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

Update and Focus on Communications

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for the Mini-Sentinel Investigators

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Mini-Sentinel

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

Mini-Sentinel Partner Organizations

Mini-Sentinel's Evolving Common Data Model

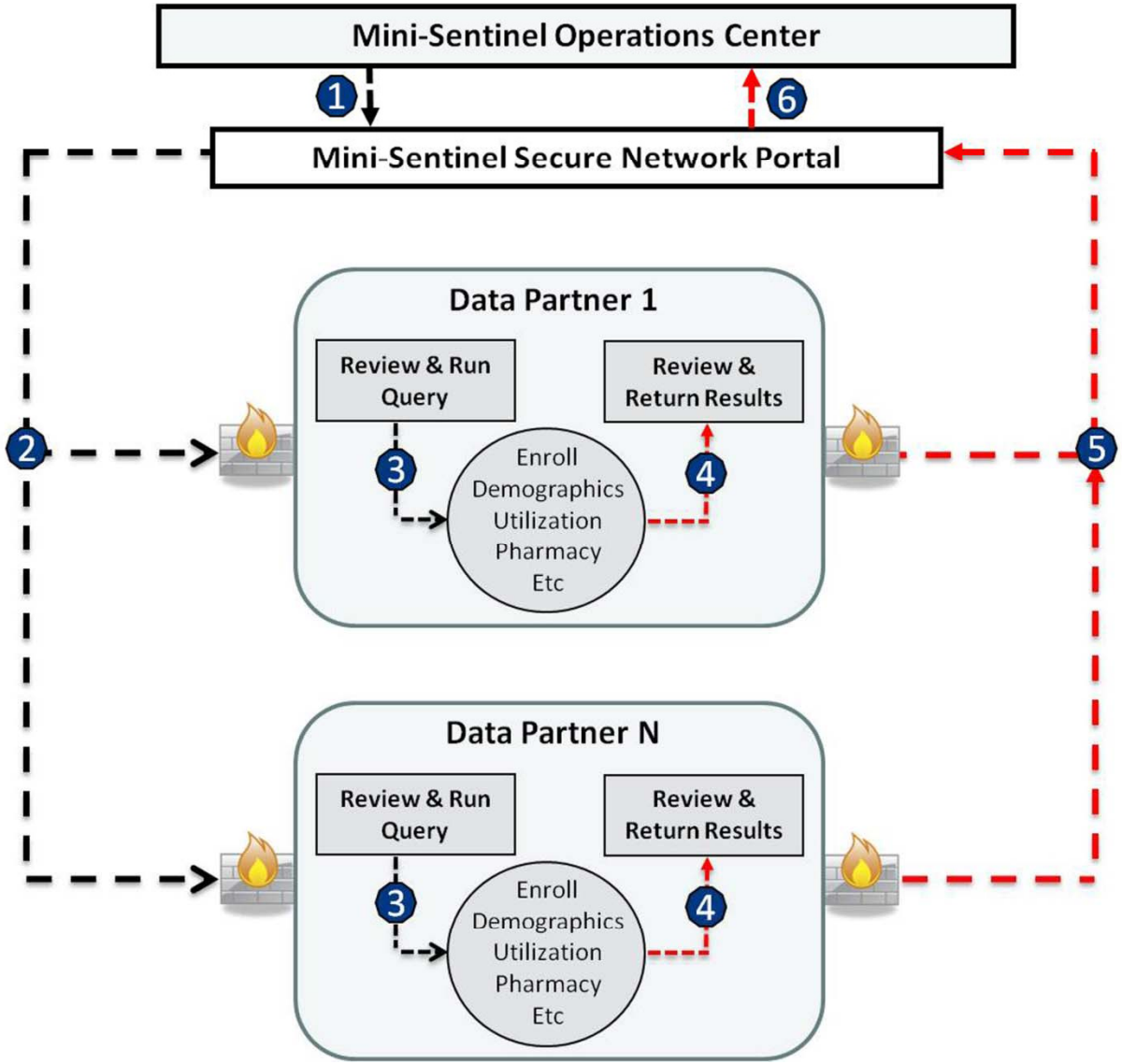
- Administrative data from health plans
  - Enrollment (start/stop dates, pharmacy coverage…)
  - Demographics (age, sex…)
  - Outpatient pharmacy dispensing
  - Utilization (encounters, diagnoses, procedures)
- Electronic Health Record data from clinicians
  - Height, weight, blood pressure, temperature
  - Laboratory test results (selected tests)
- Registries – public and private
  - Immunization
  - Mortality (death and cause of death)

The Mini-Sentinel Distributed Database

- Populations with well-defined periods for which medically-attended events are known
- 126 million individuals*
- 3 billion dispensings
  - Accumulating 37 million dispensings per month
- 2.4 billion encounters
  - Accumulating 41 million encounters per month
  - 40 million acute inpatient stays
- 13 million people with ≥1 laboratory test result

*As of 12 December 2011. The potential for double-counting exists if individuals moved between data partner health plans.

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

Active surveillance: actively assessing treatments & outcomes

- Characterize treatments and health events
- For older products, assess concerns arising from any source
- For new products, monitor accumulating experience for pre-specified potential adverse outcomes
- Assess impact of FDA actions

Rapid Queries of Exposures – Examples

- Drugs
  - Analeptics, Analgesics, Antihypertensives, Antiarrhythmics, Antiretrovirals, Antidepressants, Antipsychotics, Antibiotics, Bronchodilators, Cancer chemotherapy agents, Growth factor inhibitors, Intravenous iron, Smoking cessation drugs, Steroids
- Vaccines
  - Measles/mumps/rubella, rotavirus, human papilloma virus
- Devices
  - Hip replacement, Negative pressure wound therapy devices

Rapid Queries of Health Events – Examples

- Cardiovascular: Acute myocardial infarction, Hyperlipidemia
- Neurologic: Parkinson's disease, Progressive multi-focal leukoencephalopathy
- Gastrointestinal: Celiac disease, Ulcerative colitis, Crohn's disease
- Allergic: Severe cutaneous conditions, Anaphylaxis, Angioedema, Milk allergy
- Other: Osteonecrosis of the jaw

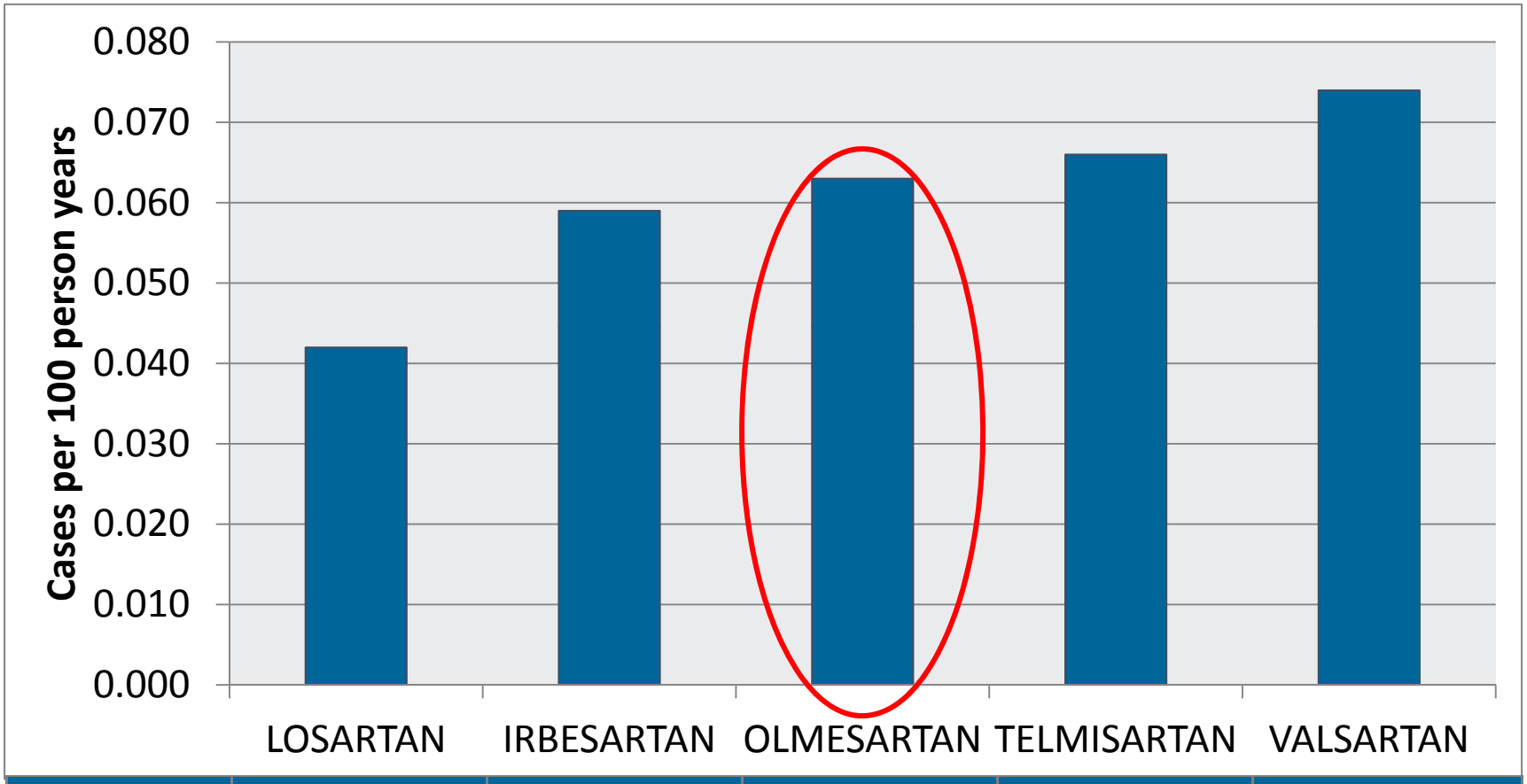
Rapid Queries of Exposure-Outcome Pairs

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

ARBs and celiac disease

- Potential signal identified in AERS database
- Review of cases inconclusive

ARBs and celiac disease



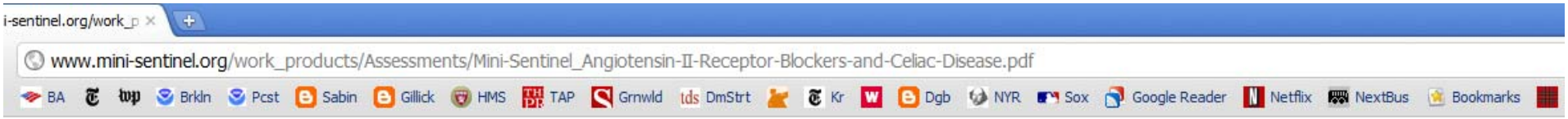
Cases	63	10	17	5	50
New users	235,630	40,071	81,560	24,596	153,159

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

Limitations

- Capture of relevant gastro-intestinal events may be incomplete
- Potential inclusion of irrelevant events
- Patients exposed to different agents may differ with respect to risk of symptoms
- Majority of exposures limited to a few months duration
- Lack of observed risk doesn't rule out an excess

ARBs and celiac disease – documentation



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

Date Posted:

Medical product exposures of interest:

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

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

One-Time Protocol-based Assessments

- Rotavirus Vaccines and Intussusception
- Influenza Vaccine and Febrile Seizures
- Influenza Vaccine and Pregnancy Outcomes
- Human papilloma virus vaccine and Venous Thromboembolism
- ACEIs/ARBs/aliskiren and Angioedema
- Aripiprazole and Venous Thromboembolism

Prospective surveillance: Antidiabetic Drugs and Acute MI

- Repeated evaluation of acute MI risk in new users of saxagliptin vs. comparator antidiabetic drugs
- Case mix adjustment via disease risk scores and propensity scores
- 280,745 eligible new users Aug, 2009 – Dec, 2010:

Antidiabetic drug	New users
Saxagliptin	5,877
Sitagliptin	31,425
Pioglitazone	55,134
Long-acting insulin	72,024
2nd generation sulfonylureas	116,285

Assessments of FDA's Regulatory Actions

Long Acting Beta Agonists

Objective: Evaluate the impact of labeling change advising against long term use of LABAs as a single agent on changes in use and health outcomes of interest

Status: Workgroup developing protocol

Challenges

- Many different exposures
- Many different outcomes
- Many patient types
- Many and diverse data environments

- Need for timeliness in both detection and followup
- Need to avoid false alarms
- Need for multiple simultaneous activities
- Need for surge capacity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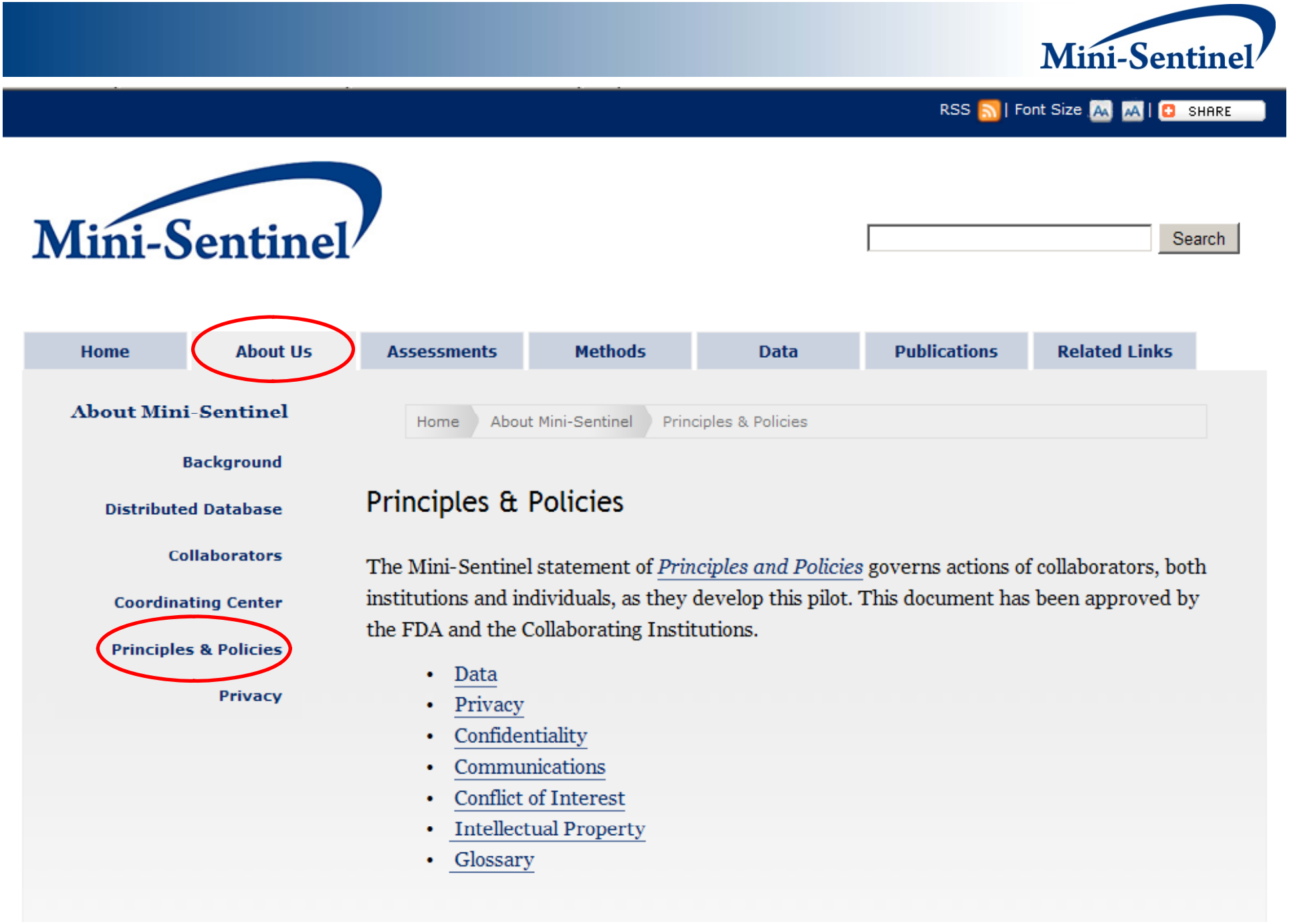
Welcome to Mini-Sentinel
Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA -regulated medical products.
Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance.
Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise.
NEW POSTINGS
Mini-Sentinel Supplement to Pharmacoepidemiology and Drug Safety
Identifying Complementary Data Sources (PRISM)
FDA's Mini-Sentinel Program Progress and Direction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Principles & Policies
The Mini-Sentinel statement of Principles and Policies governs actions of collaborators, both institutions and individuals, as they develop this pilot. This document has been approved by the FDA and the Collaborating Institutions.
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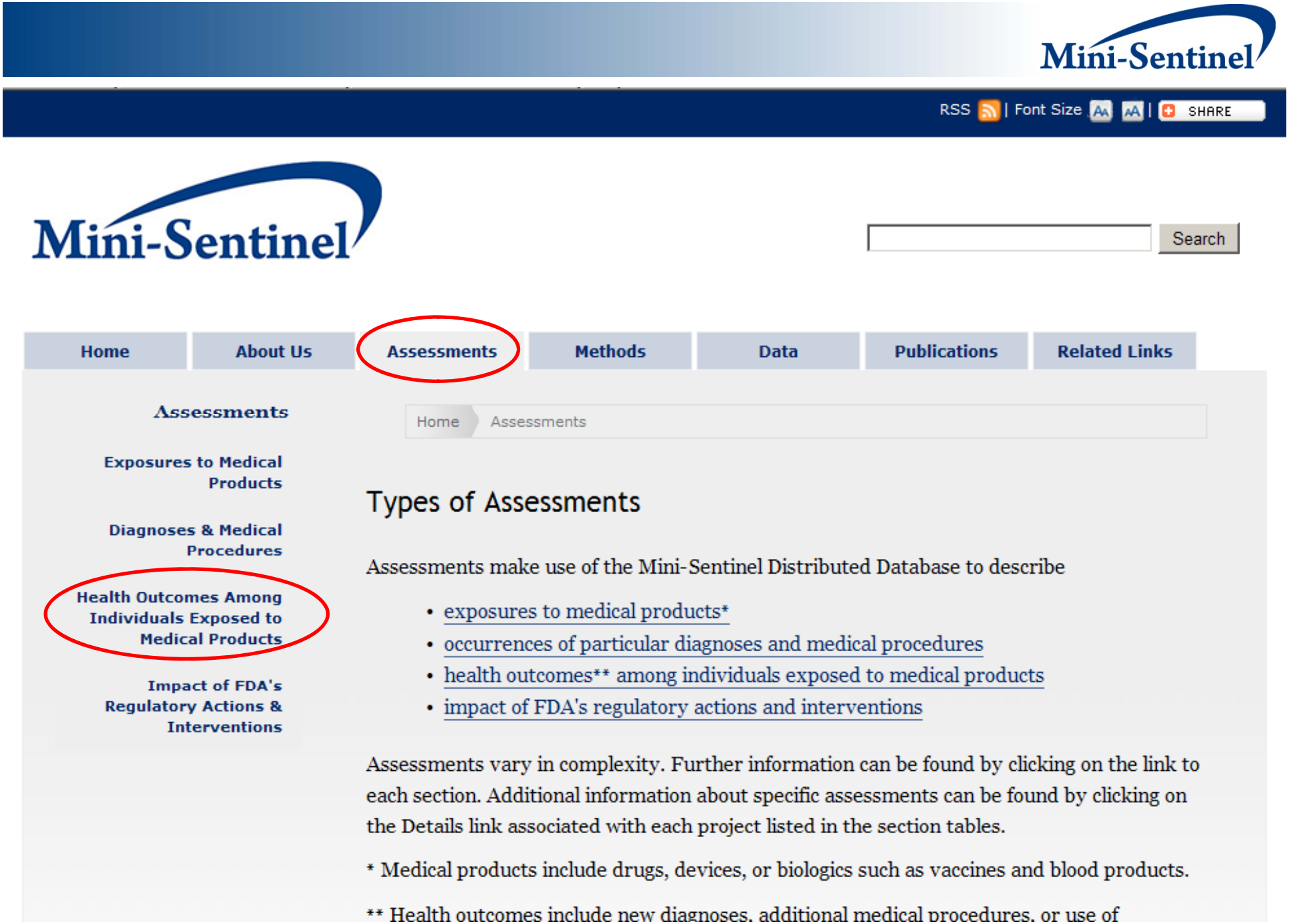
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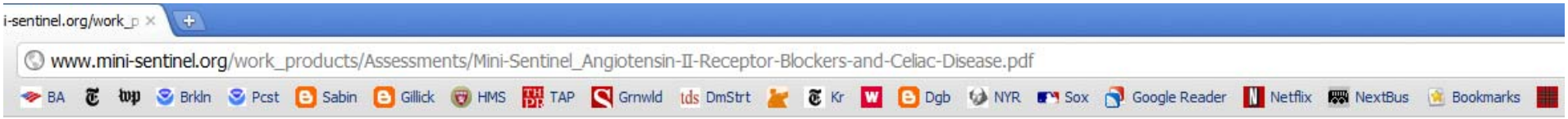
Assessments
Types of Assessments
Assessments make use of the Mini-Sentinel Distributed Database to describe
exposures to medical products*
occurrences of particular diagnoses and medical procedures
health outcomes** among individuals exposed to medical products
impact of FDA's regulatory actions and interventions
Assessments vary in complexity. Further information can be found by clicking on the link to each section. Additional information about specific assessments can be found by clicking on the Details link associated with each project listed in the section tables.
* Medical products include drugs, devices, or biologics such as vaccines and blood products.
** Health outcomes include new diagnoses, additional medical procedures, or use of

ARBs and celiac disease



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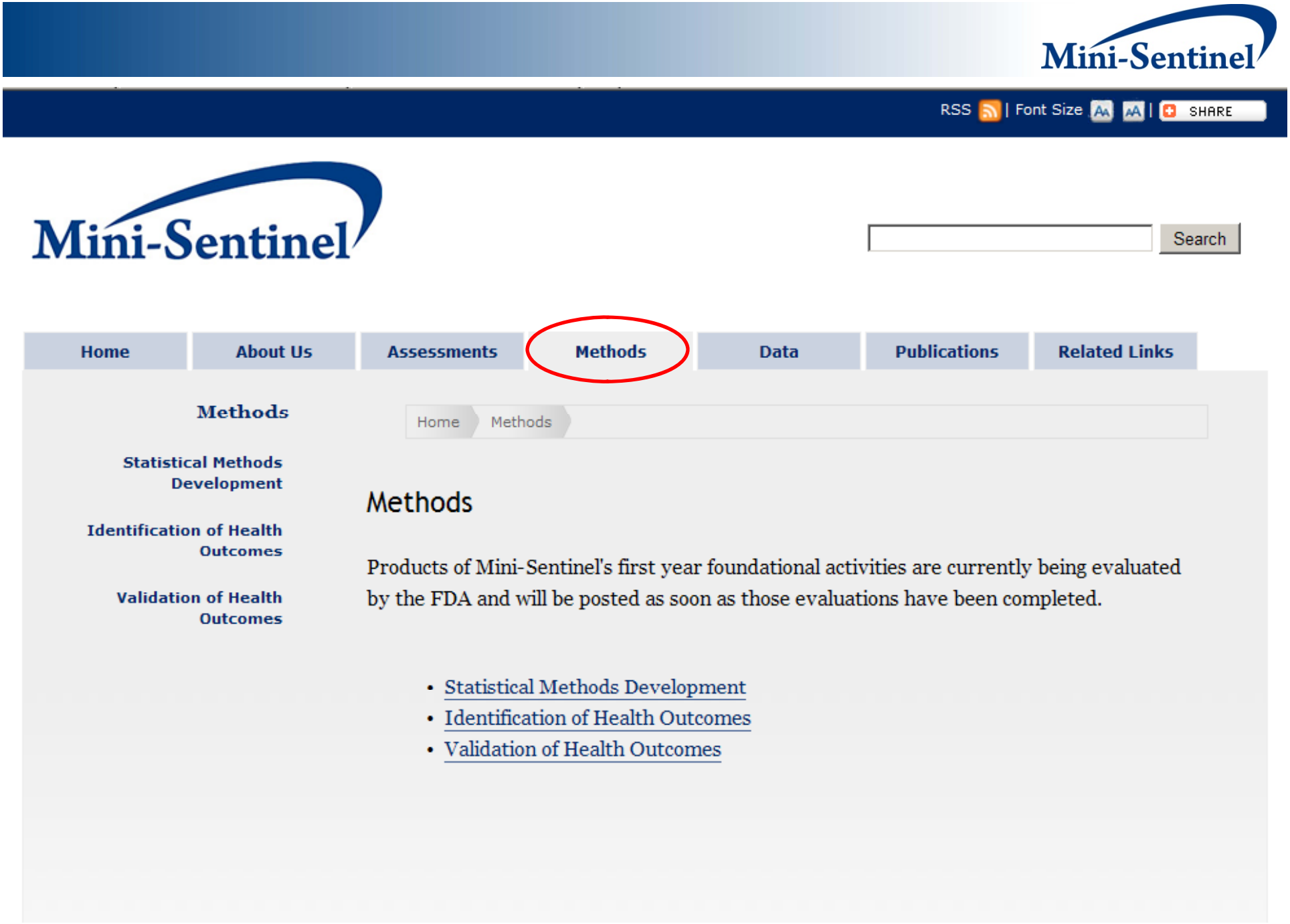
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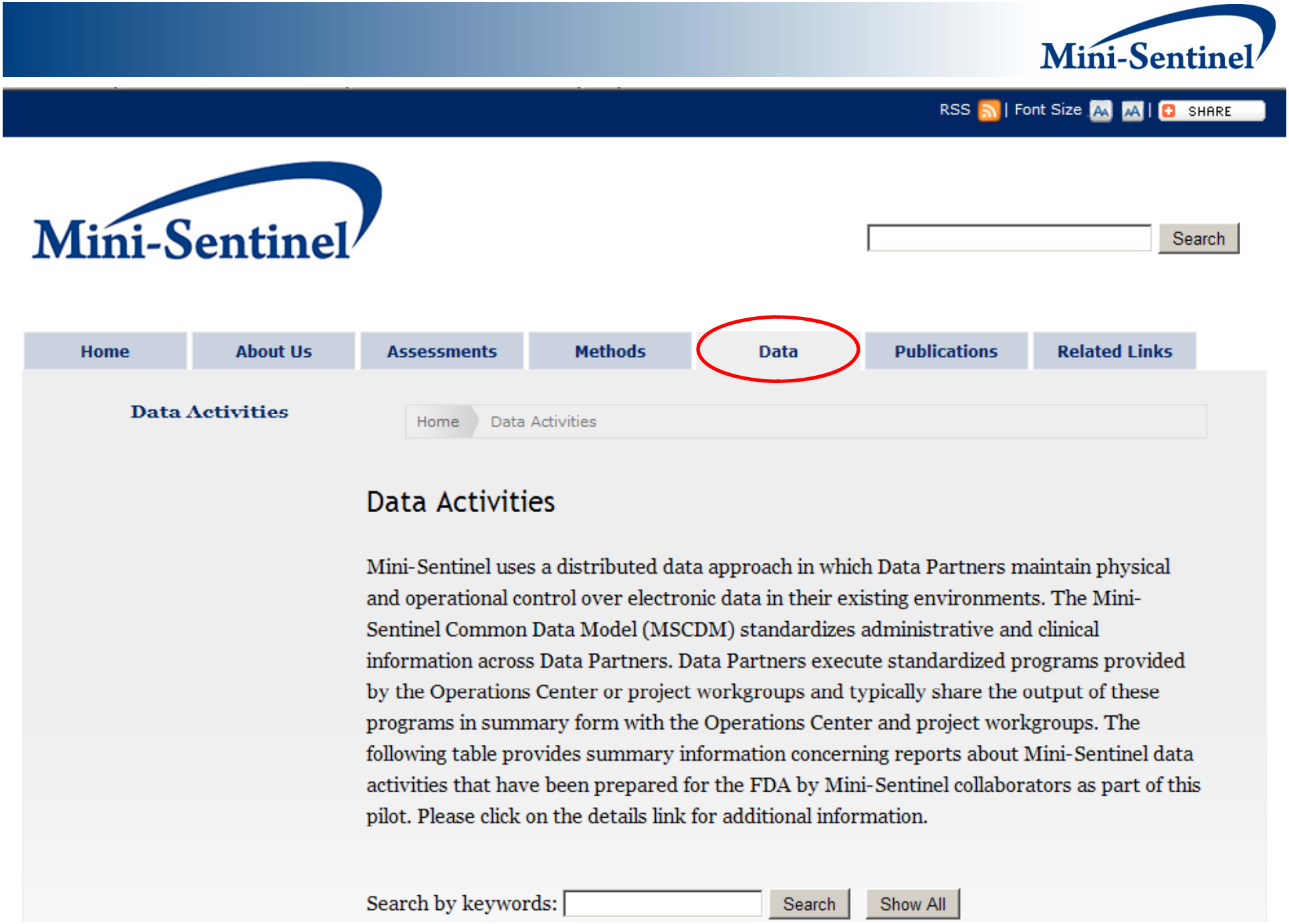
Products of Mini-Sentinel's first year foundational activities are currently being evaluated by the FDA and will be posted as soon as those evaluations have been completed.
Statistical Methods Development
Identification of Health Outcomes
Validation of Health Outcomes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Mini-Sentinel uses a distributed data approach in which Data Partners maintain physical and operational control over electronic data in their existing environments. The Mini-Sentinel Common Data Model (MSCDM) standardizes administrative and clinical information across Data Partners. Data Partners execute standardized programs provided by the Operations Center or project workgroups and typically share the output of these programs in summary form with the Operations Center and project workgroups. The following table provides summary information concerning reports about Mini-Sentinel data activities that have been prepared for the FDA by Mini-Sentinel collaborators as part of this pilot. Please click on the details link for additional information.
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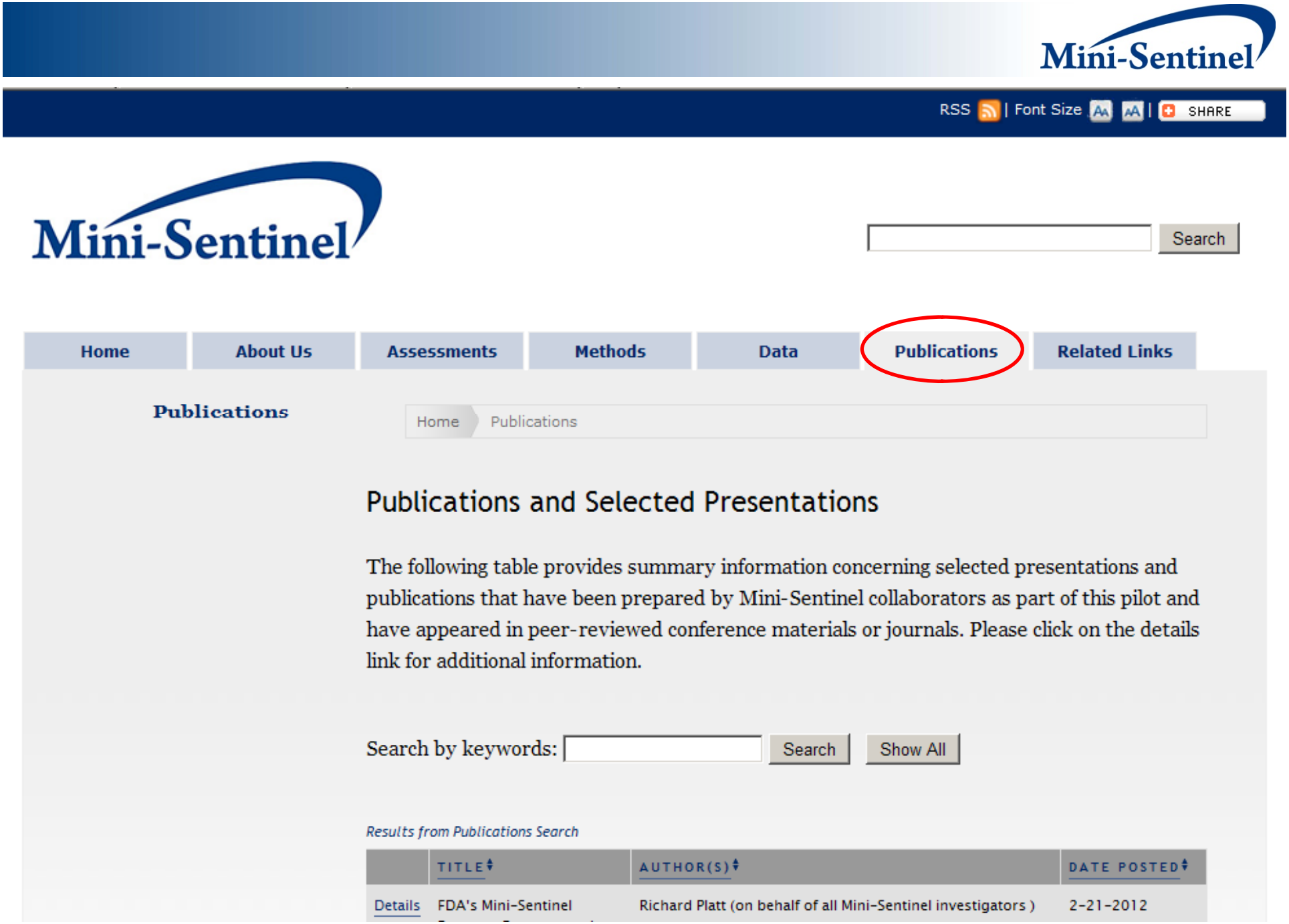
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Publications and Selected Presentations
The following table provides summary information concerning selected presentations and publications that have been prepared by Mini-Sentinel collaborators as part of this pilot and have appeared in peer-reviewed conference materials or journals. Please click on the details link for additional information.
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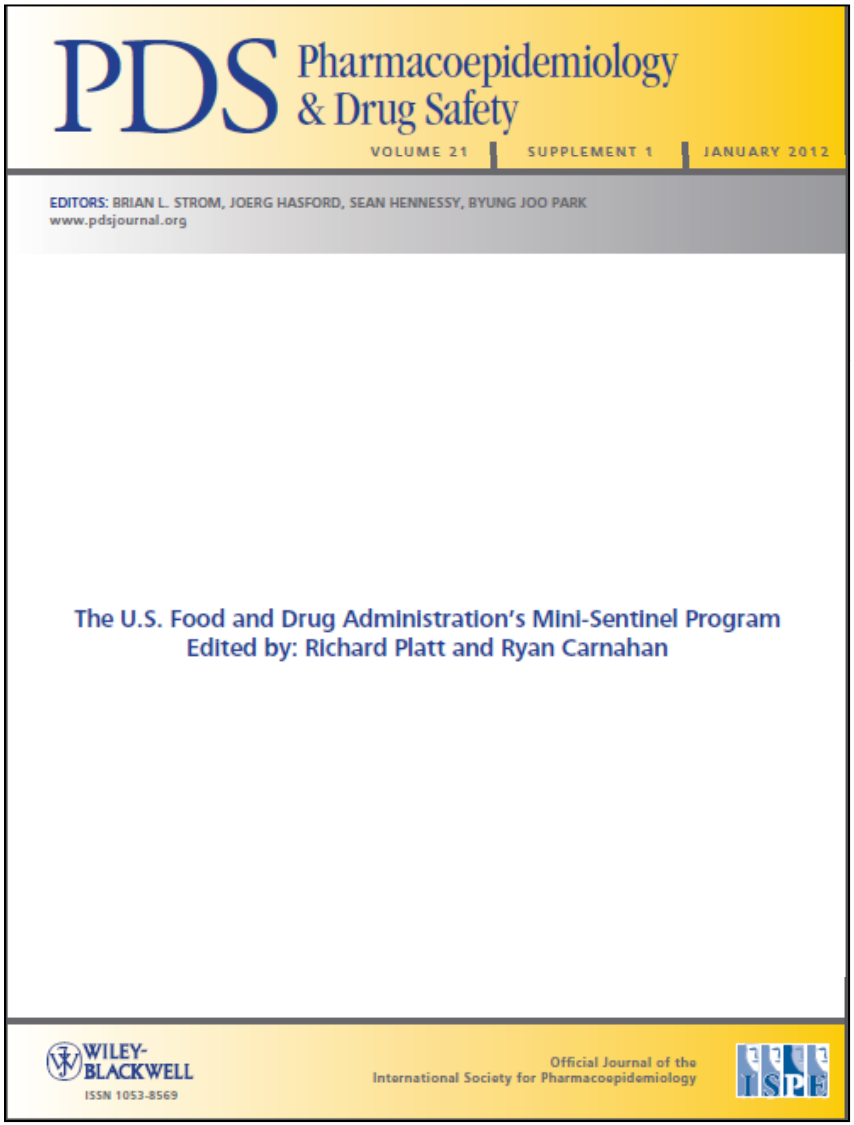
FDA's Mini-Sentinel
Richard Platt (on behalf of all Mini-Sentinel investigators)
2-21-2012

Mini-Sentinel Journal Supplement



- Supplement to Pharmacoepidemiology and Drug Safety
- 34 peer reviewed articles; 303 pages
- Goals, organization, privacy policy, data systems, systematic reviews, stats/epi methods, record retrieval and review, protocols for drug/vaccine studies...
- Open access!
- http://onlinelibrary.wiley.com/doi/10.1002/pds.v21.S1/issuetoc

PDS Pharmacoepidemiology & Drug Safety

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ORIGINAL REPORTS

Thank you!