. Mini-Sentinel uses pre-existing electronic healthcare data from multiple sources. Collaborating Institutions provide access to data as well as scientific and organizational expertise. Mini-Sentinel is part of the FDA's Sentinel Initiative, which is exploring a variety of approaches for improving the Agency's ability to quickly identify and assess safety issues.

Spotlight

- Brookings Seventh Annual Sentinel Initiative Public Workshop (February 5, 2015 from 9am–4pm - registration required)
- Employment Opportunities
- FDA Sentinel Contract Awarded to Harvard Pilgrim Health Care Institute

TreeScan

Software for the Tree-Based Scan Statistic

- Home
- Download [TreeScan v1.1 November 25 2014]
- Technical Documentation
- Bibliography
- Contact Us

Other Scan Statistics Software

Follow @martinkulldorff

Purpose

TreeScan™ is a free data mining software that implements the tree-based scan statistic, a data mining method that simultaneously looks for excess risk in any of a large number of individual cells in a database as well as in groups of closely related cells, adjusting for the multiple testing inherent in the large number of overlapping groups evaluated. Developed for disease surveillance, it can be used for the following types of problems:

- In pharmacovigilance, it can be used to simultaneously evaluating hundreds or thousands of potential adverse events and groups of adverse events, to determine if any one of them occur with higher probability among patients exposed to a particular pharmaceutical drug, device or vaccine, adjusting for the multiple tests inherent in the many adverse events evaluated.
- Also in pharmacovigilance, for a particular disease outcome such as liver failure, it can be used to simultaneously evaluate if it occurs with increased risk among people exposed any of hundreds of pharmaceutical drugs, or groups of related drugs, adjusting for the multiple testing inherent in the many drugs evaluated.
- In occupation disease surveillance, it can be used for a particular disease to evaluate whether certain occupations, or group of related occupations, are at higher risk to die from that disease.

It can also be used for data mining in other subject areas unrelated to disease surveillance or medicine.

Key Features

Three key features of the tree-based scan statistic data mining method are:

- It will simultaneously look for an excess risk in any of a large number of cells in a database. This is what makes it a data mining method.
- It will not only evaluate single cells, but also overlapping groups of cells that are closely related to each other in a pre-defined tree structure. That is, it is not necessary to pre-specify the granularity of the analysis.
- The analysis is adjusted for the multiple testing inherent in the hundreds, thousands or millions of cells and overlapping cell groupings that are evaluated. When a 0.05 alpha level is used, this means that if the events occur randomly with equal risk in each cell, there is only a 5% probability of detecting a significant excess risk in any of the cells or cell grouping an there is a 95% probability that there will not be a single cell or cell grouping with a statistically significant excess risk.

Data Types and Probability Models

TreeScan uses either a Poisson-based probability model, where the number of events (or cases) in a cell is Poisson-distributed, according to a known underlying population at risk; or a binomial model, with 0/1 event data such as cases and controls. Both conditional or unconditional analyses can be performed. In a conditional analysis, the analysis is conditioned on the total number of cases observed.

Developers and Funders

The TreeScan™ software was developed by Martin Kulldorff together with Information Management Services Inc. Financial support for TreeScan has been received from:

- Agency for Health Research and Quality, Centers for Education and Research on Therapeutics
- National Institutes of Health, National Library of Medicine
- Food and Drug Administration, Center for Biologics Evaluation and Research, Mini-Sentinel Post-Licensure Rapid Immunization Safety Monitoring Program

Their financial support is greatly appreciated. The contents of TreeScan are the responsibility of the developer and do not necessarily reflect the official views of the funders.

TreeScan™ 2014 For questions and inquiries please contact us.

Please also visit Mini-Sentinel Disclaimer

http://www.treescan.org/

FDA News Release

FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV

For Immediate Release December 10, 2014

Release

Español

The U.S. Food and Drug Administration today approved Gardasil 9 (Human Papillomavirus 9-valent Vaccine, Recombinant) for the prevention of certain diseases caused by nine types of Human Papillomavirus (HPV). Covering nine HPV types, five more HPV types than Gardasil (previously approved by the FDA), Gardasil 9 has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal and anal cancers.

Inquiries

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888-INFO-FDA

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http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426485.htm

Sponsor's Pharmacovigilance Plan: Gardasil 9

	Health Outcome	Action Plan
Identified Risks	1. Hypersensitivity reactions 2. Exposure during pregnancy 3. Syncope causing injury	•Routine pharmacovigilance •Pregnancy registry
Potential Risks	1. Guillain-Barre Syndrome	•Routine pharmacovigilance
Missing Information	1. Unanticipated adverse events	•Routine pharmacovigilance •Observational study (N=10,000)

http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm428241.htm
http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm426445.htm

Sentinel Enhancements to Sponsor's Gardasil 9 Pharmacovigilance Plan

- **General safety study**
  - **TreeScan**: detect serious and unexpected adverse events
  - **PROMPT**: near real-time active surveillance for prespecified outcomes
  - **Autoimmune surveillance study**: observational study to evaluate immune-mediated conditions that are theoretical safety concerns common to all vaccines
- **Pregnancy outcomes study**
- **Proposed studies seek to enlarge existing safety database and monitor safety in real-world healthcare settings**

Key Time Points

18 Month Postmarket Safety Evaluations

Section 915 Review	Pediatric Advisory Committee
▪ All ages included	▪ Pediatric focus only
▪ 18 months or 10,000 patient exposures, whichever is later	▪ 18 months
▪ Conclusion posted online	▪ Full analysis presented publically and posted online ▪ Committee input and vote
▪ Required since Sept 2007	▪ Required since Sept 2007

*http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/default.htm

**http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm

Impact on 18 Month Safety Evaluations

Pre-Sentinel Safety Review

- Spontaneous reports and data mining (VAERS, FAERS)
- Manufacturer postmarket studies (PMC, PMR)
- Manufacturer safety reports to FDA
- Literature review

Sentinel Options Added*

* Actual use is customized based on needs of the product and totality of safety data

Impact on 18 Month Safety Evaluations

Pre-Sentinel Safety Review

- Spontaneous reports and data mining (VAERS, FAERS)
- Manufacturer postmarket studies (PMC, PMR)
- Manufacturer safety reports to FDA
- Literature review

Sentinel Options Added*

+ **TreeScan**
+ **PROMPT**
+ **Modular programs**

* Actual use is customized based on needs of the product and totality of safety data

Sentinel Studies Can Arise From FDA 18 Month Postmarket Safety Reviews

Prevnar 13 (Pneumococcal 13-valent Conjugate Vaccine, Diphtheria CRM_{197} Protein) BLA 125324 December 30, 2011	Active immunization for children 6 weeks through 5 years of age (prior to the 6th birthday) for the prevention of invasive disease caused by *Streptococcus Pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, and for the prevention of otitis media caused by *Streptococcus Pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F	Adverse event reports of cyanosis, pallor, and hypotonia were identified. Adverse event reports of Kawasaki disease were identified.	FDA is continuing to evaluate the cyanosis, pallor, and hypotonia events to determine if the current labeling, which includes Hypotonic hyporesponsive episode (HHE) in the Adverse Reactions section, is adequate. FDA intends to initiate a larger study of Kawasaki's disease risk following PCV13 vaccination in the Post-licensure Rapid Immunization Monitoring System.

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm355034.htm

Sentinel Studies Can Arise From FDA Advisory Committees on Post-Approval Safety

In December 2010, this information was presented to the FDA Pediatric Advisory Committee as part of a routine safety review.[7] The committee recommended that additional surveillance studies be conducted to further evaluate the potential risk of VTE following Gardasil vaccination. This protocol describes the methods used to monitor VTE after Gardasil vaccination in the PRISM program.

MONITORING FOR VENOUS THROMBOEMBOLISM AFTER GARDASIL VACCINATION

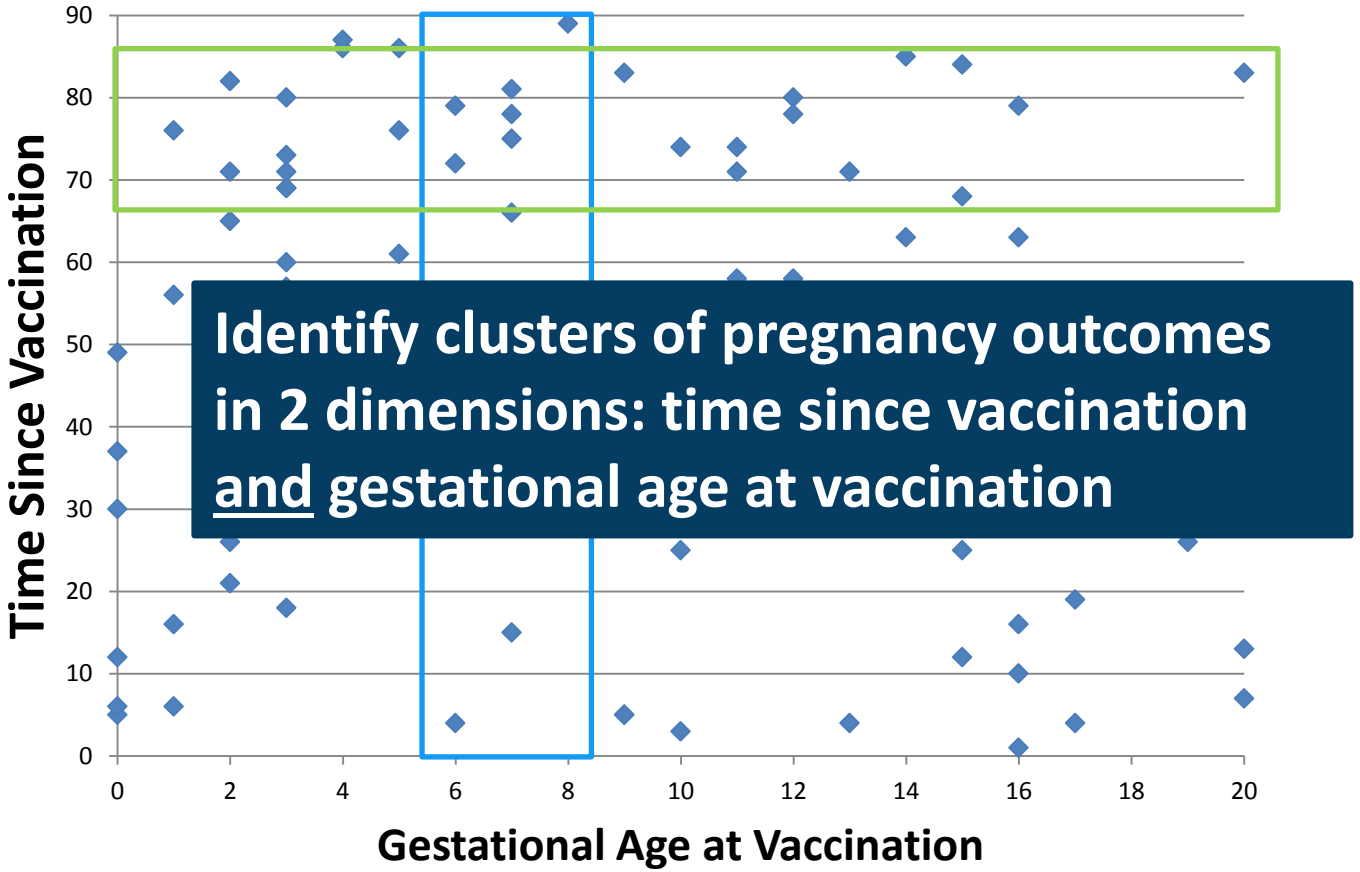
Version 2.1

http://mini-sentinel.org/assessments/medical_events/details.aspx?ID=123

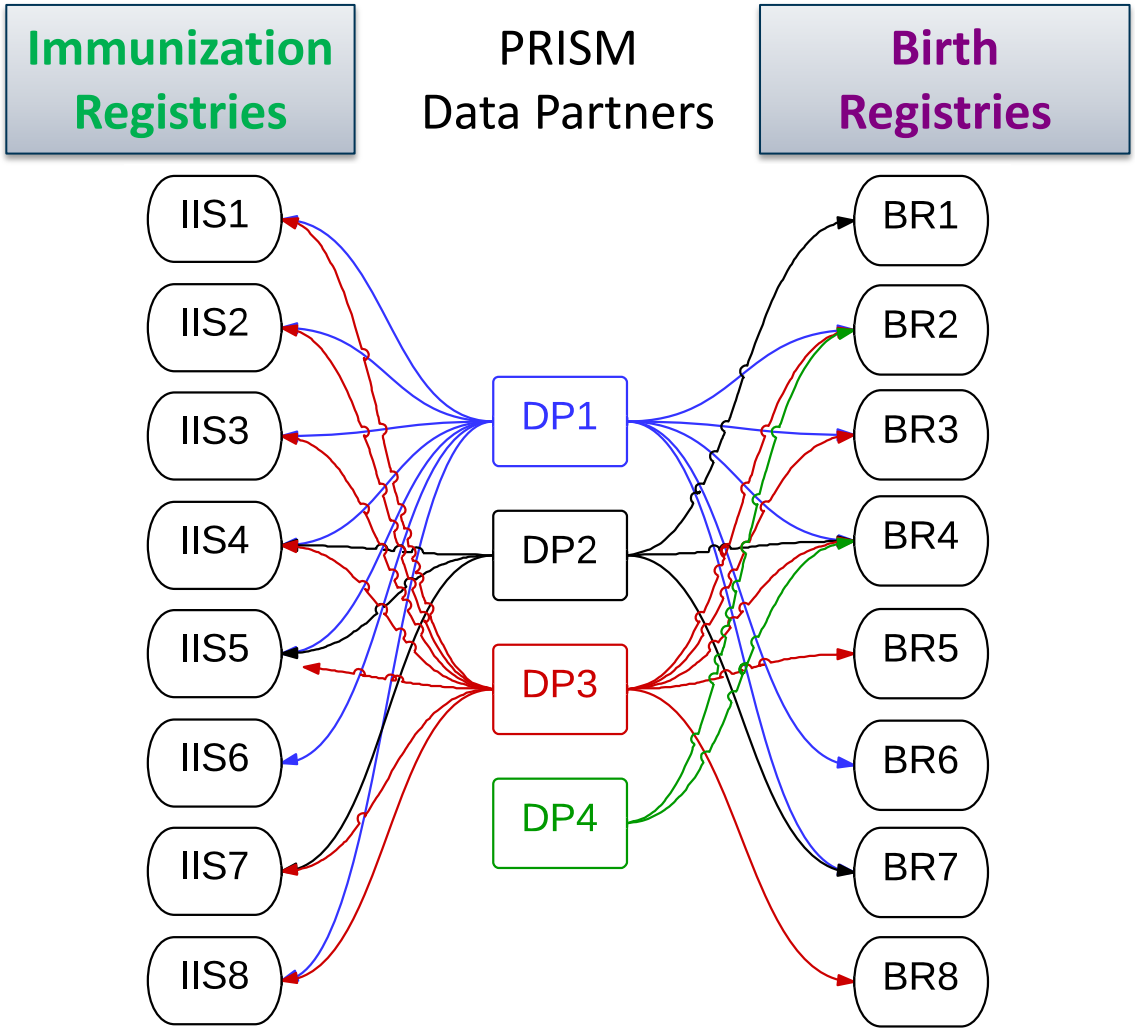
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm201871.htm

Key Time Points

Strengthening Evaluation of Safety of Vaccines Administered During Pregnancy



Enhancing Sentinel Through Data Linkages

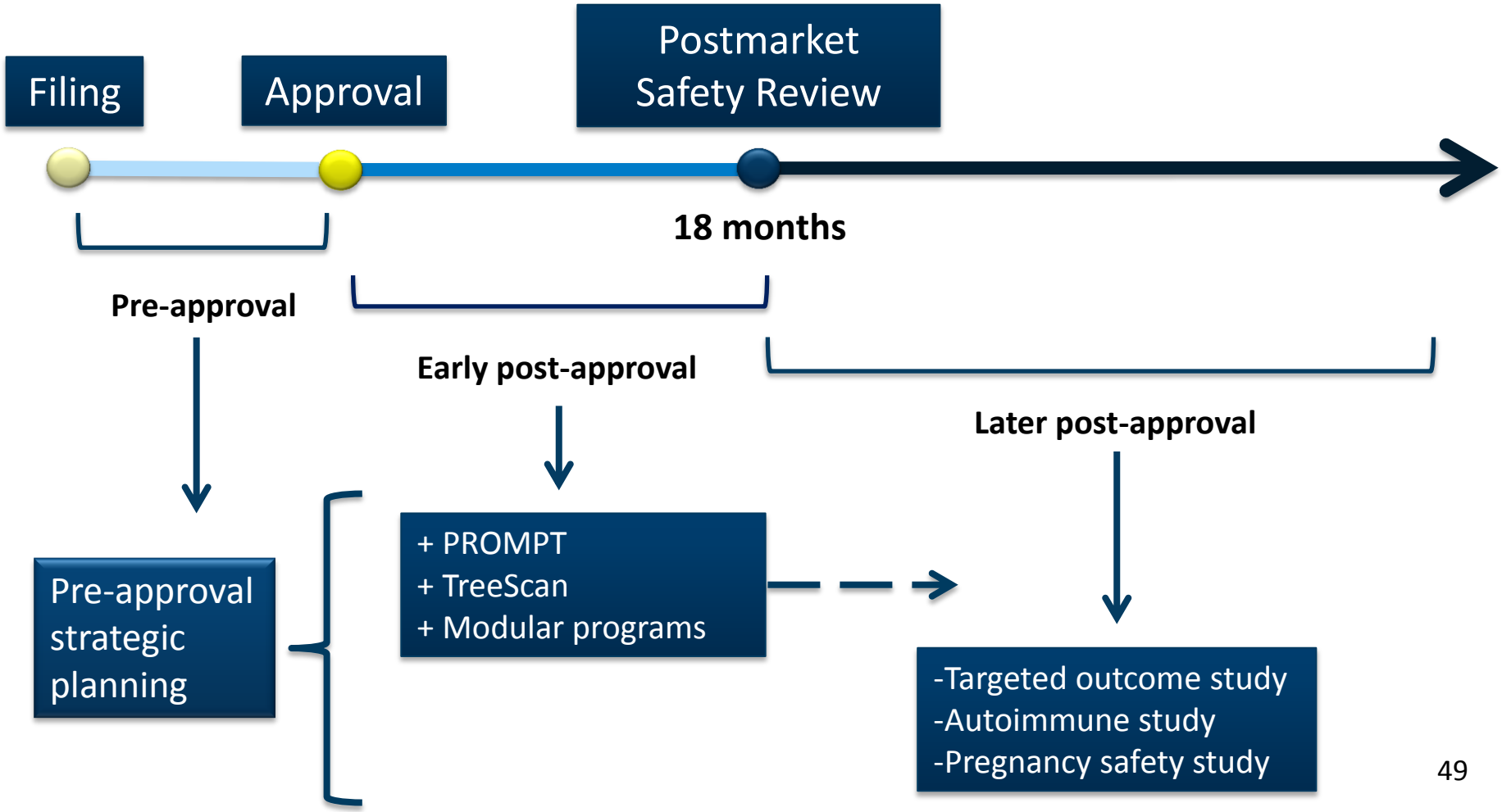


Blood Products and Plasma Protein Therapies

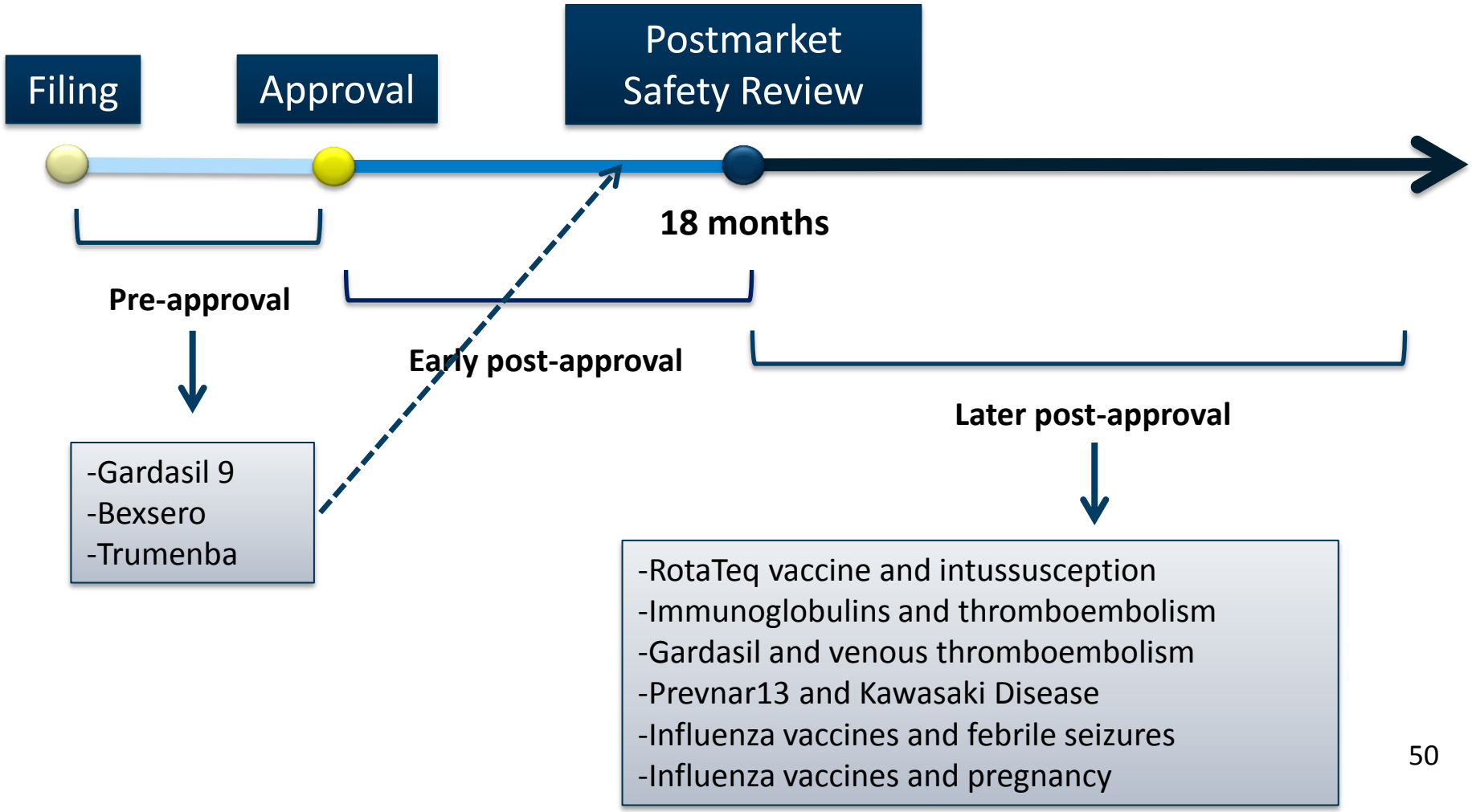
	Surveillance Assessment	Protocol Posting Date	Final Report Posting Date
1	Rotavirus vaccines and intussusception	Posted 10/24/2011	Posted 6/14/2013
2	Gardasil vaccine and venous thromboembolism	Posted 3/30/2012	Spring 2015
3	Influenza vaccines and febrile seizures	Posted 1/25/2013	Posted 5/15/2014
4	Influenza vaccines and birth outcomes	Posted 2/25/2013	Fall 2016
5	Influenza vaccine safety sequential analysis	Posted 8/2/2013	Spring 2015
6	Influenza vaccines and pregnancy outcomes	Posted 9/18/2013	Spring 2016
7	Thromboembolic events after immunoglobulin administration	Posted 9/20/2013	Winter 2017
8	Prevnar 13 vaccine and Kawasaki Disease	Fall 2015	TBA
9	TRALI after platelets, plasma, and red blood cells	Winter 2016	TBA
10	Gardasil vaccine (HPV4) TreeScan pilot (methods development)	Winter 2015	TBA
11	Influenza vaccine and febrile seizures in 4 influenza seasons	Spring 2015	TBA
12	Gardasil 9 general safety study	Fall 2015	TBA
13	Gardasil 9 and pregnancy outcomes	TBA	TBA

http://mini-sentinel.org/assessments/medical_events/details.aspx?ID=188

Developing Tools for Every Need



Impact on CBER Medical Products Thus Far



Summary

- Sentinel integrated into routine postmarket safety regulatory processes
  - Impacts both pre-approval planning and postmarketing phases
  - Developing tools for signal detection, refinement and evaluation
- Majority of CBER projects have two-fold impact:
  - Addresses immediate regulatory concern
  - Builds infrastructure or advances methods for future studies
- Working to apply Sentinel to all classes of CBER-regulated products
  - Vaccines
  - Blood components and plasma protein therapies
  - Human cells, tissues, and cellular and gene therapies

Acknowledgments

- Mini-Sentinel Operations Center
  - Rich Platt, Jeff Brown, Tiffany Woodworth, Roberta Constantine, Nicolas Beaulieu, Grace Lee, Darren Toh, Meghan Baker, Carolyn Balsbaugh, David Cole, Martin Kulldorff, Lingling Li, Diana Santiago, Judy Maro, Katherine Yih, Alison Kawai, Noelle Cocoros, Betsy Chrischilles, Lesley Curtis, Robert Rosofsky, Candace Fuller, Crystal Garcia, Bruce Fireman, Megan Reidy, Catherine Rogers, and many more.
- Center for Biologics Evaluation and Research
  - Karen Midthun, Peter Marks, Barbara Buch, Adrienne Hornatko-Munoz, Sandra Menzies, Diane Maloney, Carolyn Wilson
- Office of Vaccine Research and Review
  - Marion Gruber, Phil Krause, Maureen Hess, Karen Farizo, Wellington Sun, Jeff Roberts, Andrea Hulse
- Office of Blood Research and Review
  - Jay Epstein, Ginette Michaud, Dov Golding, Paul Mintz, Nisha Jain, Alan Williams
- Office of Biostatistics and Epidemiology
  - Steven Anderson, Darren Jansen, Telba Irony, Chris Jankosky, Scott Winiecki, Manette Niu, Rich Forshee, Yun Lu, Estelle Russek-Cohen, John Scott, Lihan Yan, David Martin, Craig Zinderman, Wei Hua, Adamma Mba-Jonas, Bethany Baer, Wambui Chege, Lori Austin-Hansberry, Garrette Martin-Yeboah, Jaqueline Johnson, David Menschik, Meghna Alimchandani, Firoozeh Alvandi, Deepa Arya, Faith Barash, Jane Baumblatt, Marthe Bryant, Bridget Davis, Ravi Goud, Wendy Paul, Laura Polakowski, Yandong Qiang, Patricia Rohan, Jane Woo.
- Office of Cellular, Tissue and Gene Therapies
  - Celia Witten, Wilson Bryan, Ke Liu, Ellen Lazarus, Uros Djekic, Ilan Irony
- Center for Drug Evaluation and Research
  - Melissa Robb, Aaron Niman, Carlos Bell, Patrick Archdeacon, Azadeh Shoabi, Marsha Reichman

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Joseph P. Drozda, Director of Outcomes Research, Mercy Health

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Sentinel and Medical Devices

Challenges:

- **Lack of device identifiers (no NDCs)**
- **Thousands of devices (band-aids to LVADs)**
- **For implanted devices: operator/patient/device paradigm**
- **Claims are a poor data source**
  - No link between patient and particular device
- **Need to capture key device attributes**

Mercy

Sentinel and Medical Devices

Path forward:

- **Wide implementation of UDI (EHRs, registries, claims)**
- **Link to device registries where they exist**
- **Link to supply chain/EHR-derived data (primary data source**
- **Grow the number of clinical data partners**
  - Small numbers of implants relative to medications
- **Pilot new approaches**
- **Link with MDEpiNet and National Postmarket Medical Device Surveillance System Planning Board**

MercyIT

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Myrl Weinberg, Chief Executive Officer, National Health Council

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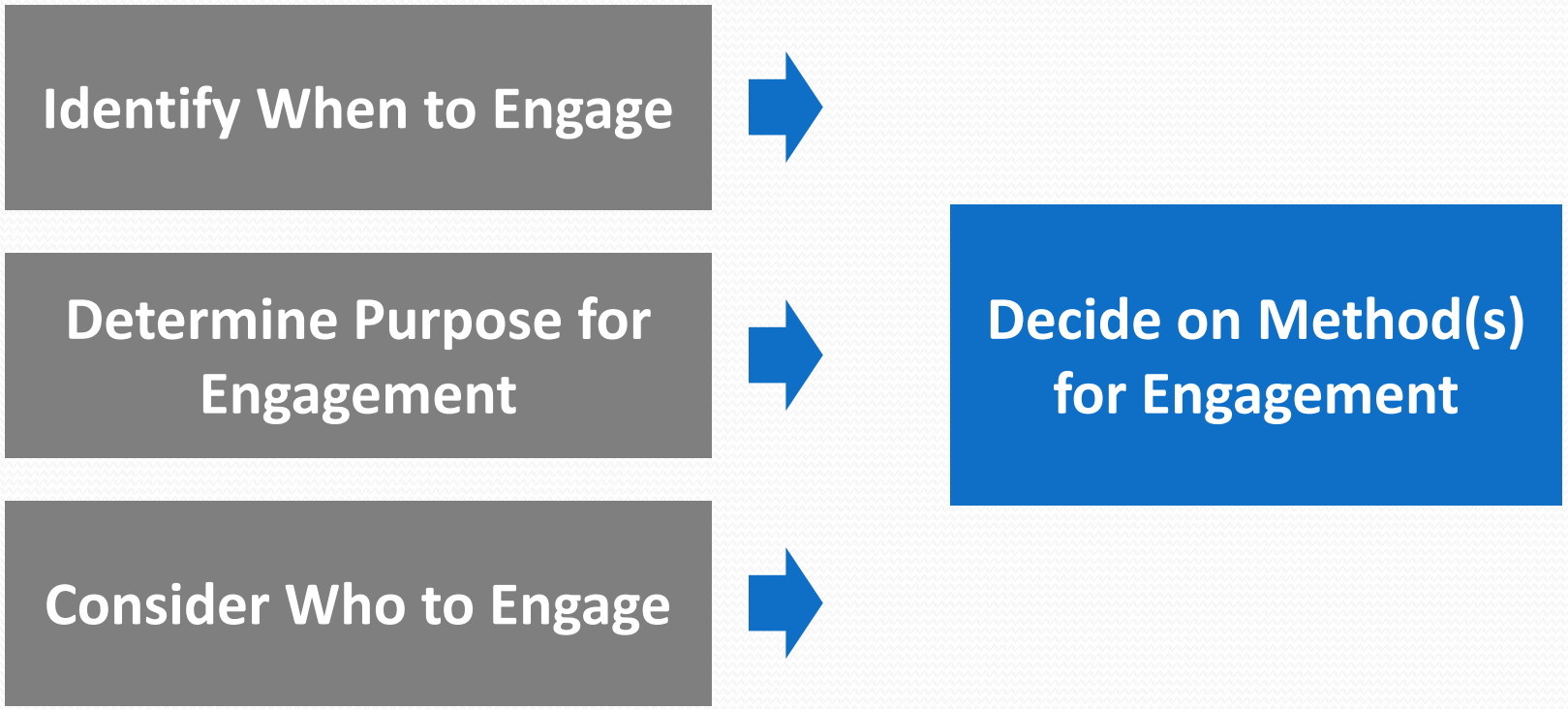
Identify Promising Patient Engagement Methods



Methods for Engaging Patients in Drug Development

Existing methods for engaging individuals can be leveraged and applied to the drug development space.

Identify When to Engage

Examples:

- Developing research questions
- Supporting drug discovery
- Guiding non-clinical development
- Informing clinical development

Determine Purpose for Engagement

Examples:

- Better understand disease and disease impact
- Gather information on unmet needs
- Help formulate research question
- Elicit patient preferences
- Propose approaches for recruitment, participation, and retention
- Provide input on trial design
- Serve as peer advocate
- Convey patient feedback

Consider Who to Engage

Examples:

- Patients
- Caregivers
- Patient Advocates

Decide on Method(s) for Engagement

Examples:

- Interviews
- Public Comment
- Surveys
- Focus Groups
- Deliberative Juries
- Open Forums
- Workshops/Working Groups
- Advisory Panel/Board Participation
- Crowdsourcing
- Market Research

Other Considerations for Selecting Methods:

- Number of participants
- Frequency of engagements
- Preferred format of engagements

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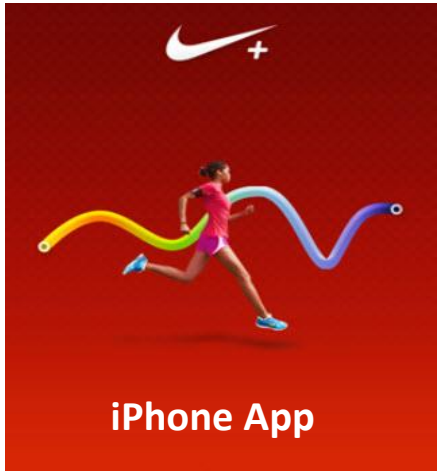
Patient Engagement: Is it time to marry?

What do personal data collection tools look like in 2014?

iPhone App
daily burn

Microsoft HealthVault

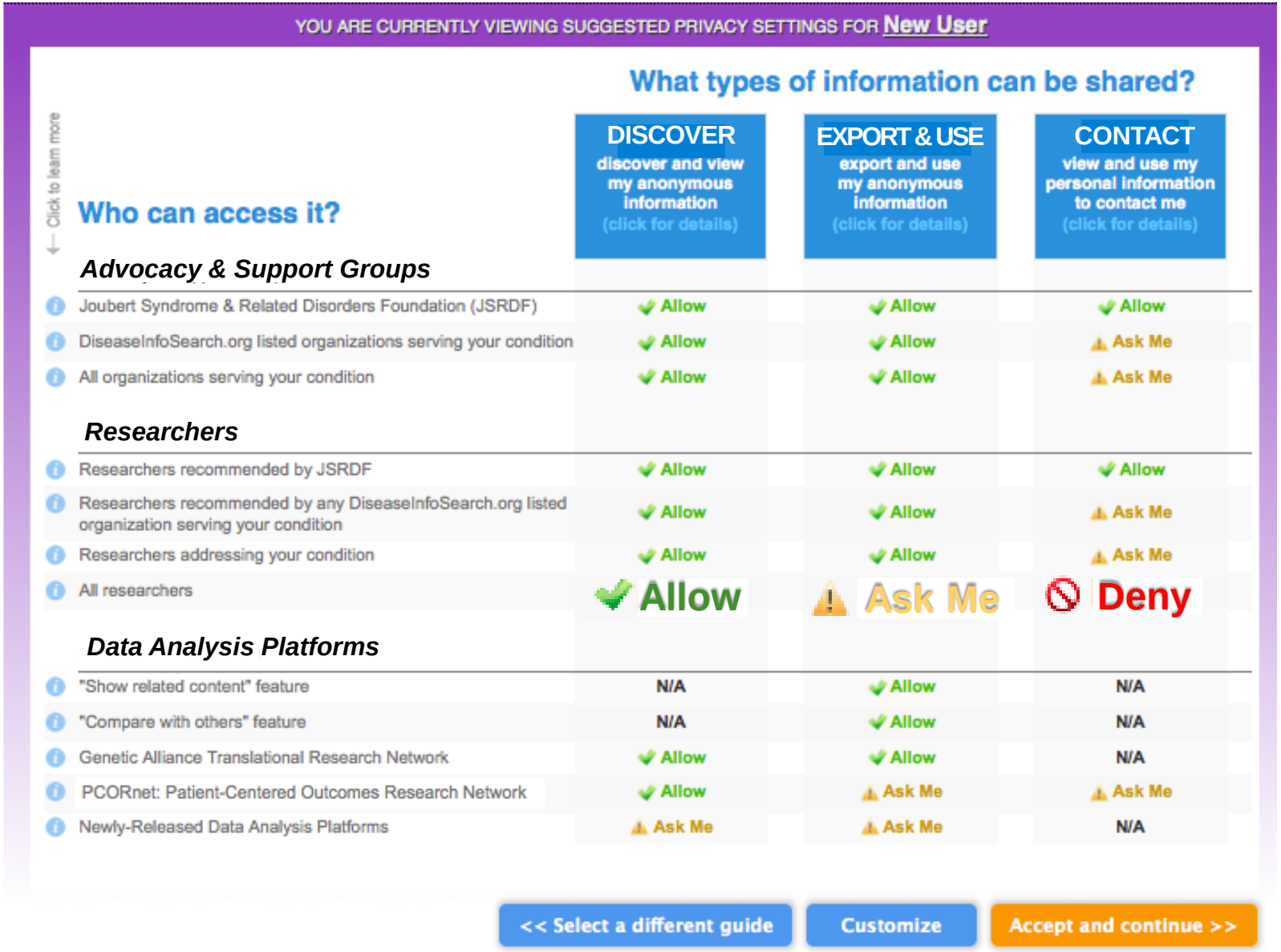


Twitter
Facebook

Wi Fi

iMapMyRUN+ iMapMyRIDE+ iMapMyWALK iMapMyFITNESS iMapMyHIKE

Participants establish their own sharing preferences based on simple "stop-light" metaphor – Allow, Deny or Ask Me

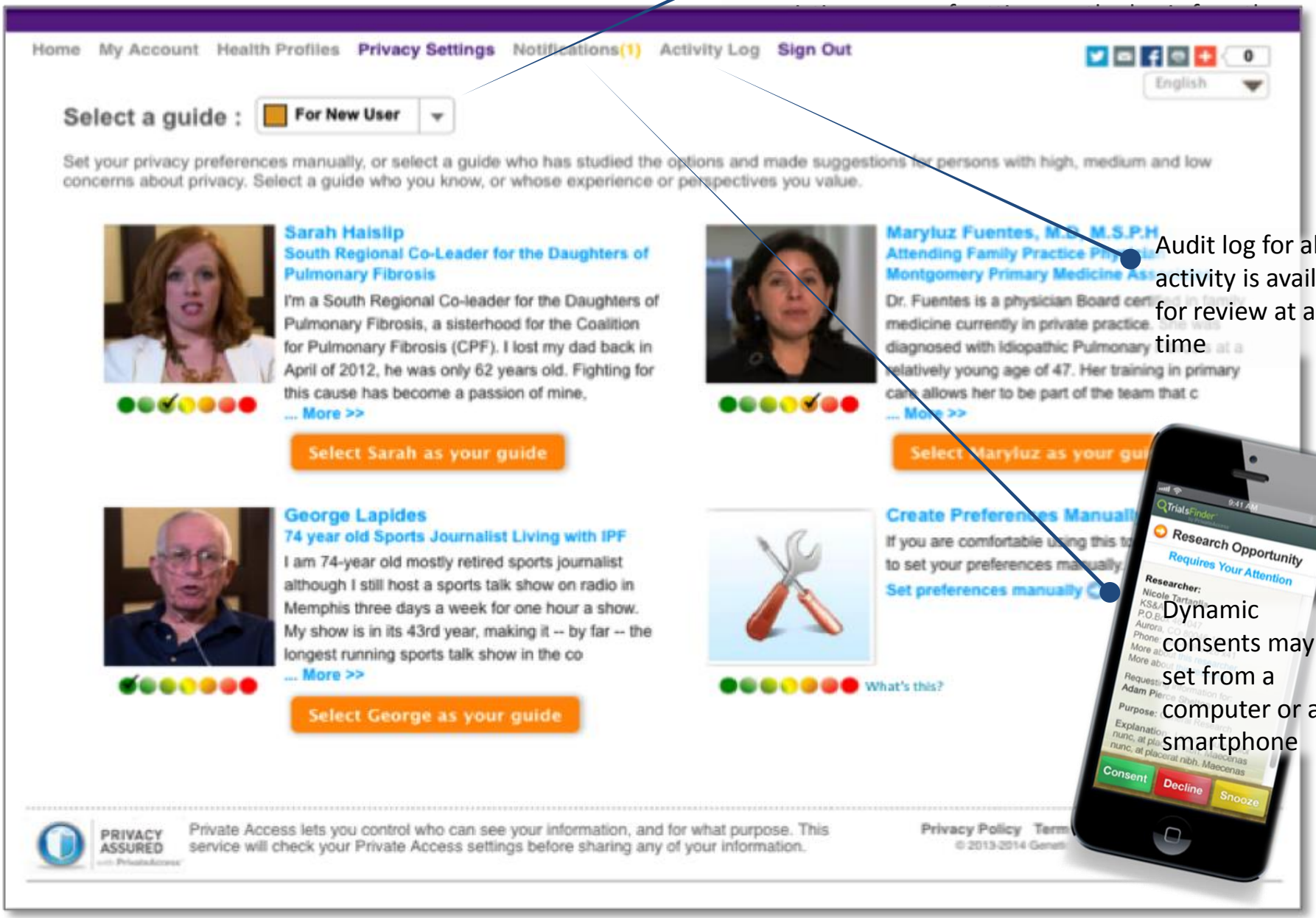


“Guides” Help Participants Decide Upon Permissions

User can set for each member of her family, or use

Audit log for all activity is available for review at any time

Dynamic consents may be set from a computer or a smartphone



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Robert F. Reynolds, Vice President,
Epidemiology in Worldwide Safety, Pfizer, Inc.

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An Industry Perspective

- Mini-Sentinel and the paradigm shift in safety
  - Impressive progress in creating an enduring surveillance tool
    - Technical and methodological success are significant
    - Provides an additional line of evidence in benefit –risk assessment
- A fully operational Sentinel – what next?
  - More, more and more data
    - Claims, EHRs, Unstructured data, Registries (e.g., NDI, birth, cancer, disease or therapy specific)
  - Evaluate capability to measure the effectiveness of risk minimization actions
  - Assess potential value for prospective, 'hypothesis-free' signal detection
- Partnering to advance Sentinel
  - Learning from, and contributing to, other initiatives globally
  - Sentinel as a national resource
    - Reagan Udall Foundation's IMEDS program

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Innovation in Medical Evidence Development and Surveillance (IMEDS)

Troy McCall, Chief Implementation Officer, IMEDS, Reagan-Udall Foundation for the FDA

February 5, 2015

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IMEDS Program

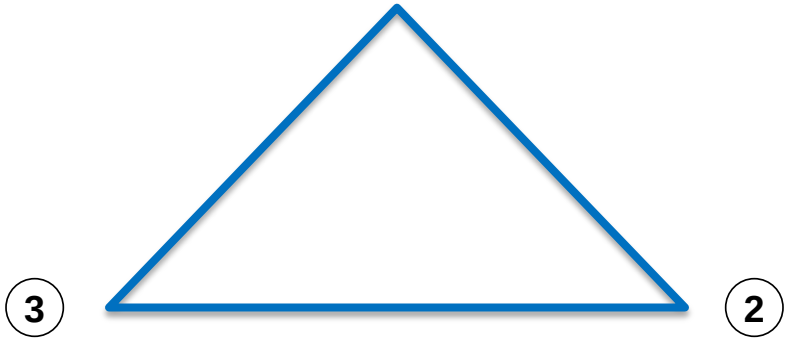
Key Areas

IMEDS will help the FDA, regulated industry, and clinicians improve patient care and the safety of medical products by focusing on three areas.

IMEDS-Methods

Facilitate methods research aimed at monitoring safety of marketed medical products.

1



3

2

IMEDS-Evaluation

Use research findings to help understand the risks and benefits of marketed medical products.

IMEDS-Education

Train scientists in how to conduct methods research using electronic healthcare data.

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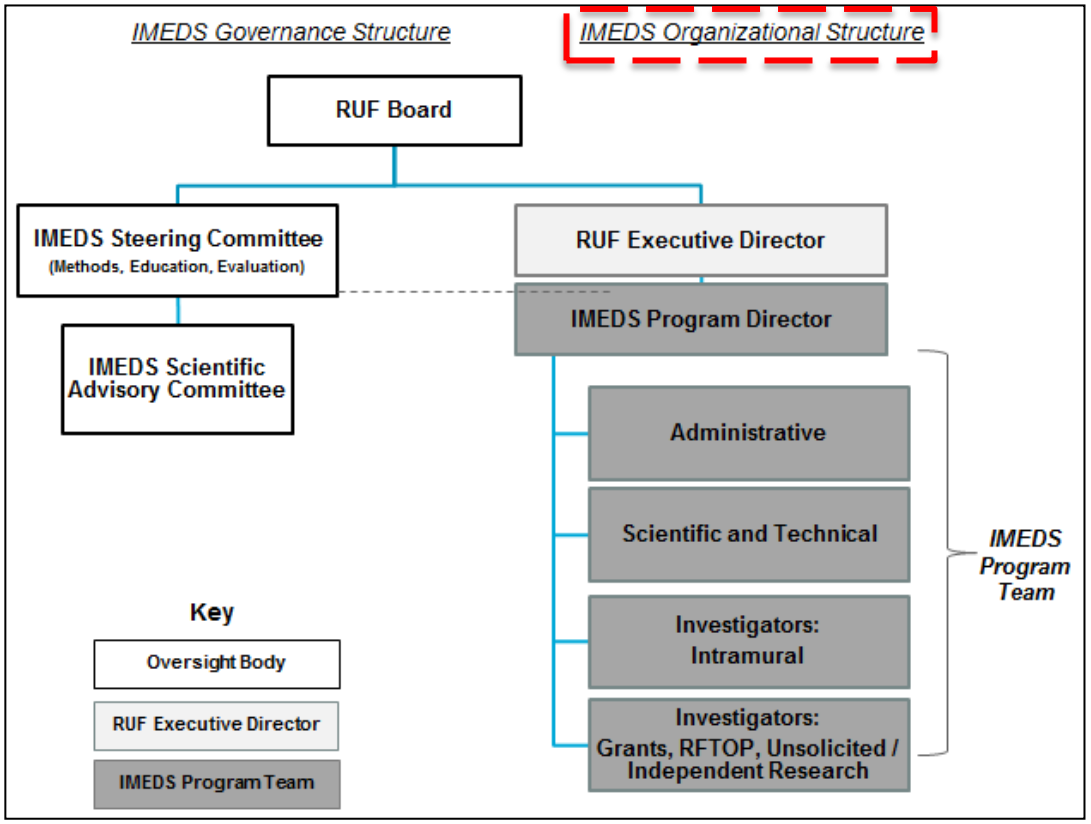
IMEDS Governance

IMEDS Key Features (as outlined in IMEDS Charter)



- **RUF Executive Director**: hires IMEDS Program Director; ensures alignment between RUF and IMEDS missions
- **IMEDS Program Director**: day-to-day oversight of IMEDS activities; manages creation of IMEDS Research Agenda and completion of research
- **Administrative:** support the IMEDS Program Director in project and contract management for all IMEDS investigators and contractors
- **Scientific and Technical:** provide support and expertise regarding the IMEDS Data Lab and its associated features
- **Investigators:** complete IMEDS research (as assigned by IMEDS Program Director); evaluate research proposals and work products

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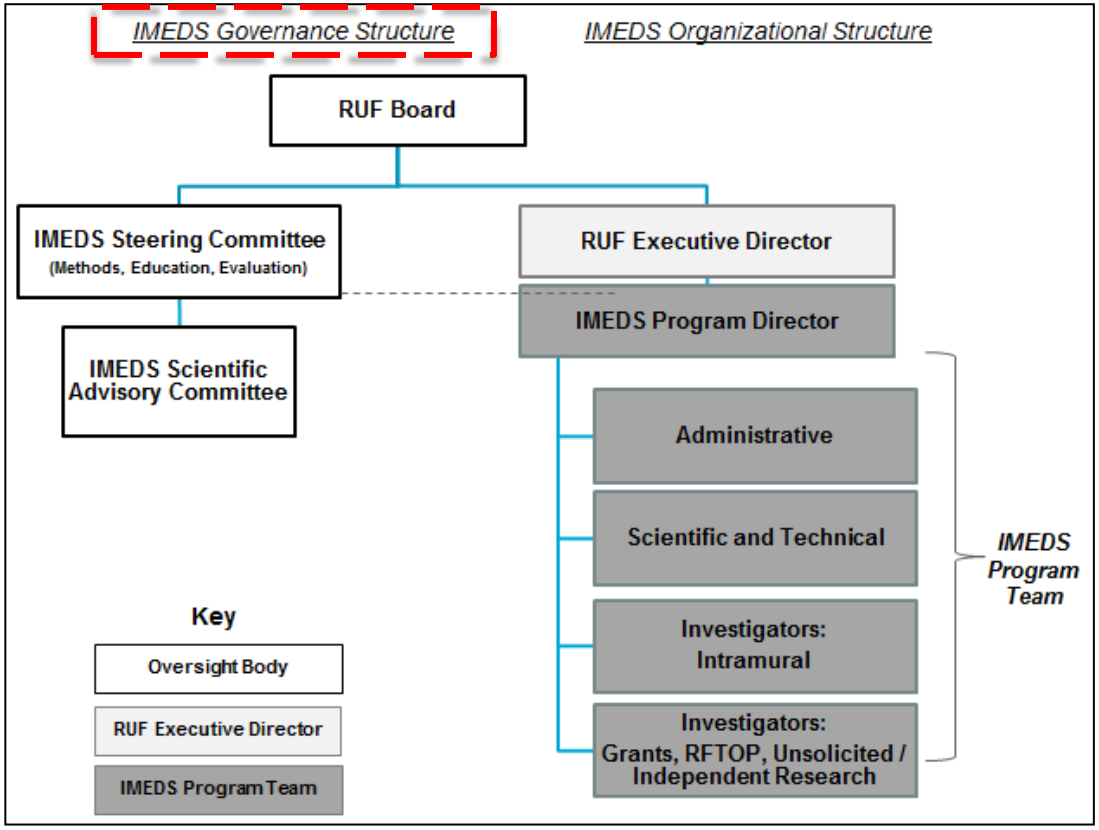
IMEDS Governance

IMEDS Key Features (as outlined in IMEDS Charter)



- **RUF Board**: selects IMEDS Steering Committee members; reviews and approves IMEDS partnerships, budget; evaluates effectiveness of IMEDS; assists with IMEDS fundraising
- **IMEDS Steering Committee**: reviews and approves IMEDS Research Agenda; provides guidance on IMEDS partnerships, external communications; selects IMEDS-Methods Scientific Advisory Committee members
- **IMEDS Scientific Advisory Committee:** provides input on IMEDS Research Agenda, research proposals and protocol

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IMEDS-Evaluation

Background

- FDA's vision for Sentinel includes leveraging the tools and system capabilities for broader public health and safety uses by stakeholders other than FDA.

- The goal for IMEDS-Evaluation is to apply lessons learned from IMEDS-Methods and the tools, capabilities used by Sentinel, to enable non-FDA entities (such as Industry) to sponsor safety assessments of marketed medical products.
  - Assessments would be completed in partnership with and using the "IMEDS distributed database" and facilitated by an IMEDS operations center.
  - The IMEDS Distributed Database is intended to describe a partnership between MS Data Partners and RUF whereby data partners agree to partner with RUF on a voluntary basis to complete work (either through IMEDS-Methods or IMEDS-Evaluation) using the MS CDM and associated tools using the distributed approach.

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Rachael L. Fleurence, Program Director, Comparative Effectiveness Research methods & Infrastructure, Patient-Centered Outcomes Research Institute (PCORI)

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PCORnet: the Patient-Centered Research Network

Rachael Fleurence, PhD

Program Director, CER Methods and Infrastructure Program,

Patient-Centered Outcomes Research Institute (PCORI)

February 5, 2015

pcornet

The National Patient-Centered Clinical Research Network

Vision for PCORnet

PCORnet will enable rapid, large-scale, patient-centered clinical research in real-world care delivery systems and communities.

"Research *Infrastructure* Done Differently"

pcornet

PCORnet Phase 1 Aim (18 Months)

PCORnet will bring together the expertise, populations, resources, and data of its participating organizations to create a national infrastructure that enables more efficient, patient-centered research.

Hallmarks of PCORnet's success will include:

1. Highly **engaged** patients, clinicians, health systems, researchers and other partners
2. A **collaborative community** supported by robust governance
3. Analysis-ready **standardized data** with strong privacy protections
4. Oversight that **protects patients**, supports the timely conduct of research, and builds trust in the research enterprise
5. Research that is **sustainably integrated** into care settings and with communities of patients

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Pivotal $100M Infrastructure Investment

11 Clinical Data Research Networks (CDRNs)

System-based networks, such as integrated delivery systems, academic medical centers, federally qualified health centers,

18 Patient-Powered Research Networks (PPRNs)

Patients with a condition in common form a research network, often in collaboration with academic researchers

Coordinating Center

Provides technical and logistical assistance under the direction of a steering committee and PCORI program staff

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Complementary and synergistic capabilities in the two types of networks

Winter 2015: Coming Into View

The world's first network infrastructure to:

- Be based primarily on **EHR data**, rather than claims data
- Support both large **observational studies** and embedded **randomized clinical trials**
- Involve **patients, clinicians, and health systems** leaders in governance and use of the network

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Coming Into View – Funded PCORnet Demonstration Projects

- **ASA for Secondary Prevention** – an RCT comparing two doses of aspirin in patients with CAD
- **CER in the Weight Cohort** – one or two large observational studies
- **Rapid-Cycle Research** with health systems and health plans – multi-system comparative research on systems improvement

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PCORnet Phase I: 2014 – 2015

2014

Jan
- ▶ Phase I Kick-Off, Washington DC

Mar

May
- ▶ Common Data Model version 1.0 Released
- ▶ PCORnet Patient Council Announced
- ▶ Patient Data and Privacy Roundtable

July
- ▶ Aspirin Clinical Trial Topic Approved by Board of Governors
- ▶ 1st Draft Governance Policies Under Review
- ▶ Aspirin Clinical Trial Process Communicated to Networks

Sep
- ▶ Test Queries Performed by the PCORnet Coordinating Center
- ▶ Network 6-month Evaluations by PCORI begin
- ▶ Phase II Pre-announcement Released

Dec
- ▶ Phase II RFP Released

2015

Jan
- ▶ Aspirin Clinical Trial Applications Due

Apr
- ▶ Aspirin Clinical Trial Recruitment Begins

May
- ▶ Observational Weight Cohort Study Begins

July

Sep

Nov
- ▶ Phase II Begins

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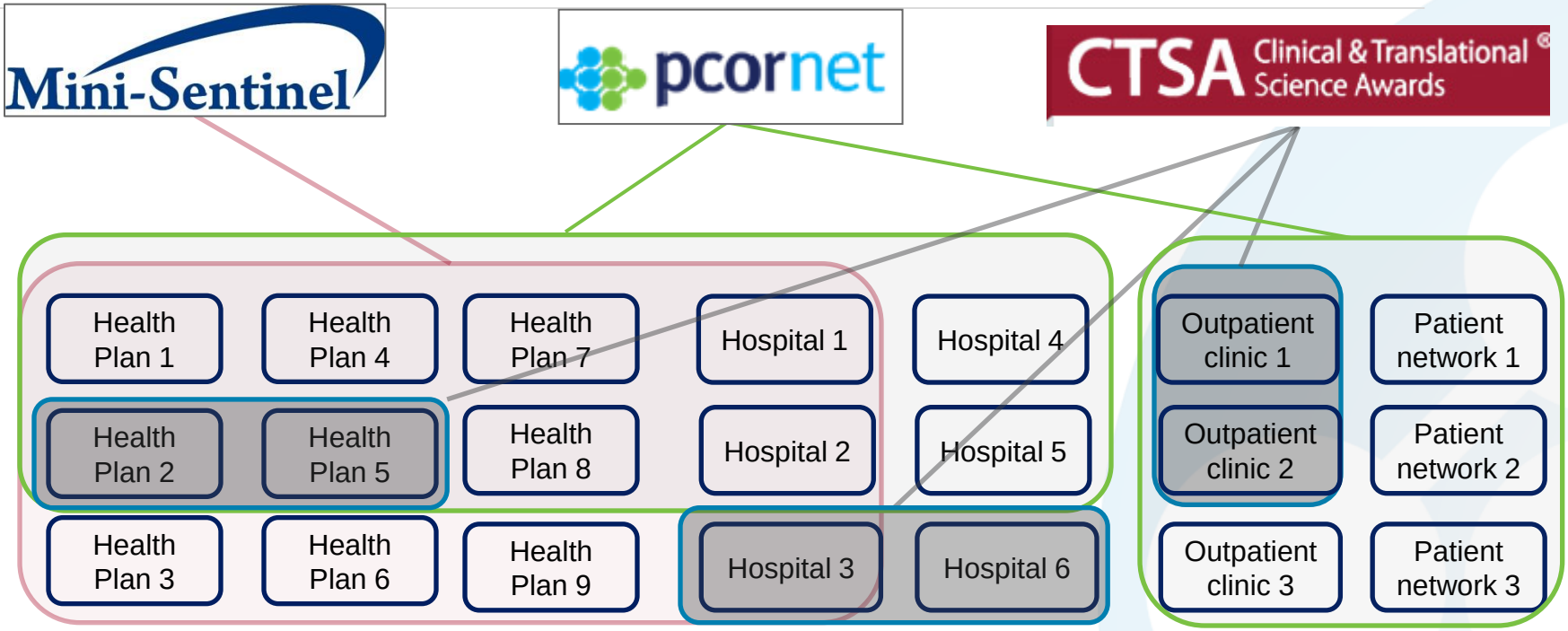
Slide credit: Rich Platt

Critical Partners in a National 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
- Other potential partners: disease or treatment-specific networks; :

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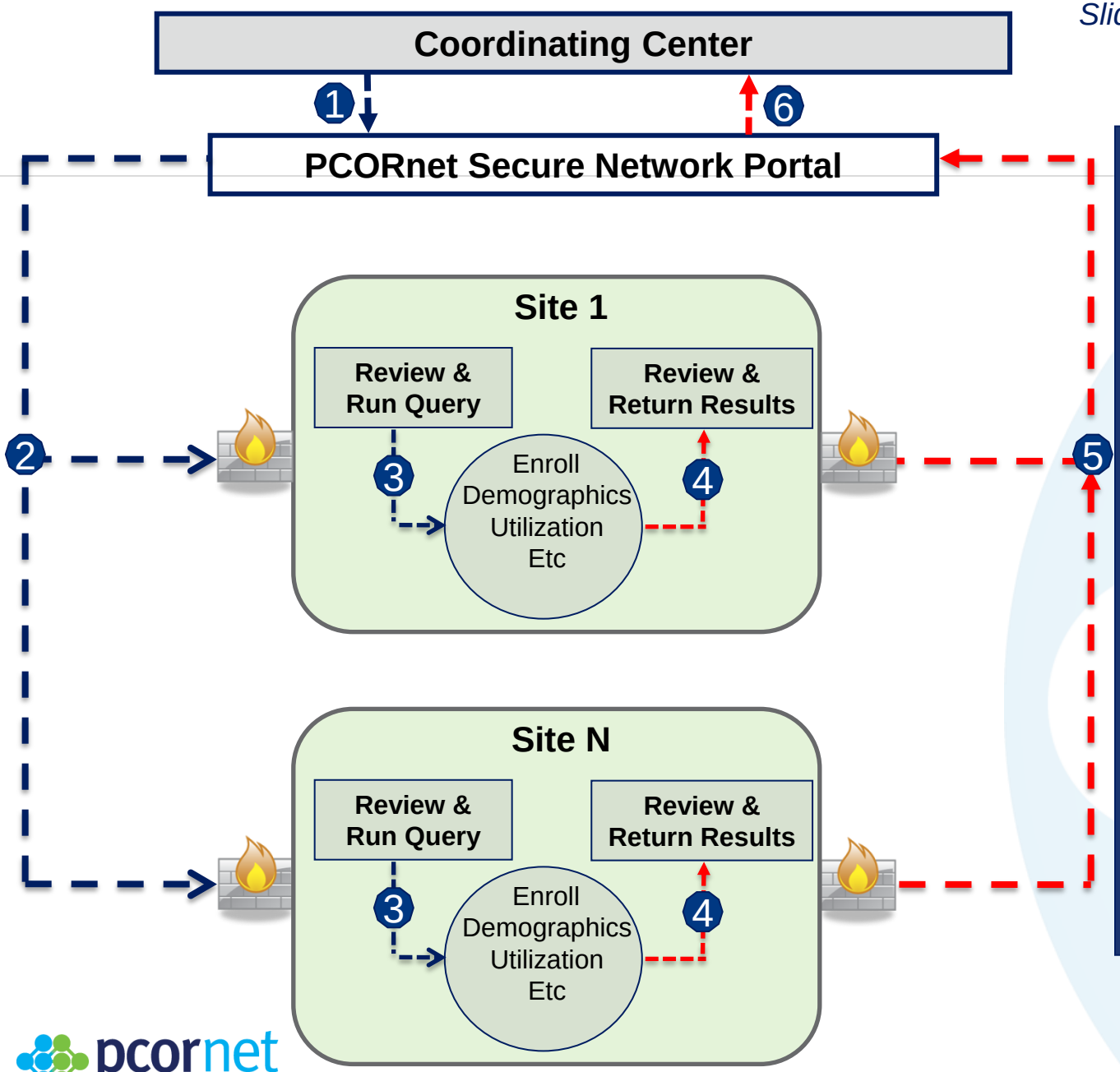
Slide credit: Rich Platt



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

2. Individual sites retrieve query

3. Sites review and run query against their local data

4. Sites review results

5. Sites return results via secure network

6. Results are aggregated

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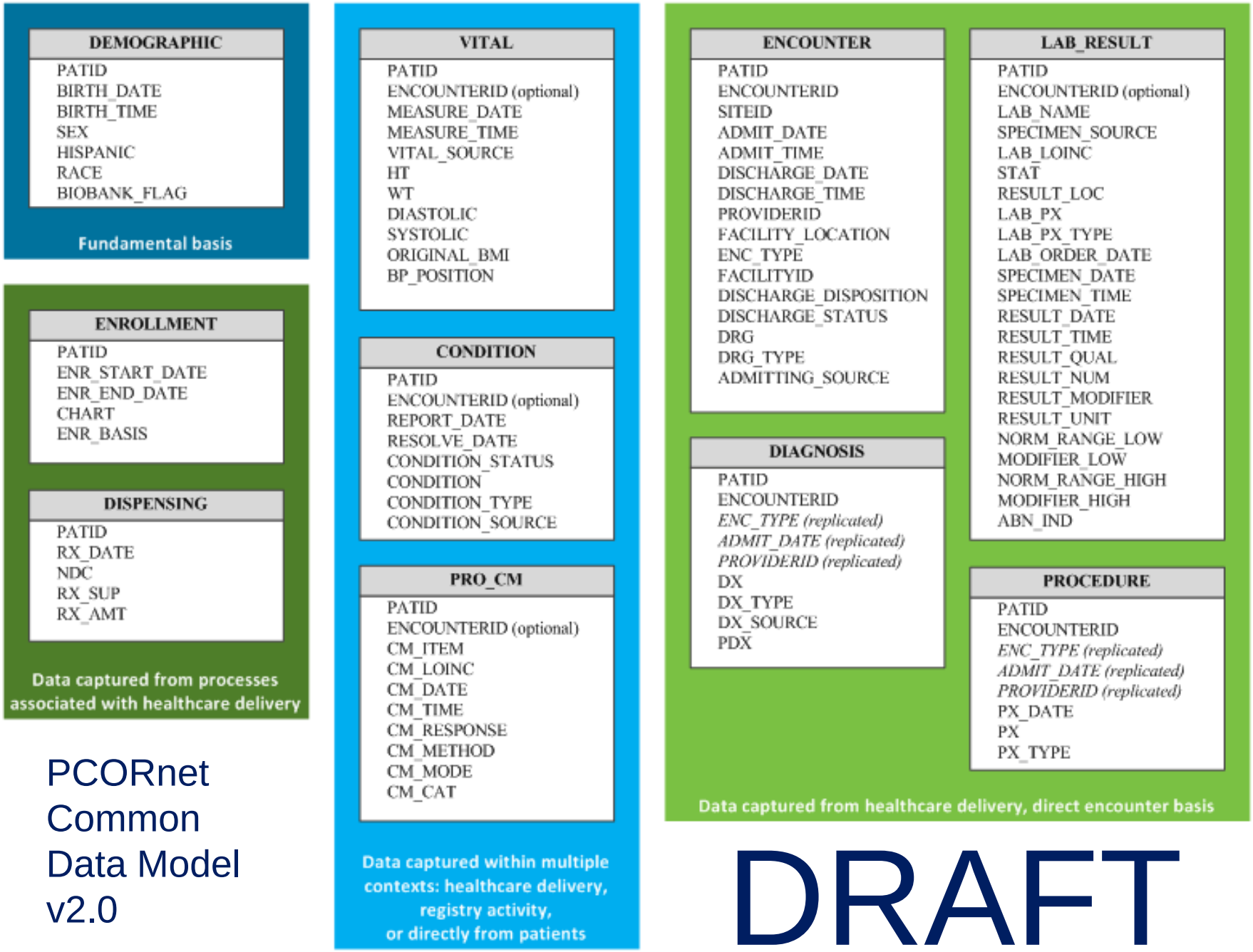
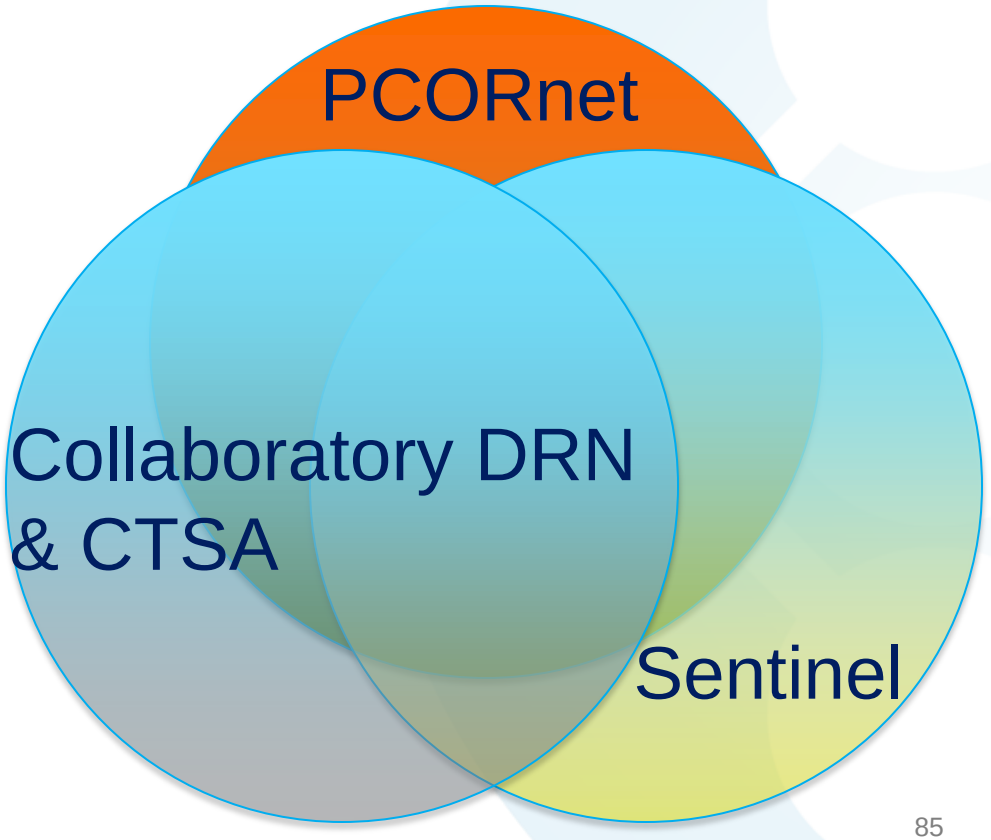


PCORnet Common Data Model v2.0

DRAFT

Multiple initiatives should share resources

- Maintaining analysis ready data
- Performing quality assessment
- Developing program libraries
- IRB reliance and contracting agreements
- Centralized consent and followup functions



Slide credit: Rich Platt

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Current Sentinel-PCORnet collaborations

- Important opportunities to leverage the **Sentinel** investment and infrastructure with the **PCORnet** infrastructure
- The PCORnet **Coordinating Center** is helping identify and leverage the **touch points** as the **PCORnet** data infrastructure is being set up
- **11 PCORnet CDRNs** have agreed to participate in Sentinel
- The PCORnet **Coordinating Center** is helping broker discussions between interested **CDRNs and PPRNs and Sentinel partners** to explore beneficial data linkages

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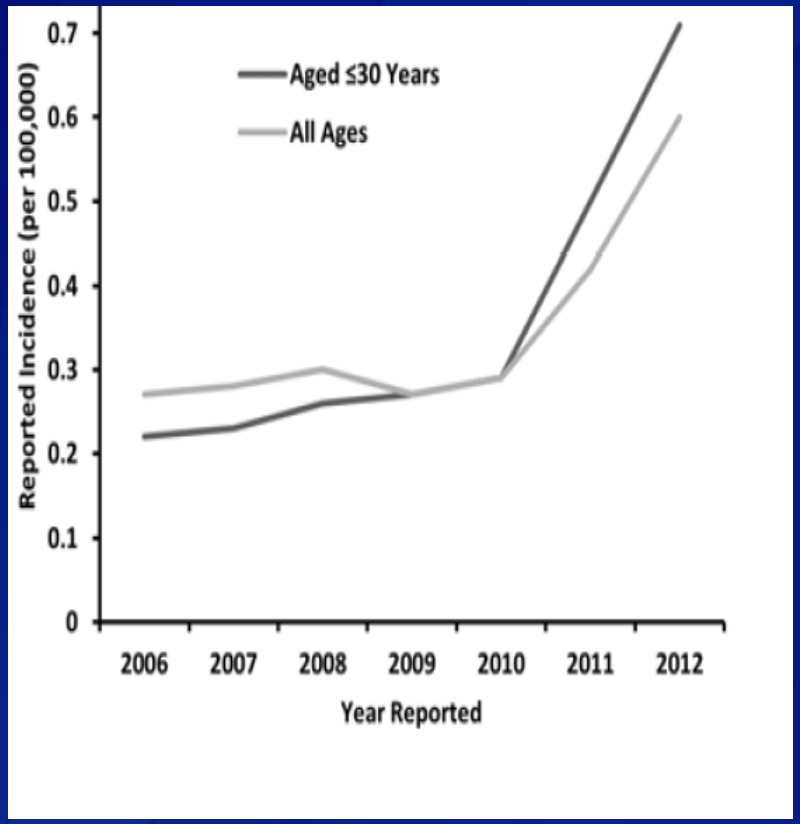
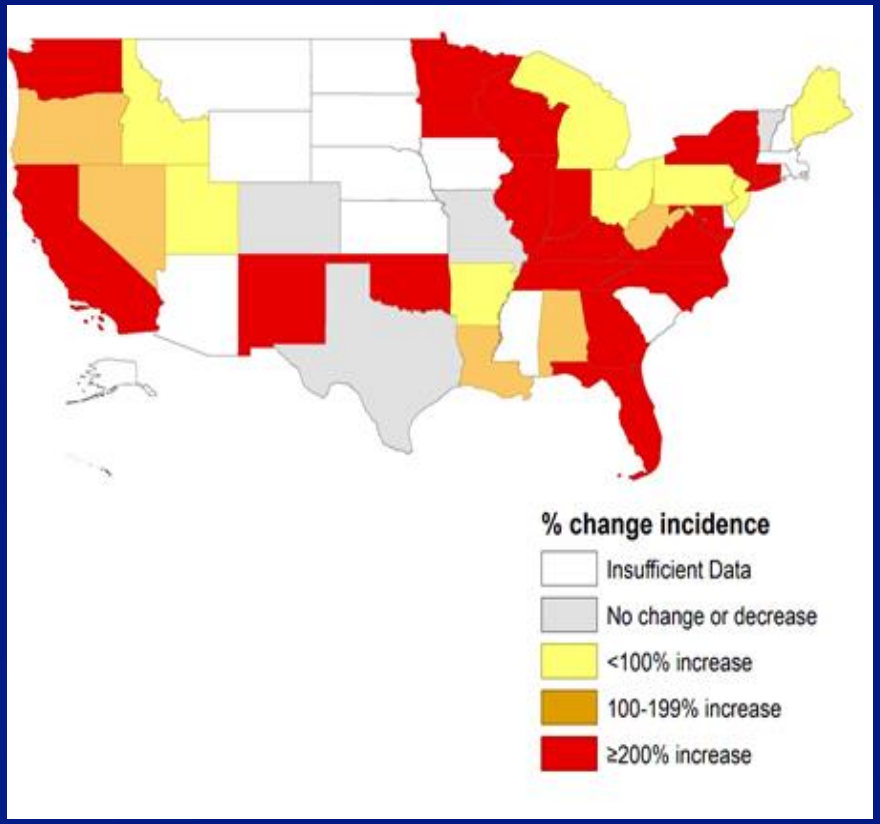
Using Sentinel for Public Health Surveillance: Hepatitis C Virus (HCV) Infection

Claudia Vellozzi, MD, MPH
Chief, Prevention Branch
Division of Viral Hepatitis
Centers for Disease Control and Prevention

Division of Viral Hepatitis

National Acute HCV Cases (2006—2013)





30 states reported increases between 2007 and 2012
15 states had > 200% increase
50% of cases < age 30 years

Suryaprasad et al., 2014, *Clin Infect Dis*

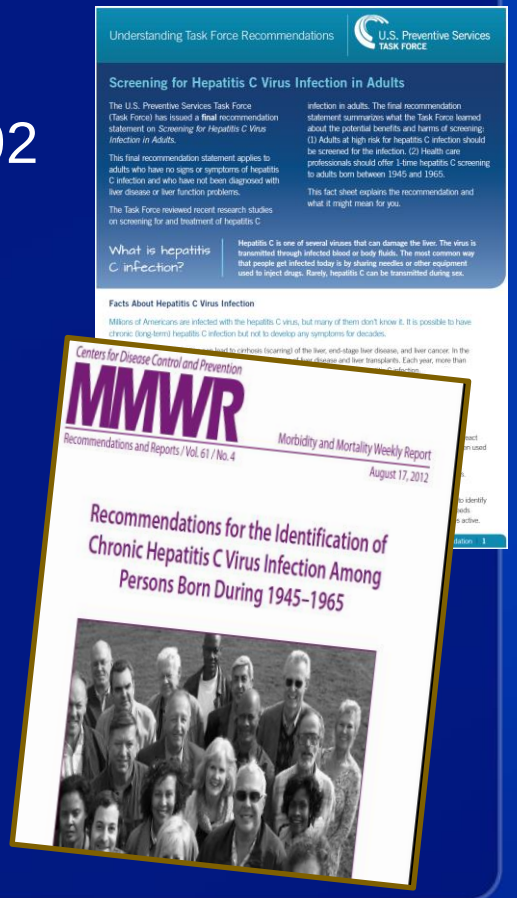
Chronic Hepatitis C Virus (HCV) Infection in the U.S.

- **3.2 million Americans living with HCV infection**
  - ~ 75% are Americans born between 1945 and 1965
- **Leading cause of chronic liver disease and hepatocellular carcinoma**
- **Deaths from chronic HCV infection increasing and exceed deaths due to HIV infection**
- **New treatments can cure > 90% of HCV infection**

MMWR 61(RR04) Aug 2012; Rosen Hr. NEJM 2011; Ly KN. Ann Intern Med; AASLD_IDSA www.hcvguidelines.org 2014

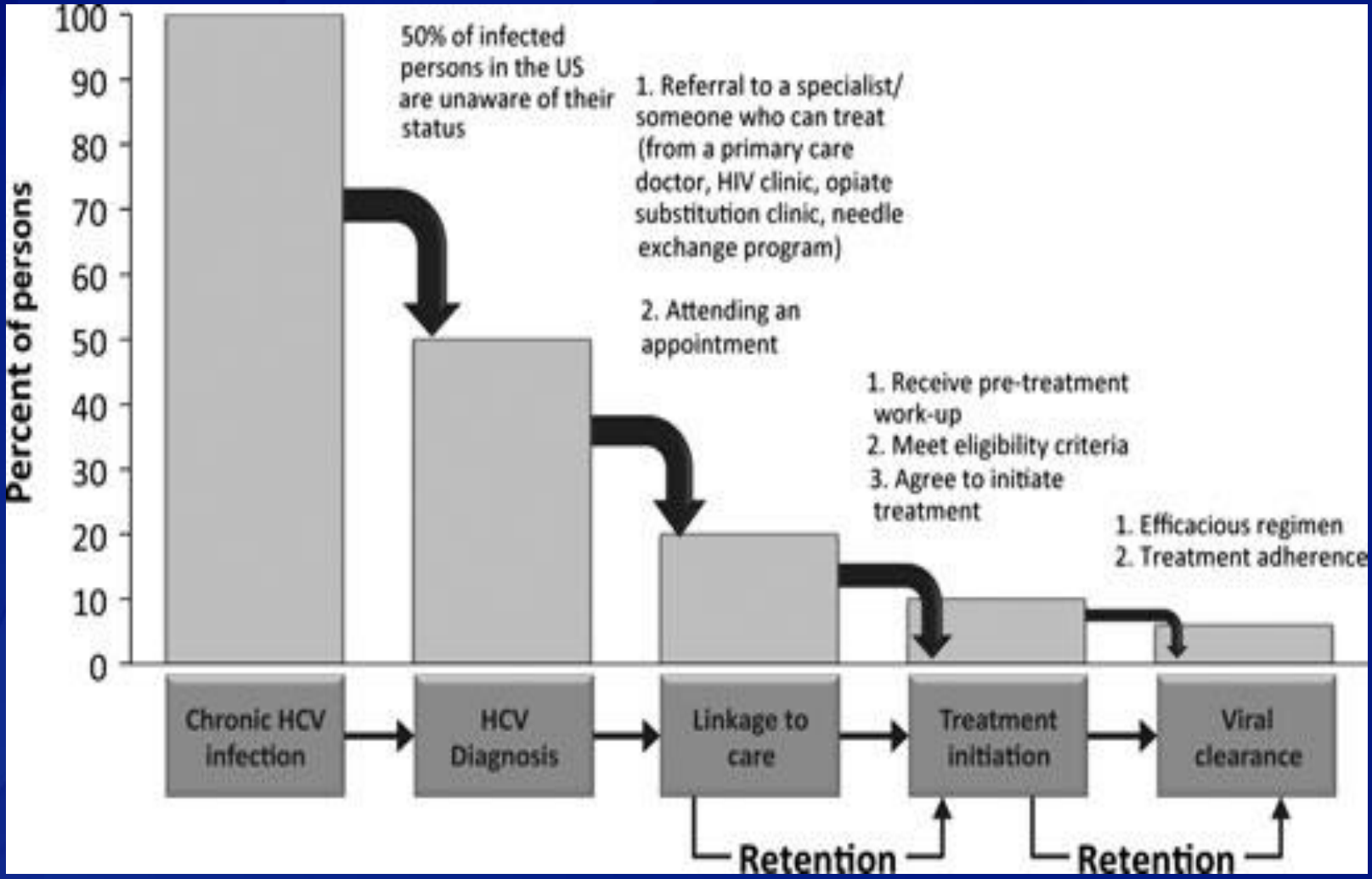
CDC and USPSTF Recommendations for HCV Testing

- **One time screening test for persons born 1945-1965**
  - **Past or present injection drug use**
- **Other risks including**
  - Received blood/organs prior to June 1992
  - Ever on chronic hemodialysis
  - Infants born to HCV infected mothers
  - History of incarceration
  - Persons with HIV



MMWR Sept 2008; MMWR Aug 2012.
Moyer VA, *Ann Int Med* 2013. http://www.hcvguidelines.org

Hepatitis C Care Cascade*



*Afdhal NH. The new paradigm of hepatitis C therapy: integration oral therapies into best practices. J of Viral Hepatitis. 2013

Core Questions for Monitoring Hepatitis C Infection Testing and Care

PH Question	Measure	Data Elements	
What are the trends in HCV testing among the target populations?	Proportion of target populations tested by year	Lab: HCV antibody	
How many people diagnosed and aware?	Proportion of HCV antibody positive persons receiving confirmatory testing	Lab: HCV RNA	
How many people diagnosed with HCV infection are in care?	Proportion of HCV infected persons receiving care	• Subspecialty care	• Lab: HCV Genotype, Liver enzymes, platelets • Liver imaging • ICD9/10 codes* • Subpopulation characteristics**
How many people diagnosed with HCV infection initiate treatment? by subpopulation? By genotype? by stage of liver disease?	Proportion of HCV infected persons on treatment	Prescriptions filled (ex Sofosbuvir)	
How many people with HCV infection were cured (SVR)? By subpopulation? By genotype? by stage of liver disease?	Proportion of HCV infected persons cured	RNA: • baseline • 3-4 weeks into treatment • End of treatment (ETR) • 12 weeks post ETR	

*Chronic hepatitis C +/- fibrosis or cirrhosis
**SES, insurance type, risk group, geo, other

Multitude of Potential Uses for Sentinel and HCV infection Testing, Care and Health Outcomes (Examples)

- **Identify barriers in the care continuum**
  - Predictors of underperformance
  - Disparities in access
- **Assess liver disease following SVR**
  - Proportion of regression/progression by stage at diagnosis
- **Assess other co-morbidities potentially associated with chronic hepatitis C infection**
  - Depression, chronic fatigue, fibromyalgia
  - Self-controlled analyses to assess pre-post treatment
- **Assess adverse events of antivirals**
- **Assess re-infection/relapse**

ENGELBERG CENTER for
Health Care Reform
at BROOKINGS

Sentinel Initiative Public Workshop

Washington Plaza Hotel • Washington, DC
Thursday, February 5, 2015