U.S. FOOD & DRUG ADMINISTRATION

INDUSTRY DAY 2018

THE SENTINEL INITIATIVE

Food and Drug Administration

26 April 2018

U.S. FOOD & DRUG ADMINISTRATION

INDUSTRY DAY 2018

Anissa Ferguson, PharmD, MS, FAC-CORIII
FDA Sentinel Contract Lead
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

CONNECTEDNESS

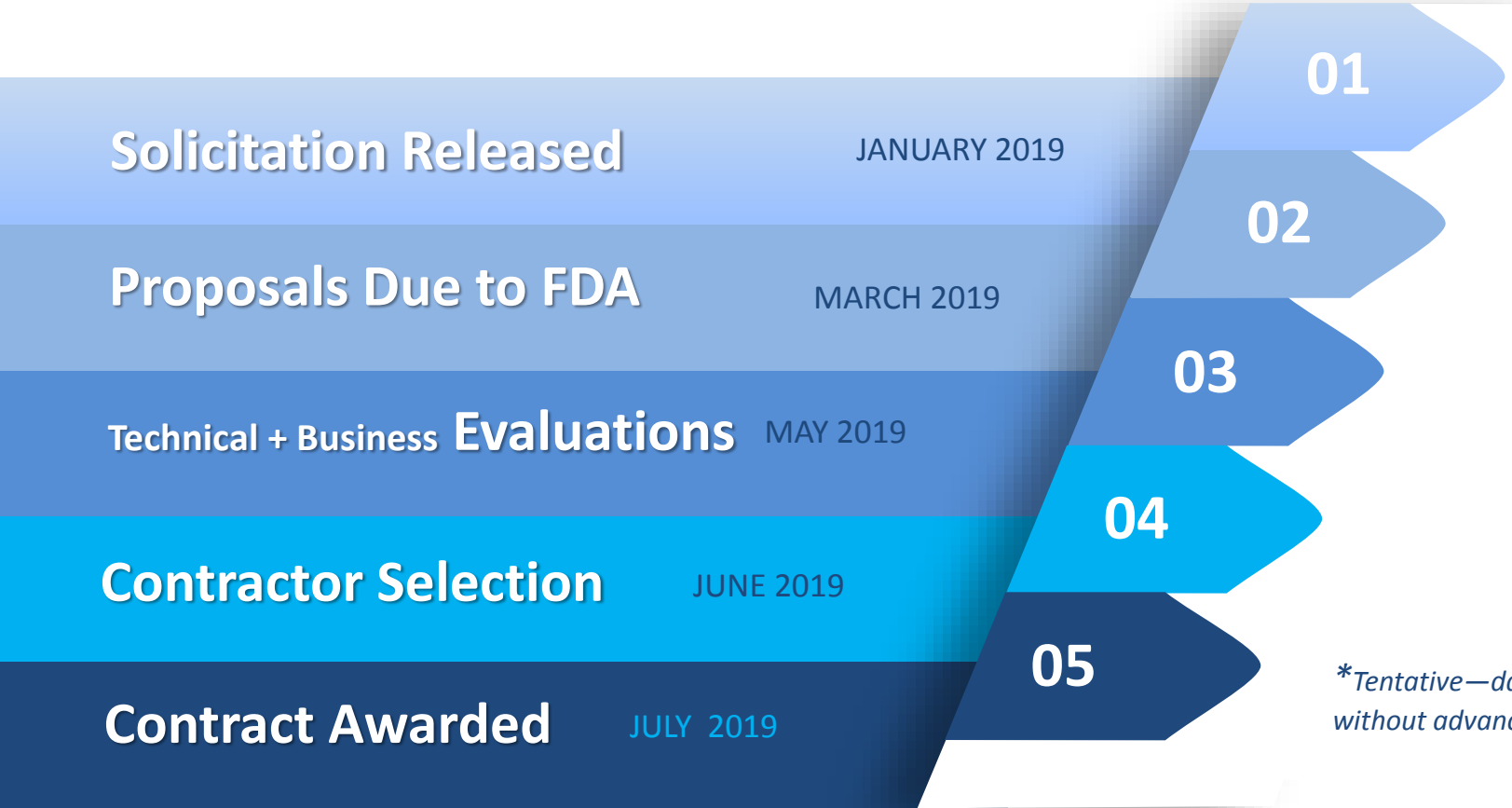
Industry Day| Objectives

1. To provide an opportunity to share the technical and organizational capabilities available to support activities related to FDA's Sentinel Initiative
2. To reiterate the needs of FDA as expressed in the FY19 Sentinel Contract Request for Information (RFI)
3. To respond to pre-submitted inquiries from industry about the RFI; and, to conduct additional market research for FDA through on-site presentations by industry and research organizations

Industry Day| Attendees

- Industry Guests: 140 registered guests
- Varying Fields of Interest:
  - Academia
  - Contract research organizations
  - Technology corporations
  - Consulting companies
  - Current Sentinel Data Partners

Sentinel Recompete | Timeline*



**Tentative—dates may change without advanced notice*

Sentinel Recompete | Timeline Disclaimer

All RFP timeline dates are

TENTATIVE

and subject to change.

AGENDA | General Session

AGENDA ITEM	PRESENTER	TIME
Introduction	Dr. Anissa Ferguson	10:00 AM
FY19 RFP Tentative Timeline		
Review of RFI	Dr. Robert Ball	10:10 AM
Overview | Rules of Engagement	Mr. Matthew Bucher | OAGS	10:25 AM
Contractor Inquiries	Dr. Michael Nguyen	10:35 AM
Plan for Afternoon Individual Sessions	Dr. Anissa Ferguson	10:55 AM

AGENDA | General Session

AGENDA ITEM	PRESENTER	TIME
Lunch—Optional (Self-Pay)	OAGS and the Sentinel Program Team	11:00 AM
Informal Meet and Greet		
Contractor Inquiries	Dr. Michael Nguyen	11:15 AM

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Sentinel Industry Day

Review of the Request for Information (RFI)

April 26, 2018
Robert Ball, MD, MPH, ScM
Deputy Director
Office of Surveillance and Epidemiology
Center of Drug Evaluation and Research

RFI | Purpose of the RFI Process

- To invite public comment to inform the future organization of the Sentinel System
- Collect and assess the scientific and technical capabilities from potential future contractors for the Sentinel System to shape the next solicitation for a five year base contract
- Capture insights about how to address current challenges, promote efficiency, and support the diverse and growing needs of FDA

RFI | Priority Areas Outlined in RFI

- Maximally efficient chart review in a distributed database environment
- Enhanced leveraging of granular, potentially-unstructured data available in electronic health records (EHRs) and other data sources
- Improving operational efficiency and reducing system cost by separating production (i.e. fulfilling queries) from development (i.e. enhancing data architecture and statistical methods)
- Understanding how new technologies (e.g., natural language processing, machine learning, blockchain) may enhance any of these areas of the Sentinel System
- Understanding how commercially available data sources might contribute to the system

Sentinel Industry Day

Overview | Rules of Engagement

April 26, 2018

Matthew Bucher
Contracting Officer
Office of Acquisitions and Grants Services
Food and Drug Administration

OAGS | Conducting Market Research

- Industry Day is a key part of FDA's market research process
- Market research aims to seek general information and not a proposal, bid, or price quotation
- The goal is a free flow of information with the vendor providing information on the marketplace, business practices, new methods, and novel technologies
- Individual market research sessions are **not** intended to be a marketing opportunity
- FDA will not share one vendor's solutions with another vendor

OAGS | Sentinel Contract Options

- A variety of contract options are available to the government
- Current Sentinel contract structure uses a single award to a single contractor to lead the Coordinating Center
- Other options include:
  - Single award with multiple vendors
  - Multiple awards
- Reimbursement options include:
  - Cost reimbursement contract
  - Time and materials contract
  - Firm fixed price contract

https://www.acquisition.gov/sites/default/files/current/far/html/FARTOCP16.html

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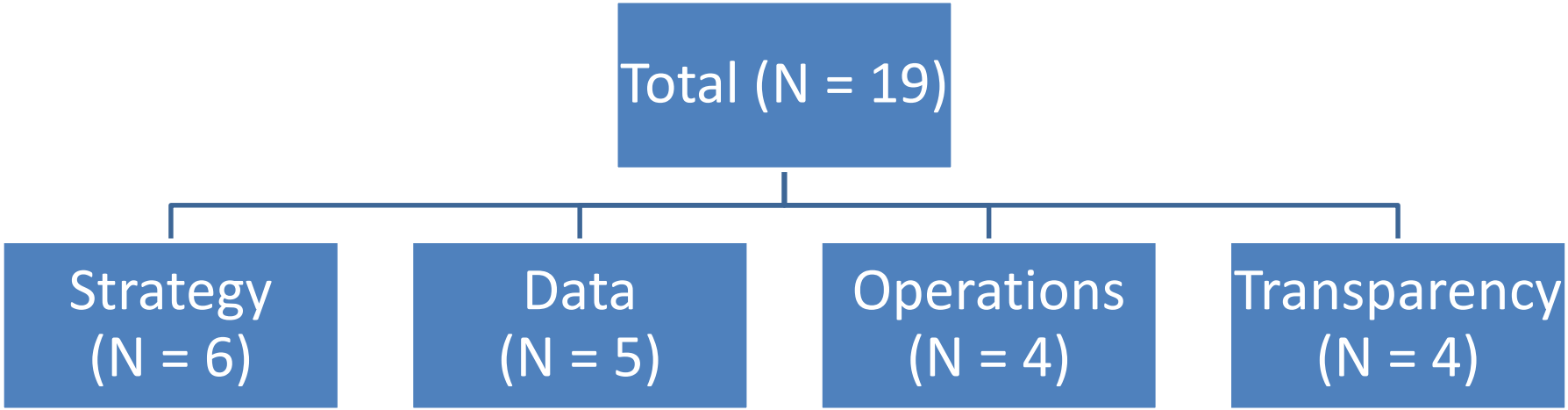
Sentinel Industry Day

Responses to Vendor Questions

April 26, 2018

Michael D. Nguyen, MD
FDA Sentinel Program Lead
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Questions Received from Vendors



All questions were listed in this presentation verbatim, unless otherwise noted.

Vendor Questions | Strategy Related

1. Who might the FDA consider as the ideal end user? (e,g. Public health epidemiologists vs physicians vs analysts)
2. What key metrics for end users would the FDA be considering (e.g. number of successful queries, number of papers)?
3. Does FDA expect that other parts of FDA will want to access the Sentinel data sources to generate information related to drug approval and other FDA activities?
4. Does the FDA believe the current federated Sentinel model could be replace by a commercial data source and analytics system with the 100 million people cited in the RFI? If so, please describe data, functional and transition expectations necessary to achieve the results provided by the current Sentinel system.
5. What new query capabilities are expected in the future (e.g. signal detection)?
6. [Is there] a greater need in the immediate term to enable more individuals/users to access and query Sentinel data or onboard more data sources to be linked to Sentinel data?

Q1 | Who might the FDA consider as the ideal end user?
(e,g. Public health epidemiologists vs physicians vs analysts)

- All Sentinel activities involve a multi-disciplinary team within FDA
- Most FDA led Sentinel product safety assessments are conducted by teams led an **epidemiologist**, supported by physicians, pharmacists, statisticians, project managers, social scientists, and others
  - Results from product safety assessments evaluated by a combination of pre-approval and post-approval offices, meaning that the final stakeholders are wider than the immediate study team
- Although external investigators are potential users of Sentinel Infrastructure, FDA study teams represent the target end user of the Sentinel System

Q2 | What key metrics for end users would the FDA be considering? (e.g. number of successful queries, number of papers)?

- Sentinel was established in response to the FDA Amendments Act 2007 mandate to create an active risk identification and analysis (ARIA) system
- Important program outcome measures include:
  - Ability of ARIA to address the serious safety issues that arise from pre- and post-market regulatory activities
  - Influence on regulatory decision making (e.g., label changes, Advisory Committees, Citizens Petitions, Drug Safety Communications)
- Important program characteristics include:
  - Validity and speed (time to results) of results
  - Flexibility and customizability of analyses
  - Reproducibility and transparency of analyses
  - Cost

Q3 | Does FDA expect that other parts of FDA will want to access the Sentinel data sources to generate information related to drug approval and other FDA activities?

- Current FDA user base includes:
  - All 3 medical product centers (CDER, CBER, CDRH)
  - Office of Commissioner and Office of Medical Products and Tobacco
  - Analyses span descriptive and inferential; safety and effectiveness; signal detection and signal evaluation
- The use of Sentinel is expected to grow proportionally with its capabilities
  - Desire to maximize regulatory and public health impact within a sustainable cost model
- Although Sentinel is primarily focused on postmarket safety, FDA Catalyst is investigating potential pilot projects to assess the use of Real World Evidence for evaluation of medical product effectiveness

Q4 | Does the FDA believe the current federated Sentinel model could be replace by a commercial data source and analytics system with the 100 million people cited in the RFI?

- Sentinel seeks to generate robust, regulatory-grade evidence to inform FDA decision making and improve public health
- Sentinel has a legislative requirement of 100 million individuals
  - Database size requirements are also driven by epidemiologic needs (to study rare health outcomes, special populations, facilitate subgroup analyses)
- To produce robust analyses, a system should be able to test key analytic assumptions, incorporate routine quality assurance processes, and understand data provenance and pursue data validation from the original source data when necessary
- FDA evaluates data sources and organizational models based on how well they meet these core needs, without prespecifying an approach

Q4 | [*Part 2*] If so, please describe data, functional and transition expectations necessary to achieve the results provided by the current Sentinel system

- Any proposed transition to use of commercial data sources would need to be able to meet current FDA data and analytic needs, if the system transitions to a new organizational model
- FDA encourages creative proposals that might capitalize on commercial data sources to meet FDA analytic and data needs in full, or in concert with other data resources
- Proposals may include a temporary transitional state to enable change
- FDA will evaluate all vendor proposals that can meet these programmatic needs

Q5| What new query capabilities are expected in the future? (e.g. signal detection)

- The Sentinel System's suite of analytic tools will continue to evolve over time to maximize the public health utility of the system
- New query tools are being developed to:
  - Conduct signal detection
  - Assess FDA safe use recommendations and the impact of FDA regulatory actions
  - Assess product switching (e.g., between brand name and generic medications)
  - Conduct propensity score matched analyses on cohorts of infants linked to their mothers to evaluate the safety of medications in pregnancy
  - Inverse probability treatment weighting and other propensity score weighting methods
- New query tools of interest include:
  - Tool to take advantage of unstructured and electronic health record data (e.g., computable phenotypes)
  - Other advanced methods for causal inference

Q6 | [Is there] a greater need in the immediate term to enable more individuals/users to access and query Sentinel data or onboard more data sources to be linked to Sentinel data?

- FDA is currently proceeding in several directions to maximize the public health impact of Sentinel
- Within FDA, we continue to expand Sentinel's use to the fullest range of medical products and make strategic enhancements to meet data gaps:
  - e.g., Mother-infant linkage, vaccine registries, National Death Index linkage
- We continue to develop Sentinel to become a national resource for evidence generation to increase the user base beyond FDA:
  - IMEDS is an important portal for public entities to access the Sentinel infrastructure
  - Hosted public training events (e.g., July 2017, February 2018)
  - Posting analytic code and fully worked examples of analyses
  - Creating a synthetic dataset formatted into the Sentinel Common Data Model
  - Development of Sentinel Github space

Engaging the Scientific Community

Submit Comment

Conversion of Medicare Claims Synthetic Public Use Files (SynPUFs) to Sentinel Common Data Model (SCDM) Format

Project Title	Conversion of Medicare Claims Synthetic Public Use Files (SynPUFs) to Sentinel Common Data Model (SCDM) Format
Date Posted	*Thursday, January 25, 2018*
Status	In progress
Description	As part of a broader intiative to enhance the accessibility of the Sentinel Common Data Model (SCDM) and related tools, this work will develop and post SCDM formatted files to the Sentinel website for public use. In addition, this work will also develop a sample Routine Analytic Framework (RAF) package so that the public may easily execute Sentinel tools on the available SCDM-formatted files.
Workgroup Leader(s)	Lauren Zichittella MS; Tiffany S. Woodworth MPH; Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA
Workgroup Members	David Cole BM; Andrew Petrone MPH; Natasha De Marco MPH; Emily Welch MPH; Tancy Zhang MPH; Ella Pestine MPH; Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA
Data Sources	Sentinel Distributed Database (SDD)

https://www.sentinelinitiative.org/sentinel/methods/conversion-medicare-claims-synthetic-public-use-files-synpufs-sentinel-common-data

Submit Comment

Ranexa (Ranolazine) and Seizures

Project Title	Ranexa (Ranolazine) and Seizures
Date Posted	*Monday, February 5, 2018*
Project ID	cder_mpl1r_wp033_nsdp_v01, cder_mpl2p_wp002_nsdp_v01
Status	Complete
Deliverables	Sentinel Modular Program Report: Ranexa and Seizures Sentinel Modular Program Report: Ranexa and Seizures, Self-controlled Risk Interval (SCRI) Design Analytic Package for Ranexa and Seizures, Self-controlled Risk Interval (SCRI) Design
Related Links	Prevalent and Incident Dispensings of Ranolazine 2017 ICPE Symposium: Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year Seizure Algorithm Defined in "Ranexa (Ranolazine) and Seizures"
Description	These reports contain the estimated rates of seizures among indiviuals exposed to ranolazine alone, as well as individuals with concomitant use of ranolazine and either beta blockers, selected oral calcium channel blockers, or non-injectable nitrates. The query was run against the Sentinel Distributed Database for the time period of January 1, 2006 to September 30, 2015. The request was distributed to 16 data partners on August 4, 2016.

https://www.sentinelinitiative.org/drugs/assessments/ranexa-ranolazine-and-seizures

Vendor Questions | Data Related

7. Does FDA expect to consider other data models for its analyses, in addition to the current Sentinel model?
8. Of the 200+ data sources the FDA has on its roadmap for integration, which type of data (e.g. registries, claims, etc) or data source does the agency consider is most difficult to integrate? To access?
9. Is all the data in the system de-identified not subject to HIPAA?
10. Does FDA have guidelines for good software development practices for software that will be used to transform data into a common data model, to build analysis data sets or to conduct analyses?
11. What unstructured data does the Sentinel Network have access to now, and what data would be desired in the future?

Q7 | Does FDA expect to consider other data models for its analyses, in addition to the current Sentinel model?

- Why use a common data models (CDM) and reusable tools?
  - Improves the system's timeliness, transparency, and reproducibility of analyses
  - Enables a system to be scalable to include multiple data sources
- A single analytic platform is defined by a set of analysis tools and quality assurance programs that are tailored to a specific CDM
- Use of different CDMs require corresponding investments in different analytic tools, QA programs, and processes
- Need to balance the potential benefits of hosting two analytic platforms, with the additional resources required to create and maintain them
- See response to Q4 for additional information

Q8 | Of the 200+ data sources the FDA has on its roadmap for integration, which type of data (e.g. registries, claims, etc) or data source does the agency consider is most difficult to integrate? To access?

- Currently, electronic health records represent potentially the most difficult data source to integrate, while theoretically having the largest potential gains
  - Within EHR, key data elements include laboratory, radiologic and pathology data
- Other important data sources include cancer and death certificate registries (e.g., National Death Index)

Q9 | Is all the data in the system de-identified not subject to HIPAA?

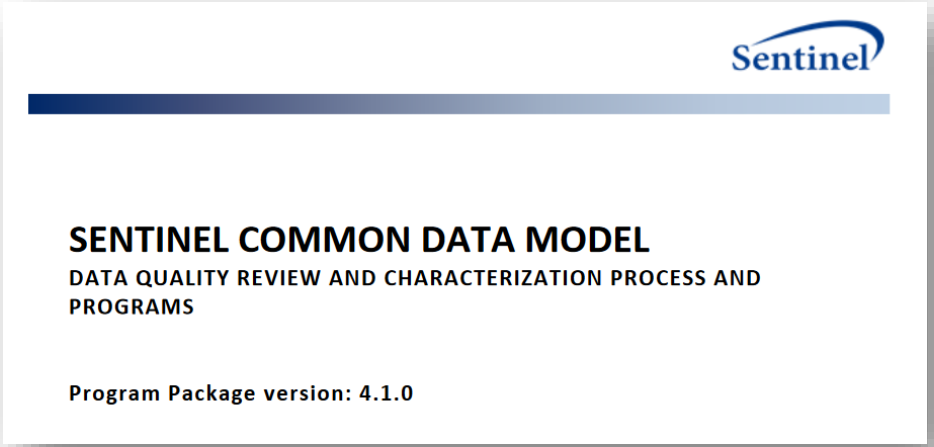
- Analyses transmitted to FDA involve de-identified data, but data in the hands of data holders is not de-identified
- Sentinel operates under FDA's public health authority and the Privacy Rule does not require individual authorization to disclose PHI to a public health authority for public health activities*

A. THE USE OF SENTINEL DATA FOR PUBLIC HEALTH PRACTICE

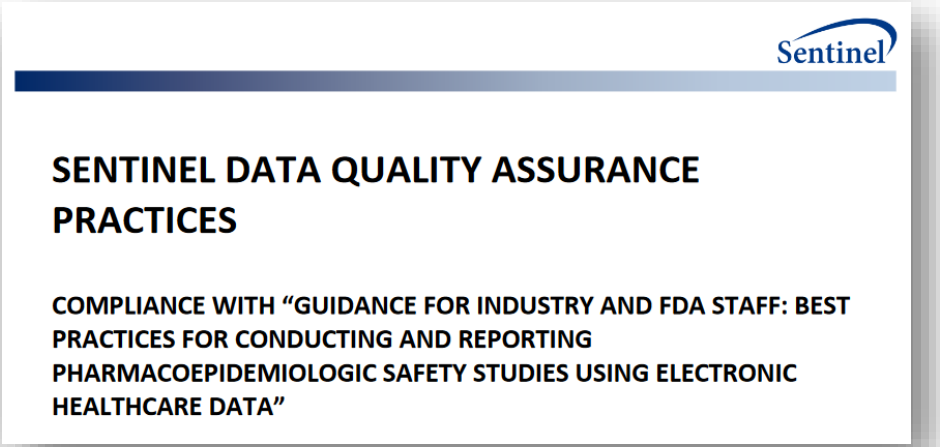
"Public health practice" is the application of existing knowledge and techniques to protect the public's health. Medical product safety surveillance and the evaluation of medical product effectiveness directly support FDA's mission to protect the public's health and fall squarely within public health practice. The HIPAA Privacy Rule[5] allows access to Sentinel Data for public health practice without individual authorization. Moreover, the Common Rule does not regulate the use of Sentinel Data for public health practice. The Director of the Department of Health and Human Services ("HHS") Office for Human Research Protections ("OHRP") determined in 2010 that the Common Rule does not apply to Sentinel Initiative medical product safety surveillance. (See **Exhibit 1**.) In addition, recent amendments to the Common Rule expressly provide that medical product safety surveillance activities will not be subject to the Common Rule when those amendments take effect (the "Amended Common Rule").[6]

*https://www.sentinelinitiative.org/sites/default/files/Communications/Publications/HIPPA-Common-Rule-Compliance-in-Sentinel-Initiative.pdf

Q10 | Does FDA have guidelines for good software development practices for software that will be used to transform data into a common data model, to build analysis data sets or to conduct analyses?



https://www.sentinelinitiative.org/sites/default/files/data/DistributedDatabase/Sentinel-Data-Quality-Review-and-Characterization-Programs.pdf



https://www.sentinelinitiative.org/sites/default/files/data/DistributedDatabase/Sentinel_DataQAPractices_Memo.pdf

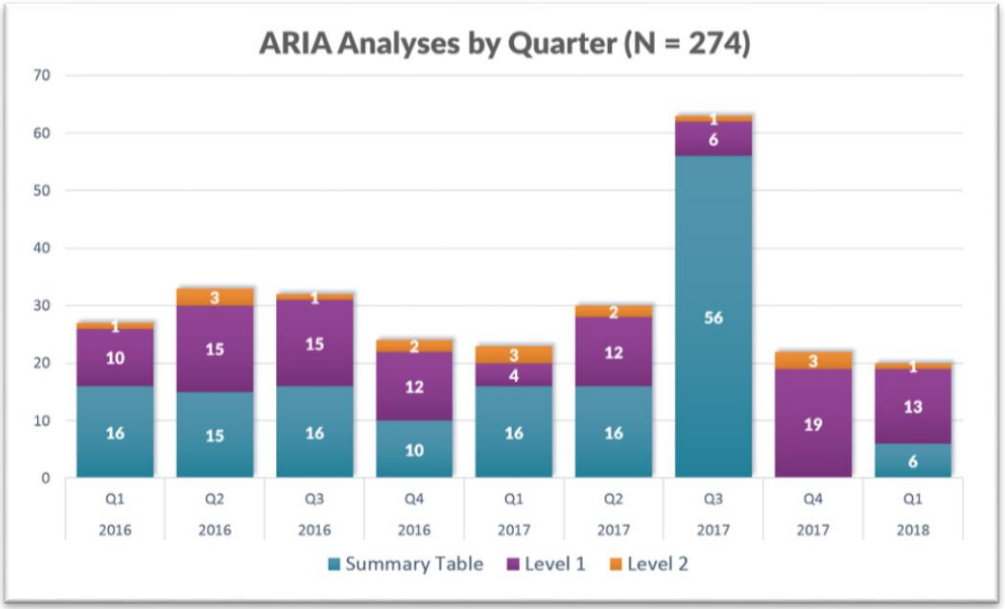
Q11 | What unstructured data does the Sentinel Network have access to now, and what data would be desired in the future?

- FDA is able to access the medical records (paper or electronic format) from data partners throughout the network to validate its electronic algorithms when deemed necessary
- A subset of Sentinel data partners that have integrated delivery systems can directly access their electronic medical records
  - FDA can partner with these organizations to explore the data that resides locally in their native formats for specific projects
- The ideal future state would involve claims linked to data from electronic health records and/or registries in a scalable and privacy-protecting analytic platform

Vendor Questions | Operations Related

12. What is the anticipated number of studies that FDA would like to be able to run in a year? We realize this can't be predicted exactly, but a sense of scale would be helpful – 100, 500, 1000?
13. How do the FDA programs interact from a governance and process perspective with the Sentinel program and contractor?
14. How is the Sentinel program currently creating, storing and reusing algorithms to identify outcomes of interest? Are they stored in Excel, in a database or some other way? (By algorithms, we are referring to the codes and logic used to identify clinical events of interest).
15. Explain the current business expectations and requirements of the data partners. E.g. are there formal contracts/grants with service levels, data agreements, etc in place; and are the data partners required to respond to every query?

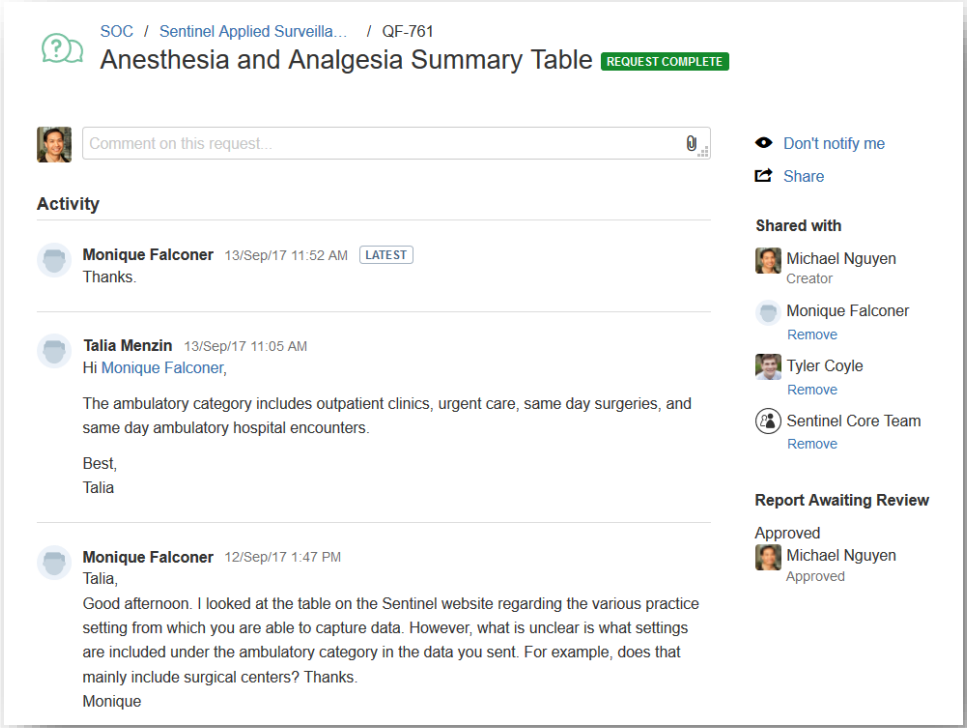
Q12 | What is the anticipated number of studies that FDA would like to be able to run in a year? We realize this can't be predicted exactly, but a sense of scale would be helpful – 100, 500, 1000?



https://www.sentinelinitiative.org/active-risk-identification-and-analysis-aria

Q13| How do the FDA programs interact from a governance and process perspective with the Sentinel program and contractor?

- Analytic teams are created with FDA and Sentinel Operations Center (SOC) staff
- Smaller teams for simple analyses: SOC data analyst and FDA epidemiologist
- Larger for complex analyses: multiple SOC, FDA, and other staff from different scientific disciplines
- FDA leads all medical product safety assessments, but methods projects typically led by non-FDA investigators



Q14| How is the Sentinel program currently creating, storing and reusing algorithms to identify outcomes of interest? Are they stored in Excel, in a database or some other way? (By algorithms, we are referring to the codes and logic used to identify clinical events of interest).

- FDA derives its algorithms from a variety of sources, including:
  - Algorithms published in the scientific literature
  - FDA funded expert literature reviews
  - FDA funded outcome validation studies
- The algorithms are stored in several places, and are reused by FDA if deemed appropriate for the study question
- Algorithms are posted online with the final results and SAS analytic packages
- See response to Q17 for more information

Q15 | Explain the current business expectations and requirements of the data partners. E.g. are there formal contracts/grants with service levels, data agreements, etc in place; and are the data partners required to respond to every query?

- Data partners participate in Sentinel under a contractual agreement formed with the Sentinel Operations Center
  - Data partners commit to transforming and quality checking their data at predefined intervals (i.e., quarterly, semi-annual, annual basis)
  - Data partners commit their local expertise to ensure completeness, consistency and accuracy of data collection and management
  - The number and type of queries to be run per quarter is specified in a service level agreement and defined annually to meet projected FDA needs. The contract sets timelines for query fulfilment.
- Data partners do not have to respond to every query and may opt out at any time

Vendor Questions | Transparency Related

16. Does FDA have guidelines for transparency, reproducibility, or validation with respect to Sentinel studies?
17. Does FDA have plans to share its study protocols publicly?
18. Does FDA have plans to share its algorithms publicly?
19. Can you please review an example of past sentinel query from signal to regulatory action?

Q18| Does FDA have guidelines for transparency, reproducibility, or validation with respect to Sentinel studies?

- The Sentinel program aims to adhere to the principles described in key consensus papers developed by the scientific community to help achieve consistent reproducible analyses

Received: 21 July 2017 | Revised: 25 July 2017 | Accepted: 25 July 2017
DOI: 10.1002/pds.4295

WILEY

ORIGINAL REPORT

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

Shirley V. Wang[1,2] | Sebastian Schneeweiss[1,2] | Marc L. Berger[3] | Jeffrey Brown[4] | Frank de Vries[5] | Ian Douglas[6] | Joshua J. Gagne[1,2] | Rosa Gini[7] | Olaf Klungel[8] | C. Daniel Mullins[9] | Michael D. Nguyen[10] | Jeremy A. Rassen[11] | Liam Smeeth[6] | Miriam Sturkenboom[12] |
on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making

Q16 | Does FDA have plans to share its study protocols publicly?

- FDA continues to post all study protocols for protocol-based assessment (i.e., studies with full custom programming)
- FDA's transition to primarily using ARIA's parameterized reusable analytic tools has resulted in fewer protocol-based assessment
- Currently, all ARIA results in CDER are posted online and the final reports include all major analytic parameters
- Going forward, CDER will post SAS analytic packages for all inferential analyses (Level 2) to enable exact replication in other systems that format their data to the Sentinel CDM and use Sentinel tools (e.g., IMEDS)

Postings | Analysis Parameters and Results

ARIA Analyses for Safety Issues Identified During Review of New Applications and Supplements

Drug Name	Outcome Assessed	Related Links	Date Posted
Siliq (brodalumab)	• Neutropenia • Serious infections • Myocardial infarction and stroke		8/23/2017
Stelara (ustekinumab)	• Serious Infection		8/23/2017
Tremfya (guselkumab)	• Short term lymphoma e.g.,within 1-3 years		9/29/2017
Sinuva (mometasone furoate)	• Cataracts • Glaucoma • Nasal perforation	Approval letter	12/18/2017

https://www.sentinelinitiative.org/drugs/ongoing-aria-assessments

How ARIA Analyses Have Been Used by FDA

This page summarizes how select analyses conducted in Sentinel's Active Risk Identification and Analysis (ARIA) system have been used by FDA since Sentinel's official launch in February 2016. ARIA can contribute to FDA's regulatory process in a variety of ways, such as contributing evidence to support a label change, respond to a Citizens Petition, or become part of an Advisory Committee deliberation. Information from ARIA can also provide evidence that alleviates concerns about a particular safety issue and might lead FDA to determine that no regulatory action is necessary based on the available information.

Each ARIA analysis listed below contributed in some material way to inform an important regulatory discussion or action. FDA makes decisions about drug safety issues based upon the totality of evidence. The listing of an ARIA analysis in the table means that Sentinel's ARIA system was one important source of evidence considered.

Drug Name	Outcome Assessed	ARIA Analy-sis	Regulatory Determination / Use	Date Posted
Keppra (levetirac-etam)	Anaphylaxis and an-gioedema	Level 1	Drug Safety Label Change, Warnings and Precautions • Results • FDA Drug Safety Labeling Changes Page	11/30/2017
Ketoconazole oral tablets	Drug use trends after safety label change and use in labeled indications	Level 1	Citizen Petition Response • Results • Letter from FDA (Docket No. FDA-2015-P-0578)	12/4/2017
Antipsychotic agents (including haloperidol injec-tion)	Ischemic and hemor-rhagic stroke	Level 1, Level 2	Sentinel data was used to support decisions around poten-tial labeling changes for antipsychotics and stroke risk. FDA decided that no action is necessary at this time, based on available information. • Level 1 Results • Level 2 Results • Results among SSRI Users • 2017 ICPE Symposium	12/8/2017

https://www.sentinelinitiative.org/drugs/how-aria-analyses-have-been-used-fda

Q17| Does FDA have plans to share its [health outcomes of interest] algorithms publicly?

- The algorithms used to identify outcomes of interest are available on the Sentinel website in several places:
  - SAS analytic package for each query
  - Final results and associated specifications
  - Health outcome of interest page that aggregates these algorithms into a single page (see next slide)

Health Outcome of Interest Validations and Literature Reviews

This webpage provides access to Sentinel Health Outcome of Interest (HOI) activities that have been conducted by the FDA. The search options below can be used to find more information about each study type or health outcome. Code lists (such as ICD-9-CM codes, ICD-10 codes, procedure codes, etc.), algorithm criteria, and literature reviews for these activities appear in the form of reports or Microsoft Excel workbooks. These materials can be found by clicking on either the hyperlinked Deliverables listed or the hyperlinked Title to navigate to the activity's webpage which also lists the Deliverables.

- **Novel Approaches to More Efficient Outcome Validation** aim to identify solutions to the governance, process, and technology barriers to support more efficient outcome validation as a starting point for greater sufficiency of Active Risk Identification and Analysis (ARIA), a stronger Sentinel System, and a more rigorous evidence generation enterprise.
- **Validations Supported by Traditional Medical Chart Review** involve checking codes derived from electronic medical records and administrative claims-based data against medical chart information to verify that the electronic codes validly and reliably identify individuals with particular medical conditions.
- **Outcomes Assessed in Inferential Analyses** identify medical conditions defined as outcomes of interest in inferential analyses and their respective code lists and algorithm criteria.
- **Literature Reviews** primarily concern identification of health outcomes and focus on determining which codes in electronic medical record and administrative claims-based data are the most valid and reliable indicators of the presence of particular medical conditions.

Health Outcome

Study Type

- Any -

Search | Show All

- Novel Approaches to More Efficient Outcome Validation
- Validations Supported by Traditional Medical Chart Review
- Outcomes Assessed in Inferential Analyses
- Literature Reviews

- Novel Approaches to More Efficient Outcome Validation
- Validations Supported by Traditional Medical Chart Review
- Outcomes Assessed in Inferential Analyses

Title	Outcomes	Reports	Status	Date Posted
Seizure Algorithm Defined in "Ranexa (Ranolazine) and Seizures"	seizure	Deliverables: Seizure Algorithm Defined in "Ranexa (Ranolazine) and Seizures" Related Links: Ranexa (Ranolazine) and Seizures	Complete	04/24/2018
Stroke Algorithm Defined in "Antipsychotics/Selective Serotonin Reuptake Inhibitors (SSRIs) and Stroke"	hemorrhagic stroke, ischemic stroke, stroke	Deliverables: Stroke Algorithm Defined in "Antipsychotics/Selective Serotonin Reuptake Inhibitors (SSRIs) and Stroke" Related Links: Antipsychotics/SSRIs and Stroke (PSM)	Complete	04/23/2018
Stroke Algorithm Defined in "Antipsychotics and Stroke"	hemorrhagic stroke, ischemic stroke, stroke	Deliverables: Stroke Algorithm Defined in "Antipsychotics and Stroke" Related Links: Antipsychotics and Stroke (PSM)	Complete	04/23/2018
Venous Thromboembolism Algorithm Defined in "Venous Thromboembolism Following Combined Oral Contraceptives Compared with Cyclic Oral Contraceptives"	venous thromboembolism (VTE)	Deliverables: Venous Thromboembolism Algorithm Defined in "Venous Thromboembolism Following Combined Oral Contraceptives Compared with Cyclic Oral Contraceptives" Related Links: Venous Thromboembolism Following Combined Oral Contraceptives Compared with Cyclic Oral Contraceptives	Complete	04/23/2018

https://www.sentinelinitiative.org/sentinel/surveillance-tools/validations-lit-review

Example: Venous Thromboembolism

Overview

Title	Venous Thromboembolism Algorithms Defined in "Venous Thromboembolism Following Combined Oral Contraceptives Compared with Cyclic Oral Contraceptives"
Request ID	cder_mpl2p_wp001_nsdp_v01
Description	This report lists International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis codes and algorithms used to define venous thromboembolism (VTE) in this request. For additional information about the algorithm and how it was defined relative to the cohort and exposures of interest in the inferential analysis, see the Modular Program reports here: https://www.sentinelinitiative.org/drugs/assessments/venous-thromboembolism-following-coc-compared-with-new-cyclic-coc.
Outcome	Venous thromboembolism
Algorithms to Define Outcome	Algorithm A: Evidence of an ICD-9-CM code used to define VTE in the Inpatient care setting in any diagnosis position. Algorithm B: Evidence of an ICD-9-CM code used to define VTE in the Outpatient or Other Ambulatory care setting plus anticoagulant treatment within four weeks following the Outpatient or Other Ambulatory VTE diagnosis. Please see the Modular Program reports to determine which algorithm was used in each comparison.
Query Period	May 22, 2007 - September 30, 2015
Request Send Date	March 28, 2017

Sentinel

International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) Diagnosis Codes Used to Define Venous Thromboembolism in this Request

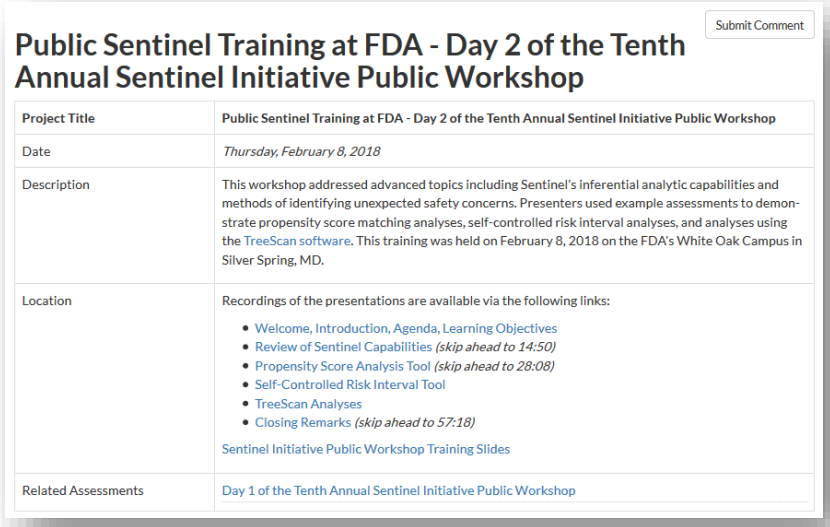
ICD-9-CM Codes	Description
415.1	Pulmonary embolism and infarction
415.1*	Pulmonary embolism and infarction
453	Other venous embolism and thrombosis
453*	Other venous embolism and thrombosis
453**	Other venous embolism and thrombosis

Note: Codes containing "*" indicate wildcards. Wildcards are used to represent a digit 0-9 or a letter A-Z. Wildcards are always indicative of one character. For example, "250*" will always expand into a four-digit code, never a five-digit code, while "250**" will always expand into a five-digit code.

https://www.sentinelinitiative.org/sites/default/files/SurveillanceTools/ValidationsAndLiterature/VTE_code_list.pdf

Q19 | Can you please review an example of past sentinel query from signal to regulatory action?

- Examples can be found in prior Sentinel training events and presentations at international scientific conferences



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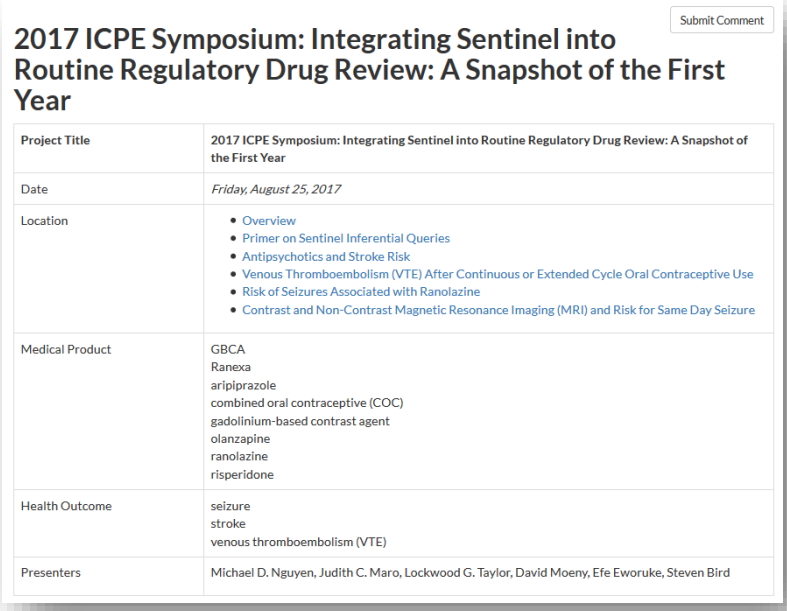
Public Sentinel Training at FDA - Day 2 of the Tenth Annual Sentinel Initiative Public Workshop

Project Title	**Public Sentinel Training at FDA - Day 2 of the Tenth Annual Sentinel Initiative Public Workshop**
Date	*Thursday, February 8, 2018*
Description	This workshop addressed advanced topics including Sentinel's inferential analytic capabilities and methods of identifying unexpected safety concerns. Presenters used example assessments to demonstrate propensity score matching analyses, self-controlled risk interval analyses, and analyses using the TreeScan software. This training was held on February 8, 2018 on the FDA's White Oak Campus in Silver Spring, MD.
Location	Recordings of the presentations are available via the following links: • Welcome, Introduction, Agenda, Learning Objectives • Review of Sentinel Capabilities *(skip ahead to 14:50)* • Propensity Score Analysis Tool *(skip ahead to 28:08)* • Self-Controlled Risk Interval Tool • TreeScan Analyses • Closing Remarks *(skip ahead to 57:18)* Sentinel Initiative Public Workshop Training Slides
Related Assessments	Day 1 of the Tenth Annual Sentinel Initiative Public Workshop

https://www.sentinelinitiative.org/communications/sentinel-initiative-events/sentinel-initiative-public-workshop-tenth-annual-day-2



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2017 ICPE Symposium: Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year

Project Title	**2017 ICPE Symposium: Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year**
Date	*Friday, August 25, 2017*
Location	• Overview • Primer on Sentinel Inferential Queries • Antipsychotics and Stroke Risk • Venous Thromboembolism (VTE) After Continuous or Extended Cycle Oral Contraceptive Use • Risk of Seizures Associated with Ranolazine • Contrast and Non-Contrast Magnetic Resonance Imaging (MRI) and Risk for Same Day Seizure
Medical Product	GBCA Ranexa aripiprazole combined oral contraceptive (COC) gadolinium-based contrast agent olanzapine ranolazine risperidone
Health Outcome	seizure stroke venous thromboembolism (VTE)
Presenters	Michael D. Nguyen, Judith C. Maro, Lockwood G. Taylor, David Moeny, Efe Eworuke, Steven Bird

https://www.sentinelinitiative.org/communications/publications/2017-icpe-symposium-integrating-sentinel-routine-regulatory-drug-review

AGENDA | Industry Presentations

PRESENTING ENTITY	TIME
Location: Building 31, Room 1404	
Booz Allen Hamilton	11:15a (25 minutes)
Columbia University	11:45a (25 minutes)
Digicon	12:15p (25 minutes)
LUNCH BREAK – 12:45p -- 30 Min	
Location: Building 31, Room 1504	
Enigma	1:15p (25 minutes)
Harvard Pilgrim Health Care	1:45p (25 minutes)
Health Core Inc	2:15p (25 minutes)
IBM	2:45p (25 minutes)
BREAK – 3:15p – 15 Min	

AGENDA | Industry Presentations

PRESENTING ENTITY	TIME
Location: Building 31, Room 1504	
McKinsey + Co.	3:30p (25 minutes)
Outcomes Insights, Inc.	4:00p (25 minutes)
Research Triangle Institute (RTI)	4:30p (25 minutes)

Each company is requested to sign in 15 minutes prior to their scheduled time for presentation. Sign-in will take place outside of Great Room 1503 Section A. Prepare to assemble at the RESERVED seating area (adjacent to registration area) at time of sign-in and kindly wait to be called for your presentation.


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