



# SENTINEL SYSTEM

## PRINCIPLES AND POLICIES

March 2018

The Sentinel System is sponsored by the [U.S. Food and Drug Administration \(FDA\)](#) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's [Sentinel Initiative](#), a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I.

## History of Modifications

The original Mini-Sentinel *Principles and Policies* document has been updated to reflect procedures developed to operationalize the Sentinel System and renamed as the Sentinel *Principles and Policies*. The Sentinel System *Principles and Policies*, and all subsequent modifications, have been approved by the FDA and the Sentinel Planning Board.

Date	Modification
November 2010	Original Mini-Sentinel document
May 2011	Revised Communications Policy
April 2012	Revised Communications Policy
August 2012	Updated document
November 2013	Revised criteria for workgroup leadership Updated document
April 2014	Revised Conflict of Interest Policy
November 2014	Revised Conflict of Interest Policy Updated document throughout
May 2016	Revised Intellectual Property Policy
March 2018	Updated document throughout for Sentinel System Revised Organizational Structure section Revised description of routine analytic tools Revised Communications Policy Revised Conflict of Interest Policy

# Sentinel System

## Principles and Policies

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## 1. INTRODUCTION

### 1.1 Purpose

The Sentinel System is an active surveillance system sponsored by the U.S. Food and Drug Administration (FDA) to monitor the safety of regulated medical products using pre-existing electronic healthcare data from multiple sources. The Sentinel System is part of the [FDA's Sentinel Initiative](#), which is exploring a variety of approaches for improving the Agency's ability to identify and assess safety issues. This system complements existing FDA surveillance capabilities that track adverse events reported after the use of FDA-regulated medical products by allowing the FDA to proactively assess the safety of these products. Information obtained through the Sentinel System is intended to complement other types of data and information compiled by FDA scientists, such as information from the FDA's adverse event reporting systems,<sup>1,2</sup> published study results, and clinical trials, which can be combined with Sentinel data and used by FDA to inform regulatory decisions regarding medical product safety. Any public health actions taken by FDA regarding products involved in Sentinel queries and protocols are communicated through existing FDA channels.

The Sentinel System *Principles and Policies* govern actions of Sentinel Collaborators as they participate in Sentinel System activities. A Collaborator is an institution or individual that provides access to healthcare data and/or scientific, technical, methodologic, and organizational expertise, as needed to meet the requirements of Sentinel. Collaborators participate in Sentinel activities in various capacities. Collaborators include, but are not limited to, the Sentinel Coordinating Center and its components, the Sentinel Operations Center (SOC) housed at Harvard Pilgrim Health Care Institute (HPHCI), Academic and Data Partners, members of project workgroups, and independent contractors.

Collaborators agree to abide by all policies and procedures expressed herein, as well as the requirements of their Sentinel System contracts and subcontracts, for the duration of their participation and all applicable post-contract restriction periods.

### 1.2 Background

In the fall of 2007, Congress passed the [FDA Amendments Act \(FDAAA\)](#), mandating the FDA to establish an Active Postmarket Risk Identification and Analysis (ARIA) system. FDAAA requires the FDA to develop, in collaboration with public, academic, and private entities, methods to obtain access to disparate sources of health data as well as validated methods for the establishment of a system to link and analyze medical product safety data from multiple sources.

In May 2008, in response to FDAAA, the Secretary of the Department of Health and Human Services (HHS) and FDA's Commissioner announced the Sentinel Initiative, a long-term, multifaceted effort to create a national electronic system for actively monitoring the safety of FDA-regulated medical products. Prior to development of the Sentinel System, FDA developed expertise in using administrative and insurance claims databases to conduct pharmacoepidemiology studies to investigate safety questions about FDA-regulated medical products. With the Sentinel Initiative, the FDA has created a scalable, efficient, extensible, and sustainable system—the Sentinel System—that leverages existing

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<sup>1</sup> FDA's Adverse Event Reporting System (FAERS) - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>

<sup>2</sup> FDA's Vaccine Adverse Event Reporting System (VAERS) - <https://vaers.hhs.gov/index>

electronic healthcare data from multiple sources to actively and quickly monitor the safety of regulated medical products. The Sentinel System will continue to be developed and implemented in stages and will augment the FDA's existing, and largely passive, postmarket safety surveillance systems.

All three FDA Centers focused on regulation of medical products, including the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiologic Health (CDRH), participate in the Sentinel Initiative and Sentinel System. Together the Centers have developed an ARIA system comprised of pretested, validated, and parameterized cohort identification and analysis programs that run against data held in Sentinel Common Data Model (SCDM) format by participating Data Partners. Within the Sentinel System, CBER has also created the Postmarket Rapid Immunization Safety Monitoring (PRISM) system focused on surveillance of vaccines and the Blood Surveillance Continuous Active Network (BloodSCAN) focused on surveillance of blood and blood products.

One of the first stages of the development of the Sentinel System included Mini-Sentinel. This pilot program was launched in 2009 to test the feasibility of creating a national medical product active surveillance system and to develop the scientific approaches needed for creating such a national system. FDAAA set specific goals that FDA be able to access data from 25 million people by July 2010 and 100 million people by July 2012. Both goals were met and exceeded during the Mini-Sentinel pilot phase of the Sentinel Initiative.

In 2014, the FDA began transitioning from the Mini-Sentinel pilot to the fully operational Sentinel System, which launched in February 2016. The Sentinel System builds upon the successes of the Mini-Sentinel pilot and leverages the Sentinel Infrastructure, including the Sentinel distributed database and common data model. This infrastructure enables the centralized development of cohort identification and analysis programs that can be run remotely in participating Data Partners' secure data environments.

## 1.3 Key Features & Terms

### 1.3.1 Key Features

**Active Surveillance:** The Sentinel System monitors the safety of FDA-regulated medical products in response to FDA concerns through assessment of routinely collected electronic healthcare data. It does not require patients or clinicians to initiate reports to FDA and does not collect new data.

**Distributed Data Network:** The Sentinel System uses a distributed data approach in which Data Partners retain control over data in their possession as a result of normal business activities. Data Partners execute standardized computer programs within their own institutions, behind their firewalls, on data that has been formatted according to a common data model and, under most circumstances, share aggregated results.

**Transparency:** Transparency is a fundamental principle of the operations of the Sentinel System. Final results of Sentinel System activities are placed in the public domain via the [Sentinel Initiative website](#).

**Privacy and Security:** Sentinel System activities adhere to applicable privacy-related laws and regulations governing public health practice. Whenever possible, aggregate data are used; when individual-level information is required, the data are stripped of all direct identifiers. The Sentinel System is subject to the security requirements of the [Federal Information Security Management Act of 2002 \(FISMA\)](#) and has implemented policies and procedures to ensure the utmost data security. FISMA certification is maintained and renewed on an annual basis.

### 1.3.2 Key Terms

**Sentinel Initiative:** A long-term effort to create a national electronic system for monitoring FDA-regulated medical products.

**Mini-Sentinel:** A pilot project, now complete, sponsored by the FDA to create an active surveillance system - the Sentinel System - to monitor the safety of FDA-regulated medical products.

**Sentinel System:** A system, being developed and implemented in stages, to expand FDA's existing postmarket safety surveillance capabilities by enabling the FDA to actively gather information about the safety of regulated medical products following FDA approval. Components of this system include ARIA, PRISM, BloodSCAN, and STAT (see below).

**ARIA: Active postmarket Risk Identification and Analysis System:** A subcomponent of the Sentinel System mandated in the Food and Drug Administration Amendments Act (FDAAA) of 2007 that is comprised of pretested, validated, and parameterized analytic programs that run against data held in SCDM format by participating Data Partners.

**PRISM: Postlicensure Rapid Immunization Safety Monitoring Program:** A subcomponent of the Sentinel System developed by CBER focused on immunization safety surveillance that is fully integrated into CBER's regulatory review process for vaccines. PRISM has been deployed for evaluation and refinement of potential safety signals identified during premarket and postmarket reviews and for evaluation of vaccine effectiveness.

**BloodSCAN: Blood Safety Surveillance Continuous Active Network:** A subcomponent of the Sentinel System developed by CBER focused on blood and blood product safety surveillance. Integration into CBER's regulatory review process for blood and blood products is ongoing.

**STAT: Surveillance of Tissues and Advanced Therapeutics:** A subcomponent of the Sentinel System developed by CBER focused on surveillance and recipient safety evaluation of human cell-, gene-, and tissue-based products, other advanced therapies, and antivenins.

**FDA-Catalyst:** A program under development intended to use the Sentinel Infrastructure to expand the FDA's ability to actively gather information about the performance of regulated medical products following FDA approval. This system relies on the Sentinel Infrastructure to identify cohorts of interest and conduct analyses. Unlike the Sentinel System, its activities may involve interventions and interactions in addition to use of routinely collected data. Participation by Collaborators in FDA-Catalyst activities will be governed separately by the *FDA-Catalyst Principles and Policies*.



## 2. ORGANIZATIONAL STRUCTURE

### 2.1 Food and Drug Administration

FDA provides all funding, determines all priorities, and retains ultimate decision-making authority for Sentinel. FDA administers the contract, issues all task orders, and reviews and approves all work products and deliverables. The 2009 Mini-Sentinel and 2014 Sentinel contracts were awarded to Harvard Pilgrim Health Care (HPHC) on behalf of the Harvard Pilgrim Health Care Institute (HPHCI). The organizational structure is subject to change in subsequent contracts.

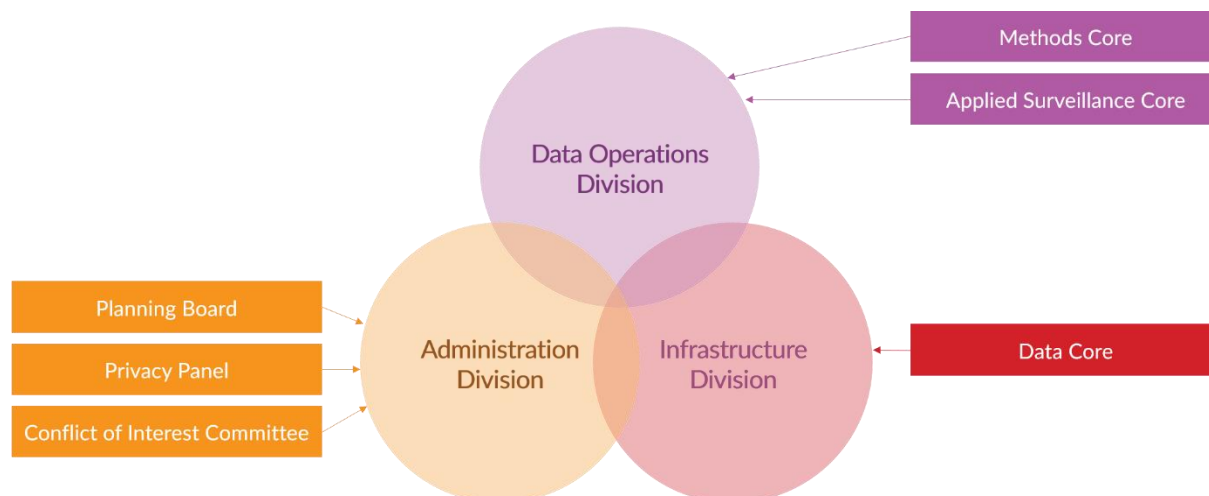
### 2.2 Collaborating Institutions

The Sentinel Collaborating Institutions include both Data and Academic Partners that provide access to healthcare data and/or scientific, technical, methodologic, and organizational expertise, as needed to meet the requirements of the project. Representatives of the Collaborating Institutions participate in various capacities, including as members of the Planning Board, the Cores (Data, Methods, and Applied Surveillance) and project workgroups engaged in task order and other Sentinel activities.

The principal Collaborating Institutions are listed on the Sentinel website. Additional institutional and individual Collaborators may be added as Sentinel evolves.

### 2.3 Sentinel Coordinating Center

The Sentinel Coordinating Center encompasses the groups depicted in the diagram below. These groups are described in greater detail in subsequent sections. The Data Operations, Infrastructure, and Administration Divisions comprise the Sentinel Operations Center (SOC), which is housed at HPHCI. Both the Sentinel Coordinating Center and the SOC are led by the Sentinel Principal Investigator.



## **2.4 Sentinel Operations Center**

The SOC is comprised of three Divisions (Infrastructure, Data Operations, and Administration), which together lead Sentinel's activities. The SOC works closely with the FDA, the Data, Methods, and Applied Surveillance Cores, the Planning Board, and all advisory committees and panels. The SOC reports to the Sentinel Principal Investigator.

### **2.4.1 Infrastructure Division**

The Infrastructure Division oversees all aspects of Sentinel data, tool development, programming, and technical systems. The Infrastructure Division is the SOC's primary liaison to the Data Core and Data Partners.

#### **2.4.1.1 Responsibilities**

- Coordinate and oversee development and implementation of the Routine Analytical Framework (RAF) which comprises the analytic tools used in ARIA
- Maintain and update the SCDM and distributed data network
- Document data sources and characteristics
- Assess data quality
- Lead programming to support workgroups and analyses
- Review and oversee data-related workgroup proposals, activities, and work products
- Develop, coordinate, and conduct data-related trainings for the FDA and Sentinel affiliate organizations
- Develop and manage FISMA-compliant secure data transfer and storage systems
- Coordinate the activities of the Data Core

### **2.4.2 Data Operations Division**

The Data Operations Division oversees all queries, surveillance plans, protocol-based assessments, and methods development activities, including ARIA, PRISM and BloodSCAN. The Division is the main point of contact for FDA's scientists, including but not limited to clinicians, epidemiologists, and biostatisticians, to address regulatory issues. The Data Operations Division is the SOC's primary liaison to the Methods and Applied Surveillance Cores.

#### **2.4.2.1 Responsibilities**

- Oversee, manage, and implement ARIA requests and other applied surveillance activities
- Provide epidemiologic and methodologic expertise
- Coordinate development of new statistical and epidemiological methods
- Review and oversee surveillance plan and protocol-related workgroup proposals, activities, and work products
- Develop, coordinate, and conduct ARIA, protocol, and methods related trainings for the FDA and Sentinel affiliate organizations
- Coordinate the activities of the Methods and Applied Surveillance Cores

### **2.4.3 Administration Division**

The Administration Division oversees all administration and finance aspects of Sentinel, including boards, committees, and panels, and is the main point of contact for the FDA and Collaborating Institutions' contracts officers and administrators. The Administration Division provides project

management support for the work of the Infrastructure and Data Operations Divisions, including Sentinel workgroup activities. The Administration Division works closely with the FDA, Data Operations and Infrastructure Divisions, and Collaborating Institutions to support strategic planning, administration, and implementation of Sentinel activities.

#### **2.4.3.1 Responsibilities**

- Manage all finance aspects of Sentinel, including workgroup opportunities, scopes of work, budgets, contracts, and responses to task orders
- Provide project management support across all Sentinel activities
- Oversee and support all boards, committees and panels
- Oversee and coordinate internal and external communications
- Coordinate the clearance of Sentinel work-products between the SOC and the FDA

### **2.5 Data, Methods, and Applied Surveillance Cores**

The Cores serve as expert advisory committees for the Infrastructure and Data Operations Divisions. Core Leaders are selected by the Sentinel Principal Investigator in consultation with the FDA. Collaborating Institution and FDA representatives are chosen by their respective institutions.

#### **2.5.1 Data Core**

The Data Core serves as an expert advisory committee that works with the Infrastructure Division concerning ongoing development, expansion, and implementation of the SCDM, distributed data network and approach, and related data standards and quality measures. The Data Core is a key conduit for communication among FDA, Data and Academic Partners, project workgroups, and other parties interested in data-related aspects of Sentinel activities. The Data Core interacts regularly with the Methods and Applied Surveillance Cores.

##### **2.5.1.1 Responsibilities**

- Work with the Infrastructure Division
  - to further develop, implement, and manage a scalable and extensible common data model to meet the needs of Sentinel
  - to incorporate national data standards into the SCDM and data analysis
  - to implement continually improving data quality measures
- Lead data-related strategic planning
- Collaborate with FDA, SOC, Methods Core, and Applied Surveillance Core

##### **2.5.1.2 Members**

1. Data Core Leaders
2. Infrastructure Division Director and staff
3. Representatives from each Data Partner
4. Representatives from FDA
5. Additional analytical, technical, and project management staff, as warranted

#### **2.5.2 Methods Core**

The Methods Core serves as an expert advisory committee that works with the Data Operations Division on development and implementation of epidemiological and biostatistical methods for Sentinel. The Methods Core is a key conduit for communication among Data and Academic Partners, project

workgroups, and other parties interested in methods-related aspects of Sentinel activities. The Methods Core interacts regularly with the Data and Applied Surveillance Cores.

#### **2.5.2.1 Responsibilities**

- Identify and evaluate available methodological, epidemiological, and biostatistical approaches and data structures to address specific medical product questions
- Identify key gaps in existing methodological approaches for performing medical product safety surveillance within Sentinel
- Lead methods development strategic planning
- Collaborate with FDA, SOC, Data Core, and Applied Surveillance Core

#### **2.5.2.2 Members**

1. Methods Core Leaders
2. Data Operations Division Director and staff
3. Representatives from FDA
4. Additional analytical, technical, and project management staff, as warranted

### **2.5.3 Applied Surveillance Core**

The Applied Surveillance Core serves as an expert advisory committee that works with the Data Operations Division on engagement and consultation with the FDA regarding active surveillance topics and development of assessment protocols and surveillance plans. The Applied Surveillance Core is a key conduit for communication among Data and Academic Partners, project workgroups, and other parties interested in applied surveillance-related aspects of Sentinel activities. The Applied Surveillance Core interacts regularly with the Data and Methods Cores.

#### **2.5.3.1 Responsibilities**

- Provide advice to the FDA and Data Operations Division regarding active surveillance topics and development of assessment protocols and surveillance plans
- Collaborate with FDA, SOC, Data Core, and Methods Core

#### **2.5.3.2 Members**

1. Applied Surveillance Core Leaders
2. Data Operations Division Director and staff
3. Representatives from FDA
4. Additional analytical, technical, and project management staff, as warranted

## **2.6 Boards, Panels, and Committees**

### **2.6.1 Planning Board**

The Planning Board includes representatives of the FDA, each of the Collaborating Institutions, and the patient community. The Planning Board advises the FDA and the Sentinel Principal Investigator on Sentinel operations and activities, works with the Sentinel Operations Center (SOC) to define overarching policies and procedures, and provides a forum for communication among the various entities involved. Additionally, the Planning Board assists the SOC in establishing Advisory Panels when warranted.

### **2.6.1.1 Responsibilities**

- Represent the FDA, Collaborating Institutions, and the patient community in Sentinel deliberations and decisions
- Provide guidance to the SOC regarding the conduct of Sentinel activities

### **2.6.1.2 Members**

1. Sentinel Principal Investigator (Chair)
2. Three FDA representatives
3. One representative from each of the Collaborating Institutions
4. One co-Leader from each of the Data, Methods, and Applied Surveillance Cores
5. Three patient representatives

### **2.6.1.3 Board Members' Terms**

Members serve at the discretion of the represented entity.

### **2.6.1.4 Selection Procedure**

The FDA and the Collaborating Institutions select their own representatives. The Sentinel Principal Investigator and individual Core co-Leads (3) decide by mutual agreement. Patient representatives are recommended by the FDA and selected by the Sentinel Principal Investigator.

## **2.6.2 Privacy Panel**

The Privacy Panel serves as a senior expert panel for privacy issues related to the Sentinel Initiative. The Privacy Panel is comprised of independent experts with extensive knowledge of legal and ethical issues related to the privacy and confidentiality of individual health information used for public health surveillance activities. The Privacy Panel advises the Sentinel Principal Investigator as needed.

### **2.6.2.1 Responsibilities**

- Provide expertise regarding federal patient privacy-related laws, regulations, and ethical standards pertaining to the conduct of Sentinel
- Guide the development of policies and procedures that are consistent with federal legislation concerning uses of individual health information in Sentinel activities

The Privacy Panel does not provide legal advice to the FDA or SOC. Consulting the Panel does not give rise to an attorney-client relationship.

### **2.6.2.2 Members**

- Up to three independent experts in healthcare privacy law
- The three patient representatives to the Sentinel Planning Board

### **2.6.2.3 Members' Terms**

Members serve at the discretion of the Sentinel Principal Investigator in consultation with the FDA.

### **2.6.2.4 Selection Procedure**

Privacy Panel members are chosen by the Sentinel Principal Investigator in consultation with the FDA.

### **2.6.3 Conflict of Interest Committee**

The Conflict of Interest (COI) Committee oversees development and implementation of the Sentinel Conflict of Interest policy (See **Section 8**) and advises the Sentinel Principal Investigator on Sentinel COI issues.

#### **2.6.3.1 Responsibilities**

- Collect and assess COI attestations and disclosures and determine conflicts
- Oversee COI management plans and mitigation of belatedly identified conflicts
- Advise the Sentinel Principal Investigator on COI issues

#### **2.6.3.2 Members**

Three individuals, identified by the Sentinel Principal investigator in collaboration with FDA, with no other engagement with Sentinel System surveillance activities, who have expertise related to COI issues in the field of medicine and medical or scientific research, including:

- One lawyer
- One scientist
- One knowledgeable member of the “lay public”

#### **2.6.3.3 Members Terms**

One-year, renewable, for the duration of the Sentinel contract.

#### **2.6.3.4 Selection Procedure**

Committee members are selected by the Sentinel Principal Investigator in consultation with the FDA. The COI Committee Chair is chosen by the Sentinel Principal Investigator.

### **2.6.4 Advisory Panels**

Advisory Panels are created, as needed, to address issues that arise in the conduct of Sentinel activities. Topics to be addressed by Advisory Panels are determined jointly by the FDA and the Sentinel Principal Investigator. Members of Advisory Panels are selected by the Sentinel Principal Investigator in consultation with the FDA and the Planning Board. Advisory Panels must include at least one FDA and one SOC member.

If the need for an Advisory Panel is identified by the FDA and the Sentinel Principal Investigator, the SOC will draft an Advisory Panel Scope of Work. This document will include the specific issue(s) to be addressed by the Advisory Panel, deliverables (i.e. proposed policy, process, or recommendations), timelines, meeting frequency, estimated hours of work, and the number of Collaborating Institution representatives and/or other experts needed. Service on the Advisory Panel will be voluntary. If the topic requires expertise that cannot be addressed by staff from Collaborating Institutions, outside consultants may be considered.

## **2.7 Sentinel Workgroups**

At the request of the FDA, Sentinel Workgroups are created to implement Sentinel-specific activities. In those cases, the SOC, in collaboration with the FDA, will develop and issue a Sentinel Workgroup Opportunity to Collaborating Institutions. The Sentinel Workgroup Opportunity will include a brief background and statement of purpose for the work to be undertaken, along with a timeline for

expressing interest in participation. Each Sentinel Project Workgroup created via a Sentinel Workgroup Opportunity will include at least one SOC investigator, one SOC Project Manager, and one FDA Lead. If FDA and Sentinel leadership determine the work should be completed by internal SOC investigators, additional investigators with relevant expertise from Sentinel Collaborating Institutions may be invited to participate via a Sentinel Expert Consultation Opportunity.

### **2.7.1 Responsibilities**

- Develop project goals, deliverables and associated timelines, including specific tasks for implementation
- Collaborate with the appropriate SOC Division and the FDA to ensure workgroup activities meet the goals and needs of the FDA
- Work with the Operations Division to determine and track budget and deliverables
- Design and implement appropriate data collection strategies and analytic methods in accordance with established Sentinel policies and standard operating procedures
- Prepare reports and other deliverables in accordance with Sentinel processes
- Work with the Operations Division and FDA to present findings of workgroup activity
- Meet deadlines established by the SOC and FDA

### **2.7.2 Workgroup Leadership**

When a Sentinel Workgroup is to be led by a SOC investigator, the Sentinel Principal Investigator, with approval from FDA, will identify the Workgroup Lead.

When a Sentinel Workgroup Opportunity is issued, qualified Sentinel Collaborators are invited to indicate their interest in leading the Sentinel Workgroup. When more than one potential leader expresses interest, the Sentinel Principal Investigator, or a designee, will confer with the interested individuals to determine a mutually acceptable leadership arrangement. If the interested individuals cannot agree, the Sentinel Principal Investigator designates the leader in consultation with the FDA. Under some circumstances, such as when a Sentinel Collaborator has unique experience and expertise or the FDA requires an expedited process, workgroup leaders may be designated without eliciting interest from all Sentinel Collaborators. The Sentinel Principal Investigator will then designate the workgroup lead in consultation with the FDA.

Investigators interested in serving as the Sentinel Workgroup Lead are responsible for preparing Workgroup Proposals outlining and describing their approach for meeting the requirements outlined in the Sentinel Workgroup Opportunity. Sentinel Workgroup Proposals should include the following:

#### **1. Required Criteria:**

- Expertise relevant to the Sentinel project, which may include knowledge of appropriate methods, clinical subject area, and data characteristics
- Demonstrated capacity to manage workgroups
- A feasible and valid approach to achieving requested deliverables
- Demonstrated capability to develop a budget and timeline consistent with the available resources and time constraints
- Detailed description outlining the timeline for meeting all project deadlines, including milestone deliverables

#### **2. Preferred Criteria:**

- Prior participation in a Mini-Sentinel or Sentinel workgroup to ensure sufficient familiarity with Sentinel data, conventions, and tools

- Representation from multiple Collaborating Institutions to promote knowledge transfer and program development
- Inclusion of mentoring opportunities to ensure continuity of expertise

Additionally, an FDA Lead will be identified to serve as the FDA point of contact for each workgroup.

### **2.7.3 Workgroup Membership**

A culture of collaboration is promoted within the constraints of the Sentinel contract. When possible, workgroup members are selected by mutual agreement. Effort is made to distribute workgroup or expert consultation opportunities over time among interested, equally-qualified Collaborators. However, the highest priority is placed on identifying the most qualified workgroup members for specific activities.

For workgroup or expert consultation opportunities distributed through the network, individuals and institutions willing to participate make their interest known to the SOC, which provides this information to the potential workgroup leader(s) and provides a forum for communication among interested individuals. Workgroup leaders are responsible for selecting members of their workgroup. Individuals and institutions may participate in more than one proposed workgroup.

For workgroups that involve data activities, all Data Partners with suitable data for the specific activity are invited to participate. FDA and workgroup leaders are responsible for selecting Data Partners if more are eligible and wish to participate than are needed.

FDA assigns at least one FDA staff member with relevant expertise to serve on the workgroup.

### **2.7.4 Evaluation Process for Workgroup Proposals**

The SOC leadership identifies investigators with relevant expertise to evaluate each proposal. Typically, this includes review by Sentinel staff from the Infrastructure and Data Operations Divisions and FDA and, if needed, outside reviewers with required expertise. Individuals submitting proposals for consideration, or those from the same institution as an individual submitting a proposal, may not participate in the review. This includes Core Leaders.

The reviewers make recommendations to the workgroup leader if there is one proposal under review. If there is more than one proposal, reviewers send their comments to the Sentinel Principal Investigator or his/her designee, who assigns workgroup responsibilities in consultation with FDA. If no proposed workgroup is considered satisfactory by the Sentinel Principal Investigator, taking into account the recommendations of the reviewers, the SOC may withdraw or reissue the project opportunity in consultation with the FDA.

### **2.7.5 Scientific Evaluation of Work Products**

Representatives of the Infrastructure and Data Operations Divisions evaluate workgroup products for adherence to the agreed upon statement of work and scientific quality. When the final report or other deliverable is approved by the SOC, it is submitted to FDA for final review and clearance.

### **2.7.6 Sentinel Operations Center Role**

Workgroups report to the SOC. The Data Operations and Infrastructure Divisions provide epidemiological and biostatistical support and expertise regarding the SCDM, distributed database, analytic tools, and programming requirements. The Administration Division provides project management and administrative support and serves as their liaison to the FDA.



## **3. DATA**

The Collaborating Institutions, the SOC, and the FDA are each responsible for the stewardship of Sentinel data in their possession. The Infrastructure Division and Data Core lead all activities related to the Sentinel Distributed Database.

### **3.1 Sentinel Distributed Data Approach and Common Data Model**

#### **3.1.1 Distributed Data Approach**

Sentinel uses a distributed data approach in which Data Partners maintain physical and operational control over their electronic health data in their existing environments (i.e., behind their respective firewalls). Data Partners execute standardized data queries distributed by the SOC and then share the output of these queries, typically in summary form, with the SOC.

#### **3.1.2 Sentinel Common Data Model**

The SCDM is a data structure that standardizes administrative and clinical information across Data Partners. Data Partners maintain and provide access to data in SCDM format. The SCDM makes it possible to execute standardized programs developed by the SOC in collaboration with the Data Partners. The SCDM relies on existing standardized coding schema (e.g., ICD-9-CM, ICD-10-CM, HCPCS/CPT and NDC) to minimize the need for ontologic mapping and enable interoperability with appropriate evolving healthcare coding standards and is compatible with other common data models using the same data types. The Infrastructure Division and Data Core coordinate and facilitate active participation by the Data Partners in the creation, implementation, updating, maintenance, enhancement, and use of the SCDM. The Infrastructure Division and Data Core work closely with the Methods and Applied Surveillance Cores and project workgroups to ensure that members fully understand the characteristics of the data and that the SCDM is designed to meet their needs. Data Partners provide knowledge and expertise to ensure appropriate use and interpretation of data in SCDM format.

#### **3.1.3 Expansion of the Common Data Model**

The SOC, in collaboration with FDA, may work with Data Partners to incorporate other data sources and new data elements into the SCDM. These additional data sources may represent “original source data” or “external source data,” as necessary.

### **3.2 Data Repositories**

#### **3.2.1 Original Source Data**

Data Partners possess several types of data acquired through their normal activities (referred to herein as “original source data”), including administrative claims data, outpatient and inpatient electronic health records (EHRs), demographic information, outpatient pharmacy dispensings, and registry data. Data Partners retain stewardship and possession of both original source data and data transformed into SCDM format. Data Partners manage and store the data in accordance with their own institutional policies.

### 3.2.2 External Source Data

As necessary, Data Partners may be asked to collect information from sources other than their own institution (referred to herein as “external source data”) for purposes such as identifying or confirming exposures or outcomes of interest. Healthcare data registries for particular diseases, medical procedures, or devices are one type of potential external sources. Data Partners must clearly differentiate external source data from the Data Partner’s original source data and SCDM-formatted data. Data Partners must limit access to external source data collected for Sentinel purposes to authorized individuals engaged in related Sentinel activities. Data transfer from external sources to Data Partners is done in keeping with customary standards of secure file sharing.

### 3.2.3 Sentinel Operations Center Data

In response to specific queries, Data Partners do not share direct patient identifiers with the SOC and adhere to the [Health Insurance Portability and Accountability Act of 1996 \(HIPAA\)](#) minimum necessary standard.<sup>3</sup> Data are provided by Data Partners in summary (i.e., aggregate) form, unless there is a specific need for person-level information. Such person-level information might include, for example, information (stripped of direct patient identifiers) regarding individuals who received specific vaccines on specific dates when such information is required to respond to a particular FDA query.

The SOC typically shares summary results with FDA at the individual Data Partner level and aggregated across all Data Partners. Under most circumstances, Data Partners are not identified when information is provided to the FDA or project workgroups. Access to the non-summarized data is limited to authorized individuals within the SOC or others authorized by the SOC to act on its behalf, such as outside individuals participating in workgroups related to task orders.

Data transfer between Data Partners and the SOC and between the SOC and the FDA is done by means of a secure web-based file sharing system. The SOC complies with standards established by HIPAA and FISMA.

## 3.3 Data Use Limitations

### 3.3.1 Original Source Data

Data Partners may use their own original source data transformed into SCDM format for other purposes, such as research, as long as they comply with applicable state and federal laws and regulations, including HIPAA and the [Common Rule](#).

### 3.3.2 External Source Data

Data Use Agreements are not required for Sentinel activities. However, Collaborators and the Sentinel Coordinating Center, including all its components, may only use data obtained from sources other than

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<sup>3</sup> Direct identifiers are those excluded in the creation of Limited Data Sets, as specified by law. Specifically, this list includes the following direct identifiers of the individual or of relatives, employers, or household members of the individual: (i) Names; (ii) Postal address information, other than town or city, State, and zip code; (iii) Telephone numbers; (iv) Fax numbers; (v) Electronic mail addresses; (vi) Social security numbers; (vii) Medical record numbers; (viii) Health plan beneficiary numbers; (ix) Account numbers; (x) Certificate/license numbers; (xi) Vehicle identifiers and serial numbers, including license plate numbers; (xii) Device identifiers and serial numbers; (xiii) Web Universal Resource Locators (URLs); (xiv) Internet Protocol (IP) address numbers; (xv) Biometric identifiers, including finger and voice prints; and (xvi) Full face photographic images and any comparable images (45 CFR Part 164.514(e)(2)).

their own institution in the conduct of Sentinel activities for Sentinel's public health purposes, unless authorized by the external source in keeping with all applicable data privacy regulations. Such data may not be reused, re-disclosed, altered, or sold for any purposes other than those defined in the base contracts and subsequent task order contracts without specific authorization. In the future, if additional uses of Sentinel are explored, the FDA, the SOC, and the Collaborating Institutions may review and revise this provision.

Unauthorized use will be reported to the SOC. The user will be allowed an opportunity to remedy the situation on terms that are satisfactory to the Sentinel Principal Investigator and those institutions whose data was used for the unauthorized purpose. Failure to reach agreement may result in exclusion of the user from future participation in Sentinel activities.

### **3.3.3 FDA Access to Data**

The FDA obtains unlimited rights to access and to use all Sentinel data in the possession of the SOC and first generated in performance of the contract for Sentinel's public health purposes. In keeping with the Confidentiality sections of the prime contract and these *Principles and Policies*, confidential proprietary data and information submitted by or pertaining to specific institutions or organizations will not be publicly disclosed without the written consent of the respective institutions, except to the extent required by law. Access to this data is governed by relevant laws and regulations.

### **3.3.4 Use of Data for Other Sentinel Activities**

Data originally obtained for a specific Sentinel purpose and subsequently identified as useful for another Sentinel activity may only be reused with the express permission of each participating Data Partner.

## **3.4 Data Retention**

### **3.4.1 Data Partners**

Data Partners will retain original source data in the SCDM format used to assess exposures to medical products, exposure-outcome relationships, or the impact of FDA regulatory actions, for at least three years from the time that the project is deemed complete by the FDA,<sup>4</sup> unless instructed otherwise by the SOC at the direction of the FDA. The SOC will provide instruction to the Data Partners regarding retention requirements for all data activities, including exactly what data must be retained.

Data Partners will retain data obtained from external sources to meet the needs of specific projects, and data derived from these external sources, for no longer than seven years after the project is deemed complete by the FDA, unless instructed otherwise by the SOC at the direction of the FDA. External source data will be subsequently destroyed in accordance with standards set by the [National Institute of Standards \(NIST\)](#) in place at that time. The FDA, the SOC, and the Collaborating Institutions may review and revise this provision if it is determined that these data retention requirements do not adequately meet the scientific needs of Sentinel activities.

### **3.4.2 Sentinel Operations Center**

The SOC will keep data resulting from assessments of exposure-outcome relationships, the impact of FDA regulatory actions, and FDA queries, at both the individual Data Partner and aggregate levels, for at

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<sup>4</sup> Completion is defined as acceptance of the final project report by FDA.

least three years from the time the project is deemed complete by the FDA,<sup>4</sup> unless instructed otherwise by the FDA.

The SOC will retain data obtained from external sources to meet the needs of specific projects, and data derived from these external sources, for no longer than seven years after the project is deemed complete by the FDA, unless instructed otherwise by the FDA. External source data will subsequently be destroyed in accordance with standards set by NIST in place at that time. The FDA, the SOC, and the Collaborating Institutions may review and revise this provision if it is determined that these data retention requirements do not adequately meet the scientific needs of Sentinel activities.

## 4. PRIVACY

Collaborators must observe all applicable federal and state privacy-related laws and regulations. As described in Section 3, Sentinel adheres to all applicable state and federal laws, including HIPAA, FISMA, and NIST standards. The structure of Sentinel protects the privacy and confidentiality of individual health information. Data Partners maintain physical and operational control over the data in their possession and execute analysis programs securely distributed by the SOC behind their own firewalls. In most cases, the output of these programs is provided to the SOC in summary format, i.e., aggregated data. The SOC aggregates Data Partner responses to queries and sends results from the individual Data Partners and aggregated across all Data Partners to the FDA. When person-level information is required for analyses, Data Partners remove direct patient identifiers from the information conveyed to the SOC. If the SOC inadvertently receives direct patient identifiers, it will return or destroy the data immediately. The FDA does not receive or possess data with personally identifiable information (PII), as defined by the [Privacy Act of 1974](#),<sup>5</sup> in the conduct of Sentinel activities.

Direct patient identifiers may be used by Data Partners when necessary to gather additional clinical and demographic information or to link their data to data from other sources, as required by specific projects. Prior to sharing information with the SOC, direct patient identifiers are stripped by the Data Partner behind their own firewalls.

Individual health information may be shared by Data Partners with other data holders, such as hospitals and registries, as necessary (for example, to validate health exposures and outcomes of interest) in accordance with these policies and all applicable state and federal regulations.

Policies concerning collection, storage, and use of data obtained from external data sources are described in **Section 3**.

### 4.1 Sentinel Activities Are Public Health Practice, Not Research<sup>6</sup>

The [HHS Office of Human Research Protections \(OHRP\)](#) determined that the regulations administered by OHRP (45 CFR Part 46, “Common Rule”) do not apply to the activities that are included in the FDA’s Sentinel Initiative. FDA stated that this assessment also applies to the Sentinel System, as it is part of the Sentinel Initiative.

Additionally, FDA determined that Sentinel activities are public health activities in support of FDA’s public health mission. It is therefore not necessary for the Collaborating Institutions to obtain approval

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<sup>5</sup> The Privacy Act of 1974 governs personally identifiable information (PII) that is maintained in systems of records by federal agencies.

<sup>6</sup> See Rosati, K., Evans, B., Jorgensen, N., and Soliz, M., [HIPAA and Common Rule Compliance in the Sentinel Initiative](#), White Paper, February 2018.

or exemption from their respective Institutional Review Boards (IRBs) or Privacy Boards, or to obtain waivers of authorization under HIPAA, to review Sentinel activities (45 CFR §164.512(b)).

## **4.2 HIPAA Compliance**

### **4.2.1 Privacy Rule**

The HIPAA Privacy Rule permits covered entities the use and disclosure of protected health information (PHI) to public health authorities without patient authorization. Public health authorities include the FDA. The SOC and Collaborating Institutions are also public health authorities for purposes of Sentinel because they are acting under contract with and under the authority of the FDA.<sup>7</sup> While de-identified information or Limited Data Sets generally are used for all Sentinel activities, the Privacy Rule permits fully identifiable information to be disclosed to public health authorities.

### **4.2.2 Minimum Necessary Standard**

Only the minimum amount of data necessary to respond to specific queries, as determined by the FDA, or by the SOC or specific project workgroups on behalf of the FDA, will be requested from data sources.

### **4.2.3 Security**

Sentinel data are managed in accordance with the national standards established by the [HIPAA Security Rule](#). Data in the possession of the SOC are also managed in accordance with FISMA. Administrative, physical, and technical safeguards are employed to ensure the confidentiality and privacy, integrity, and security of electronic health information (45 CFR Part 160 and Subparts A and C of 45 CFR Part 164; 44 U.S.C. § 3541, *et seq*).

## **4.3 Specially Protected Health Information**

### **4.3.1 State Laws and Regulations**

It is the responsibility of Sentinel Data Partners to determine whether state laws regulate the use and disclosure of health information for Sentinel purposes and to comply with any such laws. Data Partners are advised to consult [Evaluation of State Privacy Regulations in Relation to the Sentinel Initiative \(FDA-2009-N-0192-0014\)](#) for guidance and reference. The SOC, with input from the Privacy Panel and in consultation with Data Partners and the FDA, may provide additional guidance to assist Data Partners in assessing whether state law applies to a particular Sentinel query and in determining how to comply. However, it is ultimately the responsibility of each Data Partner to assess and maintain compliance with relevant state laws and regulations.

### **4.3.2 Federal Substance Abuse Regulations**

Federal regulations contained in 42 CFR Part 2 address information held by federally-assisted alcohol or drug abuse treatment programs. These regulations protect information that identifies an individual as someone who has applied for or received substance abuse treatment. The Part 2 regulations do not apply to information that does not identify an individual. If Data Partners request medical record

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<sup>7</sup> [HIPAA and Common Rule Compliance in the Sentinel Initiative](#), *op cit*.

information from a federally-assisted substance abuse treatment program to confirm a medical product safety signal, the program will be required to obtain individual patient authorization to provide that information if it reveals that the patient received substance abuse treatment.

## 5. CONFIDENTIALITY

The FDA and the SOC strive to be as transparent as possible in the operations of the Sentinel System. Nevertheless, each recognizes that some information utilized as part of the Sentinel System must be kept confidential. Confidential Information includes, but is not limited to:

- Protected health information (PHI)
- Information that is proprietary to and maintained as confidential by the Sentinel Collaborating Institutions
- Data, results and/or communications concerning medical product queries and assessments not yet made public by the FDA

Confidential Information may appear in documents, discussions, responses to surveys, other communications, or queries, and data and may be oral, written, or electronic.

In order to facilitate identification of Confidential Information, the FDA and the SOC will endeavor to identify and label documents that may contain Confidential Information as “Confidential.” All Collaborators providing information as part of their participation in Sentinel should also identify and label such documents as “Confidential.”

Collaborators may only use Confidential Information obtained in the conduct of Sentinel for the purposes of Sentinel unless approved in writing by the original source of the information. Collaborators may only use individual health information obtained from external sources in the conduct of Sentinel activities for Sentinel’s public health purposes, as described in **Section 3**.

Collaborators must exercise good judgment and care to avoid unauthorized use or improper disclosure of Confidential Information. The obligation to maintain confidentiality of information discussed in this section continues after the contract period for at least 5-7 years.

[The FDA and the SOC will provide updates as needed to Collaborators regarding the protection of Confidential Information.](#) All questions concerning confidentiality issues should be addressed to the Administration Division.

### 5.1 Confidential Information Provided by FDA

#### 5.1.1 Non-Public Information

Each individual Collaborator who comes in contact with Confidential Information provided by the FDA certifies, by signing the FDA’s Contractor’s Commitment to Protect Non-Public Information (NPI) Agreement, that he or she will not disclose Non-Public or Confidential Information to any unauthorized person. Non-Public or Confidential Information is information not available to the general public. Signed agreements will be kept on file by the SOC until five years after the last participation of the signatory in the Sentinel and will be made available to the FDA upon request.

#### 5.1.2 Uses of Non-Public Information

Non-Public Information shared between the FDA and Collaborators may not be used to solicit or otherwise encourage funding by industry or other organizations or agencies. Collaborators who have

received Non-Public Information about a topic may accept engagements in non-FDA supported activities related to that topic if:

- The FDA has not engaged the individual in any capacity to participate in activities on that issue
- The Collaborator does not divulge Non-Public Information previously disclosed to that Collaborator by the FDA
- The Collaborator discloses potential COI, in accordance with the Sentinel conflict of interest policy, prior to or concurrent with any communications with the FDA about any issue concerning the safety of the involved regulated product(s) related to the work done with Sentinel

### **5.1.3 FDA Queries**

Sentinel Collaborators are required to keep confidential all communications with the FDA, the SOC, and other Collaborators concerning all Sentinel activities, including but not limited to, queries, responses to queries, sequential surveillance and protocol-based assessments, TreeScan analyses, and Patient Episode Profile Retrieval (PEPR) analyses until the FDA determines that such communications are no longer confidential.

## **5.2 Confidential Information Provided by Sentinel Collaborators**

All information marked as “confidential” or “proprietary” by Collaborating Institutions, which is shared with or transferred to other Collaborators, the SOC, or the FDA, must be held as confidential and protected from unauthorized use or disclosure. Collaborators, the SOC, and the FDA may not disclose Confidential Information without the prior written consent of the institution that provided the Confidential Information, unless required by law.

## **5.3 Confidential Information Acquired via or Derived from Sentinel Activities**

All participants in Sentinel, both individuals and institutions, are prohibited from trading on or otherwise benefiting financially from information obtained in the course of or produced as a result of work done for under Sentinel that has not yet been made public. This includes Confidential Information generated as a result of Sentinel activities as well as Confidential Information provided by the FDA and/or Sentinel Collaborating Institutions. Inappropriate use of Confidential Information may constitute insider trading or violate other federal and state laws. Prior to participating in any Sentinel activities, all Sentinel participants must sign the Sentinel Confidentiality Agreement to acknowledge that they are aware of and understand this policy.

## **5.4 Non-Confidential Information**

Confidential information does not include information that:

- Can be demonstrated to have been in the public domain at the time of disclosure
- Can be demonstrated to have been readily available from another source
- Becomes publicly known not due to any unauthorized act by the Collaborator
- Can be demonstrated to have been independently developed or acquired by the Collaborator



## 6. COMMUNICATIONS

Transparency is a fundamental principle of the operations of the Sentinel System. Knowledge acquired from Sentinel activities is placed in the public domain. To accomplish this, information concerning Sentinel activities will be made available on the Sentinel website, as well as other locations when appropriate. Sentinel Collaborators are encouraged to publish and present Sentinel findings in scientific venues.

If findings of an FDA Sentinel query or any applied surveillance sequential surveillance activity, including protocol-based assessments, yield information suggesting the presence of a health risk associated with exposure to a particular regulated product, FDA will evaluate that evidence and consider what action, if any, is appropriate. Sentinel Collaborating Institutions are not required or expected to take any action based solely on individual institutional responses to FDA queries or any other Sentinel applied surveillance activity, or on information they receive about assessments of those responses.

### 6.1 Dissemination of Results

#### 6.1.1 Release of Information by FDA

The FDA reserves the right to release the results of contracted analyses at any time if it considers such action to be in the best interest of the public. To the extent feasible, FDA will authorize posting of query and assessment reports on the Sentinel website in advance of all related presentations or safety communications.

#### 6.1.2 Safety Communications

Upon receipt of an advance notice for a planned FDA safety communication (typically 24 hours or less prior to FDA posting) that mentions or otherwise refers to an assessment or query done within the Sentinel System, the SOC will forward the notice via email to the project lead of the relevant workgroup and a representative from each of the Data Partners that participated in the assessment or query. If the notice is received during business hours, it will be sent the same day; if the notice is received after the close of business, it will be sent by 11am the following day. The SOC will:

- Include a brief note referencing the relevant Sentinel project and project leader
- Instruct recipients that the advance information is for internal use only within the recipient's organization and confidential until the information is made publicly available by the FDA
- Provide a link to additional information on the Sentinel website (if available)

#### 6.1.3 Modular Program and Summary Table Assessments

Modular programs and summary tables facilitate rapid querying of the data to glean information such as counts of enrollment, diagnoses, procedures, drug, device, biologic utilization, and other cohort size measures.

At the present time, results of summary table queries and non-sequential modular program assessments, also known as modular program Level 1 and Level 2 assessments, aggregated across Data Partners, are posted on the Sentinel website if the results will be released publicly (e.g., presentations, manuscripts, etc.) or at the Agency's discretion. At the Agency's discretion, summary table and modular program Level 1 and Level 2 queries that are part of sequential surveillance or protocol-based assessments (see **Section 6.1.4**), or other larger projects, may not be posted until after final reports from those projects have been accepted and deemed final by FDA.



#### **6.1.4 Sequential Surveillance and Protocol-Based Assessments**

Sequential surveillance assessments, also known as modular program Level 3 queries, perform active safety surveillance of medical products in a prospective and semi-automated manner. Sequential assessments use a small number of automated study designs and analytical methods that can be modified to accommodate specific products, outcomes, populations, and time periods for evaluation. The assessment parameters and surveillance plan are outlined in sequential surveillance plans created by the assessment team or project workgroup.

Protocol-based assessments use detailed plans for assessing medical product safety that adjust for anticipated complications in the data. These assessments formally evaluate medical product-outcome associations using study designs and analytical methods that are tailored to accommodate specific products, outcomes, populations, and time periods for evaluation. The assessment parameters and analysis plans are outlined in study protocols created by the assessment team or project workgroup.

First drafts of sequential surveillance plans and protocols are posted on the Sentinel website for two weeks for public review and comment. Workgroup leaders are required to consider but not to accept or respond to comments.

The FDA reserves the right to determine whether sequential surveillance plans and protocols will be implemented as written or with modifications, including those based on available resources or Agency priorities. Upon this determination, if changes are made prior to or during implementation, a revised version will be posted on the Sentinel website. Revised plans/protocols do not require a public comment period.

Results of completed sequential surveillance and protocol-based assessments are posted on the Sentinel website following acceptance of the final report by the FDA. The FDA may delay posting if the Agency determines that a delay is in the public interest.

## **6.2 Publications and Presentations**

After the FDA has had 30 days to review (as further discussed in **Section 6.2.3**), Sentinel Collaborators are encouraged to present and publish results that do not include Non-Public or Confidential Information as defined in **Section 5**. Collaborators must inform the SOC and the FDA when a manuscript or other written material is published and furnish a copy of it as finally published to the SOC. Collaborators are required to provide the SOC with links to publications, presentations, and related materials for posting on the Sentinel website.

### **6.2.1 Data Checking**

Collaborators who choose to submit results of completed protocols for publication or presentation in public forums must first satisfy Sentinel standard data checks and evaluations, as determined by the Infrastructure Division.

### **6.2.2 Authorship**

Workgroup participants identify potential publications and presentations and assign authorship roles among themselves. Ideally, this will occur early during the collaboration before analyses occur. Sentinel authorship guidelines are defined by the [Uniform Requirements for Manuscripts Submitted to](#)

[Biomedical Journals](#)<sup>8</sup>. Participants may include FDA staff members, who are required to adhere to FDA policies regarding authorship.

### 6.2.3 FDA Review

Collaborators must submit a copy of each presentation or manuscript to be submitted for publication to the FDA via the SOC for review of the accuracy of factual data and interpretation at least 30 days prior to presentation or submission of the materials. For presentations, slides must be accompanied with information concerning the venue and anticipated date of the presentation. The FDA may take up to 30 days from receipt to review, comment, and return the document. Authors and presenters may accept or reject FDA comments, unless the comments concern findings of medical product assessments that have not yet been posted on the Sentinel website or concern Non-Public or Confidential Information, in which case presenters may not include any findings FDA determines should not yet be released.

The SOC will provide final copies of proposed presentations and manuscripts to the FDA Sentinel Center Lead and Sentinel Core Team, which will provide copies to all others within FDA responsible for reviewing and sharing the content prior to public release.

## 6.3 Disclaimers

### 6.3.1 Risk Disclaimers

Sentinel website postings related to assessments of exposures to medical products linked to health outcomes of interest must include the following disclaimers:

#### ***Disclaimers***

#### ***Assessments - Information for Patients and Consumers***

*The information contained on this website is provided as part of FDA's commitment to place knowledge acquired from the Sentinel System in the public domain as soon as possible.*

*Much of the content on this site is technical and intended for use by scientists in various areas of expertise.*

*The fact that FDA requests and receives data on a particular product through Sentinel does not necessarily mean there is a safety issue with the product.*

*FDA may access the data available through Sentinel for a variety of reasons beyond assessing potential safety risks for a specific product. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, or seeking to better understand the capabilities of the Sentinel System.*

*When evaluating a potential safety issue, FDA scientists consider the data obtained through Sentinel with information from various other data sources, such as adverse event reports, published study results, and clinical trials, to help make the most informed decisions possible.*

*FDA communicates its interpretation of Sentinel activities through existing channels, such as FDA's press announcements, MedWatch Alerts, and Drug Safety Communications, rather than on this website.*

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<sup>8</sup> [International Committee of Medical Journal Editors](#)

*Information from this site should not affect your use of a medical product in any way. Patients who have questions about the use of a medical product should contact their health care professional.*

### **Assessments - Information for Industry**

*The information contained on this website is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. To most effectively interpret results from observational studies, it is important to consider not only the studies that supported a hypothesis, but also the studies that did not. The website serves as a public data repository that archives all the activities of Sentinel and provides important context to those seeking to understand the significance of any specific activity. This information is being provided to the public in the interest of transparency and for purposes of demonstrating the extent of use and the various ways FDA is utilizing the Sentinel System. While the data posted here may contribute to important overall conclusions, FDA relies on other mechanisms for communicating such conclusions to the public.*

*When reviewing this information please be aware that there are times when FDA may access the data available through Sentinel for a variety of reasons beyond seeking direct access to information that can help assess potential safety risks for a specific product. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand the capabilities of the Sentinel System.*

*Data obtained through Sentinel are intended to complement other types of data and information compiled by FDA scientists, such as adverse event reports, published study results, and clinical trials, which can be combined with Sentinel data and used by FDA to inform regulatory decisions regarding medical product safety. However, data obtained from the Sentinel System are not necessarily used by FDA to take regulatory actions or to make safety decisions. Any public health actions taken by FDA regarding products involved in Sentinel queries and protocols are communicated through existing channels.*

*FDA also wants to emphasize the fact that the Agency may access data and report findings from the Sentinel System for a number of reasons. Such activity does not necessarily lead to an Agency recommendation regarding the use of the drug. Patients who have questions about the use of an identified medical product should contact their health care professional.*

### **6.3.2 Endorsement Disclaimer**

Publications and presentations resulting from work performed under the Sentinel contract must include the following disclaimer:

*The views expressed in written conference materials or publications and by speakers and moderators at conferences do not necessarily reflect the official policies of the Department of Health and Human Services, nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. government.*

## **6.4 Use of Logos**

### **6.4.1 Sentinel Logo**

Collaborators are expected to use the Sentinel logo on all presentations, reports, and other written materials that are products of Sentinel. Collaborators may not display the Sentinel logo on any conference materials or publications unless authorized by the FDA.

#### **6.4.2 Collaborators' Logos**

By participating in Sentinel, Collaborators authorize the use of their institutional logos by the FDA, the SOC, and other Collaborators solely for the purposes of Sentinel related presentations, reports, and other written materials and so long as such uses do not denigrate the respective institutions, unless otherwise authorized by those institutions.

#### **6.4.3 FDA Logo**

Collaborators may not display the FDA logo on any conference materials or publications unless authorized by the FDA.

#### **6.4.4 HHS Logo**

Collaborators may not display the Health and Human Services (HHS) logo on any conference materials or publications unless authorized by the FDA.

### **7. INTELLECTUAL PROPERTY**

#### **7.1 Data and Materials Furnished by FDA**

##### **7.1.1 FDA's Rights**

All data and materials, and any and all intellectual property rights therein, furnished by the FDA for use in Mini-Sentinel and/or Sentinel shall be owned by the FDA ("FDA Data and Materials"). The term "intellectual property rights" as used in **Section 7** shall mean any rights in inventions, concepts, ideas, designs, processes, software, works of authorship, know-how, patents, patent applications, trade secrets, copyrights and copyright registrations.

##### **7.1.2 License**

The FDA hereby grants to all Collaborators a license to use the FDA Data and Materials for all purposes required in their respective roles for the duration of their participation in Mini-Sentinel and/or Sentinel.

##### **7.1.3 Limitations on License**

Collaborators in Mini-Sentinel and/or Sentinel are not permitted to retain, reproduce, or use for private or commercial purposes, the FDA Data and Materials.

#### **7.2 Data and Materials Furnished by Collaborators**

##### **7.2.1 Collaborator's Rights**

All data and materials, and any and all intellectual property rights therein, furnished by each Collaborator for use in Mini-Sentinel and/or Sentinel shall be owned by that respective Collaborator ("Collaborator Data and Materials"). As stated above in **Section 7.1.1**, the term "intellectual property rights" as used in **Section 7** shall mean any rights in inventions, concepts, ideas, designs, processes, software, works of authorship, know-how, patents, patent applications, trade secrets, copyrights and copyright registrations. This includes Collaborators' raw data held in Mini-Sentinel or SCDM format and in their portion of the Mini-Sentinel and/or Sentinel Distributed Database.

### 7.2.2 License

Each Collaborator hereby grants to the FDA, and others acting on its behalf, a license to use their Collaborator Data and Materials for all purposes required in their respective roles for the duration of their participation in Mini-Sentinel and/or Sentinel.

### 7.2.3 Limitations on License

Parties to Mini-Sentinel and/or Sentinel are not permitted to retain, reproduce, or use for private or commercial purposes, Collaborator Data and Materials that did not originate with their own institution without the express permission of the original owner.

## 7.3 Data and Materials First Produced in the Performance of the Mini-Sentinel and/or Sentinel Contracts<sup>9</sup>

### 7.3.1 Collaborators Rights

Except as otherwise specifically provided in subcontracts, Collaborators may assert copyright in any Data and Materials first produced by their institution in the performance of this contract. The prior, express written permission of the Contracting Officer is required to assert copyright in all other data first produced in the performance of this contract. When asserting copyright, the Collaborator shall affix the applicable copyright notice of 17 U.S.C. 401 or 402, and an acknowledgment of FDA sponsorship (including contract number), to the data when such data are delivered to the FDA, as well as when the data are published or deposited for registration as a published work in the U.S. Copyright Office.

### 7.3.2 FDA's Rights

For data other than computer software, Collaborators grant to the FDA, and others acting on its behalf, a paid-up, nonexclusive, irrevocable, worldwide license for all such data to reproduce, prepare derivative works, distribute copies to the public, and perform publicly and display publicly, by or on behalf of the FDA. For computer software, the Contractor grants to the FDA and others acting on its behalf, a paid-up, nonexclusive, irrevocable, worldwide license for all such computer software to reproduce, prepare derivative works, and perform publicly and display publicly (but not to distribute copies to the public), by or on behalf of the FDA.

### 7.3.3 Publications by Collaborators

Sentinel Collaborators (1) are encouraged to present and to publish results of their work in keeping with the stipulations described in **Section 6**, and (2) are permitted, without prior approval of the FDA, to assert copyright in technical or scientific articles based on or containing Sentinel Data first produced in the performance of this contract and published in academic, technical, or professional journals, symposia proceedings, and similar works. Per **Section 6**, the FDA may post these results at the Agency's discretion.

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<sup>9</sup> The Sentinel Intellectual Property Policy is governed by Federal Acquisition Regulation (FAR) (52.227-14, Alt IV, Rights in Data – General, section (c)(1)).

## 8. CONFLICT OF INTEREST

It is important to maintain public confidence in the integrity and credibility of the Sentinel Initiative and its findings. Participants, both individuals and institutions, must avoid actions and engagements that may cause a reasonable person to question the impartiality of either the FDA or Sentinel or to question the scientific integrity of Sentinel activities.

“Conflicts of interest are defined in terms of the risk of undue influence and not actual bias or misconduct. Whether they are at the individual or the institutional level, conflict of interest policies seek to prevent compromised decision-making rather than to try to remedy its consequences.”<sup>10</sup> In Sentinel, conflicts of interest (COI) are determined in the context of specific project activities. In general, COI exist in any of the following situations:

- activities or relationships with other persons or organizations affect a participant’s ability, or potential ability, to render impartial assistance or advice, or give the appearance of doing so
- the participant’s objectivity is or might be impaired
- the participant has or might acquire an unfair competitive advantage

COI may arise not only from financial interests, but also from non-financial engagements with or commitments to other organizations and associations with interests related to the subject matter being addressed by specific Sentinel activities.

In this COI policy, **Section 8.1** applies to protocol-based assessments of FDA-regulated medical products. **Section 8.2** applies to both protocol-based assessments and inferential assessments of FDA-regulated medical products that use the Sentinel Routine Analytic Framework (RAF) tools. These inferential tools currently include modular program Level 2 and Level 3 assessments based on the RAF nomenclature. Descriptive RAF assessments, including summary table, and modular program Level 1 assessments, are not included in the COI policy.

### 8.1 COI Policy for Protocol-Based Assessments

**Section 8.1** applies to protocol-based assessments of FDA-regulated medical products. The FDA reserves the right to extend this policy to additional Sentinel projects as deemed appropriate by the Agency. The COI policies applicable to RAF assessments delineated in **Section 8.2** (below) also apply to protocol-based assessments.

For all Sentinel protocol-based assessments, the SOC will prepare a *Cover Memorandum* that FDA will verify after the statement of work is approved and before workgroup participants are selected. The *Cover Memorandum* will provide a project-specific list of products and firms for which individual financial and non-financial interests must be disclosed.

The Sentinel COI Committee will evaluate individual disclosures before individuals can participate in these projects. The COI Committee is described in **Section 2.6.3**. Members of the committee are chosen by the Sentinel Principal Investigator<sup>11</sup> and approved by the FDA. Committee members must have no other vested connections to Sentinel.

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<sup>10</sup> Institute of Medicine (US) Committee on Conflict of Interest in Medical Research, Education, and Practice; Lo B, Field MJ, editors. Washington (DC): National Academies Press (US); 2009. <http://www.ncbi.nlm.nih.gov/books/NBK22934/>.

<sup>11</sup> In this policy, “Sentinel Principal Investigator” refers to the Principal Investigator responsible for Sentinel as a whole rather than project-specific or site-based Principal Investigators.

### 8.1.1 Disclosure

Required disclosures do not necessarily constitute conflicts and, for the purposes of this policy, interests that do not meet the threshold for disclosure will not be considered conflicts. Disclosures will be evaluated by the COI Committee in consultation with others as described in **Section 8.1.2**.

#### 8.1.1.1 Who Is Required to Disclose

Individuals who have, or propose to have, substantive roles related to Sentinel protocol-based assessments are required to disclose financial and other interests that are significant as defined by this policy and related to their engagement, or potential engagement, in work on these specific projects. Substantive roles include those in which individuals have decision-making authority<sup>12</sup> or provide advice to those who have decision-making authority with respect to any of the following:

- The design of projects
- The conduct of the work
- The reporting of results

For the purposes of this policy, such individuals are also referred to as investigators.

#### 8.1.1.2 What Is Required to Be Disclosed

Required disclosures include significant financial and non-financial interests held at the onset of potential engagement in a Sentinel protocol-based assessment or during the twelve months preceding the disclosure that are related to the project-specific list of products and/or firms named in the relevant *Cover Memorandum*.

##### 8.1.1.2.1 Significant Financial Interests

Significant financial interests include anything of monetary value or potential monetary value (whether or not the value is readily ascertainable) that meets the reporting thresholds specified in the regulations issued by the U.S. Department of Health and Human Services (HHS) in August 2011 (42 CFR Part 50 and 45 CFR Part 94) and is related to the project-specific list of products and/or firms named in the relevant *Cover Memorandum*. The precise details of the HHS financial conflict of interest regulations that are being applied to Sentinel are provided in **Section 8.4, Part VII**. More generally, significant financial interests include any of the following types of assets held currently or during the previous 12-month period:

- investments, options, contracts, grants, gifts, employment, fees, intellectual property, and patents and patent applications
- interests in publicly traded and non-publicly traded entities, both domestic and foreign
- financial interests related to the participant's institutional responsibilities<sup>13</sup>

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<sup>12</sup> FDA retains ultimate decision-making authority for Sentinel-related activities.

<sup>13</sup> Per Federal Register / Vol. 76, No. 165 / Thursday, August 25, 2011 / Rules and Regulations p.53284: "Institutional responsibilities means an Investigator's professional responsibilities on behalf of the Institution, and as defined by the Institution in its policy on financial COI, which may include for example: activities such as research, research consultation, teaching, professional practice, institutional committee memberships, and service on panels such as Institutional Review Boards or Data and Safety Monitoring Boards."



- financial interests held by spouses/domestic partners<sup>14</sup> and dependent children
- reimbursed or sponsored travel that is not reimbursed or sponsored by a government agency or an institution of higher education

#### **8.1.1.2.2 Significant Leadership Interests**

Significant leadership interests include any relationship or role in which the individual (and/or the individual's spouse/domestic partner and/or dependent children) participates with decision-making authority on boards, committees, professional societies or associations, or in processes that are related to the project-specific list of products and/or firms named in the relevant *Cover Memorandum*. This includes institutional responsibilities that relate to the subject matter of the Sentinel activity in which the participant proposes to become involved, such as participation with decision-making authority on committees that oversee purchases of medical products.

#### **8.1.1.2.3 Significant Other Interests**

Significant other interests include any relationship or role in which the individual (and/or the individual's spouse/domestic partner and/or dependent children) is engaged that might pose a significant conflict of interest, or appearance of a conflict, such as a pending lawsuit that is related to the project-specific list of products and/or firms named in the relevant *Cover Memorandum*. If an individual is aware that his or her institution has a significant conflict of interest with respect to the products and/or firms named in the *Cover Memorandum*, that conflict should be reported under this heading.

#### **8.1.1.3 How Interests Are Disclosed**

A *Cover Memorandum* will be provided to the FDA by the SOC that describes project-specific products and firms for which individual financial and non-financial interests must be disclosed. FDA will approve the *Cover Memorandum* after the statement of work is approved and before workgroup participants are selected.

If the individual is required to file a disclosure form based on his/her proposed role in the Sentinel protocol-based assessments but has no interests related to the products and/or firms listed in the *Cover Memorandum*, then the individual may submit an *Absence of Individual Conflicts of Interest Attestation* ("*Individual Attestation*") in lieu of a *Sentinel Confidential Disclosure Form for Project Specific Individual Interests* ("*Individual Disclosure Form*").

If the individual is required to file a disclosure form based on his/her proposed role in the Sentinel protocol-based assessments and has interests related to the products and/or firms listed in the *Cover Memorandum*, then the individual must submit a *Sentinel Confidential Disclosure Form for Project Specific Individual Interests* ("*Individual Disclosure Form*") with the SOC for review by the COI Committee. This form covers required disclosures of both financial and non-financial interests.

#### **8.1.1.4 When Interests Are Disclosed**

The appropriate Sentinel COI form must be submitted:

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<sup>14</sup> Domestic partner is defined to include those individuals bound by domestic partnership agreements recognized as legally valid instruments in their state of primary residence.



- a. Upon initial engagement, or proposed engagement, with the project prior to participation in the project
- b. Annually thereafter for the duration of the period of participation in the project
- c. Within 30 days of acquisition of any new and reportable interests related to any of the products and/or firms noted in the relevant *Cover Memorandum*

*Individual Disclosure Forms* and *Individual Attestations* will be stored by the SOC for at least three years from the time that the final project report is accepted by the FDA.

#### **8.1.1.5 To Whom Interests Are Disclosed**

*Individual Disclosure Forms* and *Individual Attestations* are submitted to and collected by the SOC. Alternatively, an individual may elect to submit an *Individual Disclosure Form* directly to the COI Committee. The SOC forwards all *Individual Disclosure Forms* and *Individual Attestations* to the COI Committee along with background information concerning the activity in which the individual proposes to participate.

When payments for an investigator's participation in a workgroup are made to the institution that employs him/her rather than directly to the individual, in addition to the Sentinel review and disposition, the institution may impose its own policies governing institutional access to information disclosed by the investigator to the Sentinel COI Committee, as well as to information about the conflict assessment, management plan, and other actions taken by the Sentinel COI Committee. Institutions are required to advise the SOC of such policies.

#### **8.1.2 Evaluation**

*Individual Disclosure Forms* are reviewed by the full COI Committee for potential conflicts in keeping with the *COI Committee Guidelines*. The COI Committee determines whether a conflict exists and, in consultation with the Sentinel Principal Investigator and the FDA, whether the individual may or may not participate if one is determined to exist. The COI Committee may request additional information concerning potential conflicts if the information is materially relevant to determining whether a conflict exists. If an individual with a recognized conflict is allowed to participate, s/he must submit to the COI Committee a proposed plan for management of the conflict.

The COI Committee may discuss concerns about potential conflicts with the disclosing individual, the Sentinel Principal Investigator, the FDA, and Sentinel legal counsel. The COI Committee may also discuss such concerns with outside experts and individuals whom the Sentinel Principal Investigator, the FDA, and the COI Committee believe are able to provide qualified advice and a "reasonable person" perspective, provided that no confidential information is revealed during the discussions. The COI Committee may consult:

1. Individuals pre-approved by the Sentinel Principal Investigator and FDA whenever it believes that obtaining their perspectives will provide valuable input. These individuals will serve as an ad hoc advisory committee for the COI Committee. This group may include other individuals known to have expertise related to COI, the patient representatives to the Planning Board, and other "reasonable person" outsiders. The names of these individuals will be made publicly available. No confidential information may be revealed in such discussions.
2. Additional outside experts with the express approval of the Sentinel Principal Investigator and FDA. The names of these individuals will be known to the Sentinel Principal Investigator and FDA but not made publicly available. No confidential information may be revealed in such discussions.

The Sentinel Principal Investigator and the FDA reserve the right to require that an individual with an actual or apparent conflict refrain from participation in the proposed activity based on the COI Committee's recommendation. If this occurs, the SOC will assist the workgroup in locating another qualified individual to perform the function at issue.

The COI Committee will prepare a written report regarding its assessment and disposition of each submitted disclosure form. Keeping such records should improve comparability of decisions over time and facilitate transitions among Committees. These reports will be stored for at least three years from the time that the final project report is accepted by the FDA.

### **8.1.3 Management**

#### **8.1.3.1 Constraints on Participation**

Individuals who have conflicts, as determined by the COI Committee, may be allowed to participate in Sentinel activities related to the topics areas in which they have conflicts under certain circumstances and in certain capacities. The following constraints apply:

1. Individuals with conflicts may not be decision-makers on matters related to the subject of the conflict. For example, an individual with a COI may not be selected as the leader of a task order workgroup related to the subject of the conflict. Further, an individual with a COI may not participate as a voting member in any committee or workgroup involving the subject of the conflict.
2. Individuals with conflicts may participate as advisers, including as members of task order workgroups, in limited circumstances. Whether such an individual will be permitted to participate will be decided by the COI Committee after it has examined the submitted COI management plan (described below) with respect to the issue that poses the conflict. Participation will be permitted under circumstances in which:
  - a. The individual has important expertise that is needed for the project and cannot be easily duplicated by another readily available individual who has no conflict or a lesser conflict
  - b. The existence and nature of the conflict is disclosed to anyone who may consider or make decisions on the basis of the advice provided by that individual, including other workgroup participants
  - c. A plan for managing the conflict has been agreed to and implemented by the individual and the Sentinel COI Committee

*For example, an individual with necessary expertise may be permitted to participate in an advisory, non-voting role as a resource if a reasonable person would not expect the conflict to result in bias. Where the potential for or appearance of bias is determined to be great enough to compromise the scientific integrity of the results, participation is not allowed. For example, an individual who has been retained by an interested party to support the party's position on the issue being considered, or who may substantially gain, financially or otherwise, from a particular outcome with respect to that issue, would not be permitted to participate.*

3. Individuals with conflicts may be permitted to participate in situations in which that participation only involves implementation of decisions that have been made and where the outcome cannot be expected to be influenced by the conflicted individual's discretionary decision-making.

### **8.1.3.2 Management Plans**

If it is determined that an actual or apparent COI exists, and also that the individual may be allowed to participate in the related Sentinel activity nonetheless, then the participating individual must submit to the COI Committee a proposed COI management plan that outlines procedures to manage, reduce, or eliminate the conflict, whether actual or apparent, throughout the duration of the contract and any applicable post-contract restriction period as defined by the FDA in the *Cover Memorandum*. The proposed COI management plan must address, in detail, the checks and balances in place to oversee the COI and describe the process of reporting on the status of the COI to the COI Committee, the Sentinel Principal Investigator, and the FDA. Further, the COI management plan must contain a statement of consent for the FDA to inspect all records, correspondence, and other documentation related to the COI. The COI management plan must be reviewed and accepted by the COI Committee, the Sentinel Principal Investigator, and the FDA. If, after discussion and negotiation, the COI management plan is deemed unacceptable by the COI Committee, the Sentinel Principal Investigator, or the FDA, then participation in the proposed activity may not occur. COI management plans will be incorporated by reference into all subcontracts. COI management plans must be renewed annually and within 30 days of any changes in the COI for the duration of participation in the relevant Sentinel activity. These updates must be reviewed and reported on by the COI Committee to the Sentinel Principal Investigator within 60 days of receipt.

When payment for an investigator's participation in a workgroup is made to the institution that employs him/her rather than directly to the individual, and the terms of the COI management plan may impact the performance of the investigator's institutional responsibilities, then representatives of the institution may be allowed to participate in development of the COI management plan.

### **8.1.3.3 Mitigation**

If a significant financial or non-financial interest was not disclosed and was not previously reviewed by the COI Committee, then the COI Committee and Sentinel Principal Investigator will, within 60 days of being made aware of such interest, evaluate and report on whether any portion of the project done prior to the identification and management of the interest was biased in design, conduct, and/or reporting. Their findings and information about corrective actions taken, or to be taken, will be reported to the FDA and on the Sentinel website, and, if warranted, a COI management plan will be instituted from that point forward.

If a significant interest was not disclosed and is upon review determined to be a conflict, then the COI Committee and Sentinel Principal Investigator will, within 120 days of this determination, complete a retrospective review consistent with the NIH regulations delineated at 42 CFR § 50.605.

## **8.1.4 Confidentiality, Reporting, and Posting**

### **8.1.4.1 Confidentiality**

All information disclosed by individuals during the disclosure and review process will be held as confidential, except as necessary to implement this policy or as otherwise required by law. Only individuals who have signed the FDA's Non-Public Information (NPI) form and the Sentinel

Confidentiality Agreement<sup>15</sup> and are charged with collecting COI-related disclosures, evaluating potential COI, or overseeing COI management plans will have access to disclosure forms and management plans. All disclosure forms and related documentation will be retained by the SOC and/or the COI Committee for at least three years from the date of acceptance of the final project report by the FDA.

#### **8.1.4.2 Reporting to FDA**

COI management plans must include:

- steps for notifying the FDA of the existence of an actual or apparent COI
- the actions that have been or will be taken to manage, reduce, or eliminate the COI

Updates must be provided annually. All communications to the FDA will be done through the COI Committee and/or the SOC.

#### **8.1.4.3 Posting Regarding Individual Conflicts of Interest on the Sentinel Website**

When it is determined that an individual has a conflict and the individual is nonetheless allowed to participate in a Sentinel activity related to that conflict, the project description on the Sentinel website will include:

- a. The individual's name
- b. The individual's position with respect to the Sentinel project
- c. A brief description of the conflict consistent with [FDA's Public Availability of Advisory Committee Members' Financial Interest Information and Waivers](#)
- d. A statement that a conflict exists and a management plan is in place, including a notice stating (a) that the individual is not a decision-maker on matters related to that specific Sentinel project, nor is s/he participating as a voting member in any committee or workgroup related to the project and (b) whether the individual is either participating as a non-voting adviser because his/her expertise is both needed and otherwise unavailable from other individuals with no or more limited conflicts, or the individual's participation only involves implementation of decisions that have been made and where the outcome cannot be expected to be influenced by discretionary decision-making

All publications and presentations related to the activity must include information concerning the existence of the conflict in keeping with these requirements, consistent with the rules of the journal or conference.

Postings concerning individuals will be updated within 60 days of the time at which the SOC becomes aware of new information and will remain posted on the Sentinel website for at least 3 years from the time of the last update or acceptance of the final project report by the FDA, whichever is later.

Information posted regarding participating individuals who have been determined to have conflicts may be reviewed by the individual prior to posting. If the individual and the COI Committee cannot agree concerning the content of the posting, the individual may elect to withdraw from the project.

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<sup>15</sup> See **Section 5** for additional information.

### **8.1.5 Penalties for Non-Compliance**

Individuals will not be permitted to participate in work on Sentinel projects until they have submitted attestations or disclosure forms for review by the COI Committee. Individuals who fail to comply with the requirements of **Section 8.1** may be banned from continued engagement in Sentinel activities related to the area of conflict if the COI Committee, the Sentinel Principal Investigator, or the FDA deems suspension or termination of engagement to be appropriate. Individuals who repeatedly fail to comply with the requirements of **Section 8.1** may be banned by the Sentinel Principal Investigator or the FDA from further engagement with Sentinel. Deliberate failure to report relevant interests may be subject to additional penalties under the law.

## **8.2 COI Policy for Routine Analytic Framework Inferential Assessments**

**Section 8.2** applies to inferential assessments of FDA-regulated medical products that use the Sentinel Routine Analytic Framework (RAF) tools. These inferential tools currently include modular program Level 2 and Level 3 assessments based on the RAF nomenclature. This section also applies to protocol-based assessments, as described in **Section 8.1**. Descriptive RAF assessments, including summary table and modular program Level 1 assessments, are not included in the COI policy.

Investigators, including epidemiologists, biostatisticians, clinicians, pharmacologists, and any others who participate as decision-makers in assessments covered under **Section 8.2** may also participate in activities funded by the following sources: U.S. Federal, state or local governmental agencies; U.S. institutions of higher education; U.S. research institutes affiliated with institutions of higher education, academic teaching hospitals, and medical centers; the Reagan-Udall Foundation for the Food and Drug Administration (RUF-FDA); the Patient-Centered Outcomes Research Institute (PCORI); and/or the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC). Investigators funded by sources not listed in the prior sentence or who have significant financial or non-financial interests as defined in **Section 8.1** held currently or during the previous 6-month period must file disclosures as defined in **Section 8.1.1**. All disclosures must be evaluated by the COI Committee based on project-specific Cover Memoranda developed by the SOC and approved by FDA. Any activities, either paid or voluntary, with organizations in categories not listed above should be discussed with the FDA Project Lead on the contract prior to initiation.

### **8.2.1 Additional Information about Select Funding Organizations That Do Not Pose Conflicts**

#### **8.2.1.1 The Reagan-Udall Foundation for the Food and Drug Administration (RUF-FDA)**

The RUF-FDA is an independent 501(c)(3) not-for-profit organization created in the Food and Drug Administration Amendments Act (FDAAA) of 2007. It is the only organization specifically established by the United States Congress to provide a framework for public-private partnerships intended to advance regulatory science on behalf of the Agency. As a result, it can be expected to receive funding from groups other than U.S. Federal, state or local governmental agencies; U.S. institutions of higher education; U.S. research institutes affiliated with institutions of higher education, or academic teaching hospitals or medical centers. Investigators who participate as decision-makers in assessments covered under **Section 8.2** may participate in activities funded by the RUF-FDA's Innovation in Medical Evidence Development and Surveillance (IMEDS) Program. The Foundation has established governance procedures for IMEDS that address scientific and technical issues, stakeholder access, and appropriate reporting, and these governance procedures have been endorsed by FDA.

### 8.2.1.2 The Patient-Centered Outcomes Research Institute (PCORI)

The PCORI is an independent 501(c)(1) not-for-profit organization created by Congress in 2010 to fund research that can help patients and those who care for them make better-informed decisions about healthcare choices. PCORI is funded through the Patient-Centered Outcomes Research Trust Fund (PCORTF), which was established by Congress through the Patient Protection and Affordable Care Act of 2010. The PCORTF receives income from three funding streams: appropriations from the general fund of the Treasury, transfers from the Centers for Medicare and Medicaid trust funds, and a fee assessed on private insurance and self-insured health plans (the PCOR fee). Investigators who participate as decision-makers in assessments covered under **Section 8.2** may participate in activities funded by PCORI.

### 8.2.1.3 The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC)

The BBCIC, affiliated with the Academy of Managed Care Pharmacy (AMCP), is a not-for-profit, scientific public service initiative established in 2015 to monitor and generate post-market evidence for novel biologics, their corresponding biosimilars, and other related products regarding effectiveness and safety. The BBCIC is the only research network dedicated to monitoring biosimilars, draws on large sets of de-identified medical and pharmacy data (100 million lives), and harnesses cutting-edge distributed research network and surveillance methods. Managed care and integrated delivery organizations have devoted significant resources to develop an infrastructure that makes possible active surveillance of biosimilars and novel in distributed research networks (DRNs). The BBCIC marshals these resources for the important public health benefit inherent in monitoring biosimilar safety and effectiveness, using ongoing sequential analyses to compare biosimilars to their innovator product. Projects are jointly funded by pharmaceutical companies and overseen by independent scientific committees. An FDA liaison sits on the BBCIC Planning Board. The BBCIC requires that BBCIC Research Reports be submitted for publication within six months after the completion of the Research Report. When published, the publication will be posted on the BBCIC.org site. If six months have elapsed after the publication submission and the publication does not give a publication date or a release, the BBCIC Science Committee may release such results at its discretion on the BBCIC.org site.<sup>16</sup> Investigators who participate as decision-makers in assessments covered under **Section 8.2** may participate in activities funded by BBCIC.

## 8.2.2 Attestations

Investigators interested in participating as decision-makers in assessments covered under **Section 8.2** must submit *Absence of Individual Conflicts of Interest Attestations* to the SOC. Forms must be submitted:

1. Upon initial engagement, or proposed engagement, with the project
2. Annually thereafter for the duration of the period of participation

Investigators are required to notify the SOC within 30 days of acquisition of any new interests funded by organizations not allowed in **Section 8.2**. Individual Disclosure Forms and Individual Attestations will be stored by the SOC for at least three years.

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<sup>16</sup> Text taken substantially from the [Biologics and Biosimilars Collective Intelligence Consortium \(BBCIC\) website](#).

### **8.2.3 Penalties for Non-Compliance**

Individuals who fail to comply with the requirements of **Section 8.2** may be banned from continued engagement in Sentinel activities related to the area of conflict if the Sentinel Principal Investigator or the FDA deems suspension or termination of engagement to be appropriate. Individuals who repeatedly fail to comply with the requirements of **Section 8.2** may be banned by the Sentinel Principal Investigator or the FDA from further engagement with Sentinel. Deliberate failure to report relevant interests may be subject to additional penalties under the law.

### **8.3 Conflict of Interest Training**

The SOC will provide instruction concerning the current Sentinel COI policy to all site Principal Investigators at Collaborating Institutions, as well as other investigators and personnel, as warranted.

### **8.4 Sample Conflict of Interest Cover Memorandum**

#### **Cover Memorandum**

#### **For Confidential Disclosure Forms and Attestations**

This memorandum lists the specific products and firms for which potential individual conflicts of interest related to a specific Sentinel System project must be disclosed and evaluated prior to participation in the design, conduct, or reporting of that project. The memorandum also describes what constitute required disclosures for the purposes of determining the existence of individual conflicts of interest.

#### **I. NAME OF SENTINEL PROJECT**

To be filled in by the SOC.

#### **II. BRIEF DESCRIPTION OF PLANNED ASSESSMENT**

To be filled in by the SOC.

#### **III. NAME OF FDA WORKGROUP LEAD**

To be filled in by the SOC.

#### **IV. DATE FDA APPROVED THIS FORM**

To be filled in by the SOC.

#### **V. LIST OF RELEVANT PRODUCTS**

To be filled in by the SOC.

#### **VI. LIST OF RELEVANT FIRMS**

To be filled in by the SOC.

#### **VII. REQUIRED INDIVIDUAL DISCLOSURES**

Required individual disclosures include significant interests, financial and non-financial, held currently and/or during the preceding 12-month period, that are related to the project-specific list of products and/or firms listed in the relevant *Cover Memorandum*. Significant individual interests are defined below.

##### **A. Significant Financial Interests**



The following specific rules concerning what constitute significant financial interests for an individual investigator in the context of the FDA's Sentinel System activities are taken verbatim from the [Federal Register / Vol. 76, No. 165 / Thursday, August 25, 2011 / Rules and Regulations \(page 29\)](#). Particular applications of these rules to individual investigators who have responsibility for the design, conduct, or reporting of a Sentinel System project are noted in footnotes to this section.

*Significant financial interest* means:

(1) A financial interest consisting of one or more of the following interests of the Investigator (and those of the Investigator's spouse<sup>17</sup> and dependent children) that reasonably appears to be related to the Investigator's institutional responsibilities:<sup>18</sup>

- (i) With regard to any publicly traded entity, a *significant financial interest* exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure and the value of any equity interest in the entity as of the date of disclosure, when aggregated, exceeds \$5,000. For purposes of this definition, remuneration includes salary and any payment for services not otherwise identified as salary (e.g., consulting fees, honoraria, paid authorship); equity interest includes any stock, stock option, or other ownership interest, as determined through reference to public prices or other reasonable measures of fair market value;
- (ii) With regard to any non-publicly traded entity, a *significant financial interest* exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure, when aggregated, exceeds \$5,000, or when the Investigator (or the Investigator's spouse or dependent children) holds any equity interest (e.g., stock, stock option, or other ownership interest); or
- (iii) Intellectual property rights and interests (e.g., patents, copyrights), upon receipt of income related to such rights and interests.

(2) Investigators also must disclose the occurrence of any reimbursed or sponsored travel (i.e., that which is paid on behalf of the Investigator and not reimbursed to the Investigator so that the exact monetary value may not be readily available), related to their institutional responsibilities; provided, however, that this disclosure requirement does not apply to travel that is reimbursed or sponsored by a federal, state, or local government agency, an Institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an Institution of higher education. The Institution's FCOI policy will specify the details of this disclosure,<sup>19</sup> which will include, at a minimum, the purpose of the trip, the identity of the sponsor/organizer, the destination, and the duration. In accordance with the Institution's FCOI policy, the institutional official(s)

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<sup>17</sup> For the purposes of Sentinel, all references to spouses include domestic partners. Domestic partner is defined to include those individuals bound by domestic partnership agreements recognized as legally valid instruments in their state of primary residence.

<sup>18</sup> For the purposes of Sentinel, the "Investigator's institutional responsibilities" are defined as those responsibilities that reasonably appear to be related to the products and/or firms named in the relevant Cover Memorandum for the specific Sentinel System project for which disclosures are being provided.

<sup>19</sup> Details of travel related disclosures required for the purposes of Sentinel are presented in the *Sentinel Confidential Disclosure Report for Project Specific Individual Interests*. The COI Committee "will determine whether further information is needed, including a determination or disclosure of monetary value, in order to determine whether the travel constitutes a financial conflict of interest (FCOI)."



will determine if further information is needed, including a determination or disclosure of monetary value, in order to determine whether the travel constitutes an FCOI with the PHS-funded research.

(3) The term *significant financial interest* does not include the following types of financial interests:

- salary, royalties, or other remuneration paid by the Institution to the Investigator if the Investigator is currently employed or otherwise appointed by the Institution, including intellectual property rights assigned to the Institution and agreements to share in royalties related to such rights;
- any ownership interest in the Institution held by the Investigator, if the Institution is a commercial or for-profit organization;
- income from investment vehicles, such as mutual funds and retirement accounts, as long as the Investigator does not directly control the investment decisions made in these vehicles;
- income from seminars, lectures, or teaching engagements sponsored by a federal, state, or local government agency, an Institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an Institution of higher education; or
- income from service on advisory committees or review panels for a federal, state, or local government agency, an Institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an Institution of higher education.

## **B. Significant Non-Financial Interests**

### **1. Significant Leadership Interests**

*Significant leadership interests* include any relationship or role in which the individual (and/or the individual's spouse/domestic partner and/or dependent children) participates with decision-making authority on boards, committees, professional societies or associations, or processes that are related to the project-specific list of products and/or firms named in the relevant *Cover Memorandum*. This includes institutional responsibilities that relate to the subject matter of the Mini-Sentinel activity in which the participant proposes to become involved, such as participation with decision-making authority on committees that oversee purchases of medical products.

### **2. Significant Other Interests**

*Significant other interests* include any relationship or role in which the individual (and/or the individual's spouse/domestic partner and/or dependent children) is engaged that might pose a significant conflict of interest, or appearance of a conflict, such as a pending lawsuit that are related to the project-specific list of products and/or firms named in the relevant *Cover Memorandum*. If an individual is aware that his or her institution has a significant conflict of interest with respect to the products and/or firms named in the *Cover Memorandum*, that conflict should be reported under this heading.

## 9. GLOSSARY

**Code of Federal Regulations (CFR)** – The Code of Federal Regulations (CFR) is the codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the federal government.

**Collaborator** – A Collaborator is an institution or individual that provides access to healthcare data and/or scientific, technical, methodologic, and organizational expertise, as needed to meet the requirements of Sentinel. Collaborators participate in Sentinel activities in various capacities. Collaborators include, but are not limited to, the Sentinel Coordinating Center and its components, the Sentinel Operations Center (SOC) housed at Harvard Pilgrim Health Care Institute (HPHCI), Academic and Data Partners, members of project workgroups, and independent contractors.

**The Common Rule** – The Common Rule (45 CFR Part 46) is a federal policy that governs the protection of human subjects in research projects. The principal components are: 1) requirements for assuring compliance with the Rule by institutions that conduct research involving human subjects; 2) requirements for researchers' obtaining and documenting informed consent from human subjects; and 3) requirements for Institutional Review Boards (IRB) to oversee and document adherence to the Rule.

**Covered Entity** – Covered entities are those entities subject to HIPAA regulations (see below). This includes: 1) healthcare providers that conduct certain transactions in electronic form; 2) healthcare clearinghouses; or 3) health plans.

**De-Identified Health Information** – De-identified health information neither identifies nor provides a reasonable basis to identify an individual. There are two ways to de-identify information, either: (1) a formal determination by a qualified statistician; or (2) the removal of specified identifiers of the individual and of the individual's relatives, household members, and employers is required, and is adequate only if the covered entity has no actual knowledge that the remaining information could be used to identify the individual. There are no restrictions on the use or disclosure of de-identified health information.

**Direct Patient Identifiers** – Direct patient identifiers are those direct identifiers listed below under protected health information (PHI), except for dates and geographic codes smaller than a state as noted below under limited data set.

**Distributed Query Tool** – The Distributed Query Tool allows rapid querying of the Sentinel Distributed Database. The Tool is based on the PopMedNet™ software application that enables simple, efficient creation and use of distributed data networks, through a set of tools and web-based services. Data Partners exercise full control over the files they make available for querying, the results returned, and the individuals who are permitted to submit queries.

**Federal Information Security Management Act (FISMA)** – The Federal Information Security Management Act of 2002 (FISMA) was passed in 2002 as Title III of the E-Government Act (Public Law No. 107-347). FISMA requires each federal agency to develop, document, and implement agency-wide programs to provide information security for the operations and assets of the agency, including those provided or managed by other agencies or outside contractors.

**Health Insurance Portability and Accountability Act (HIPAA)** – The Health Insurance Portability and Accountability Act (HIPAA) of 1996 (Public Law No. 104-191) is a federal law that governs: 1) health insurance coverage for workers and their families when they change or lose their jobs; and 2) the establishment of national standards for electronic healthcare data transactions.

**HIPAA Privacy Rule** – The HIPAA Privacy Rule (45 CFR Part 160 and Subparts A and E of Part 164) establishes national standards to protect individuals' medical records and other individual health information and applies to health plans, healthcare clearinghouses, and those healthcare providers that conduct certain healthcare transactions electronically. The Rule requires appropriate safeguards to protect the privacy of individual health information and sets limits and conditions on the uses and disclosures that may be made of such information without patient authorization. The Rule also gives patients' rights over their health information, including rights to examine and obtain a copy of their health records, and to request corrections.

**Limited Data Set** – HIPAA makes provisions for the creation of a limited data set as an alternative to using fully de-identified information. Creation of a limited data set require removal of 16 direct identifiers (see list below) but allows for the inclusion of dates, geographic location (not as specific as street address) and any other code or characteristic not explicitly excluded (45 CFR Part 164.514 Subpart E).

**Minimum Necessary Standard** – The minimum necessary standard of the HIPAA Privacy Rule (45 CFR 164.502(b), 164.514(d)) generally requires covered entities to take reasonable steps to limit the use or disclosure of, and requests for, protected health information to the minimum necessary to accomplish the intended purpose.

**Modular programs** – Modular programs are adaptable standardized programs that can be reused with variations in specified parameters. Modular programs facilitate rapid querying of the Sentinel Distributed Database. Each program focuses on a specific type of question and executes against the Sentinel Common Data Model (SCDM). The programs have several required input parameters; the standardized output contains summary-level counts (e.g., number of members exposed to a medical product, number of members with a specific diagnosis/condition) stratified by various parameters (e.g., age group, sex, year).

**National Institute of Standards (NIST)** – The National Institute of Standards (NIST) is a non-regulatory federal agency within the U.S. Department of Commerce. NIST's purpose is to promote innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve quality of life. NIST oversees implementation and adherence to non-national security information systems standards, such as FISMA.

**Office for Human Research Protections (OHRP)** – The Office for Human Research Protections (OHRP) is the department within the U.S. Department of Health and Human Services (HHS) that oversees all research involving human subjects.

**Personally Identifiable Information (PII)** – Personally identifiable information (PII) refers to individually identifiable information that is maintained in systems of records belonging to federal agencies.

**Privacy Act of 1974** – The Privacy Act of 1974 (5 U.S.C. § 552a) establishes a Code of Fair Information Practice that governs the collection, maintenance, use, and dissemination of personally identifiable information (PII) about individuals that is maintained in systems of records by federal agencies. A system of records is a group of records under the control of an agency from which information is retrieved by the name of the individual or by some identifier assigned to the individual.

**Protected Health Information (PHI)** – Protected health information (PHI), defined by the HIPAA Privacy Rule, includes individually identifiable health information that directly identifies individuals, as well as information for which there is a reasonable basis to believe it could be used to identify individuals (such as small cell counts and dates of service). The HIPAA Privacy Rule protects all individually identifiable health information held or transmitted by a covered entity or its business associate, whether electronic,

paper, or oral. The specific list of 18 common identifiers that constitute individually identifiable information includes:

- Names
- Geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of a ZIP code
- All elements of dates (except year) for dates directly related to an individual (e.g., date of birth, admission)
- Telephone numbers
- Fax numbers
- Electronic mail addresses
- Social security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web universal locators (URL's)
- Internet protocol (IP) address numbers
- Biometric identifiers, including finger and voiceprints
- Full-face photographic image and any comparable images
- Other unique identifying number, characteristic, or code

**Protocols** – Protocols are detailed plans for assessing information that adjust for anticipated complications in the data. Development of protocols depends upon collaborative efforts by many experts in relevant medical areas.

**Query** – A query is a request by the FDA for information on a particular topic of interest.

**Sequential Surveillance Plans** – Sequential surveillance plans are detailed specifications for active surveillance of newly approved medical products in a prospective and semi-automated manner.

**Summary Tables** – Summary tables are static tables, held by participating Data Partners behind their institutional firewalls, that provide summary information about the data organized by age group, sex, and year stratified prevalent and incident counts of occurrences of diagnoses and medical procedures and exposures to medical products based on standard classifications such as ICD-9-CM codes, CPT codes, and HCPCS codes, and NDC codes. These tables are updated whenever a Data Partner refreshes their data.