REAGAN-UDALL FOUNDATION FOR THE FDA

**Innovation in Medical Evidence
Development and Surveillance
(IMEDS)**

Policies and Procedures

September 2020

*The Foundation reserves the right to modify the Policies and
Procedures document as necessary.

Contents

Table of Abbreviations

Abbreviations	
IMEDS	Innovation in Medical Evidence Development and Surveillance
IDD	IMEDS Distributed Database
OC	Operations Center
AC	Analytic Center
SC	IMEDS Steering Committee
Foundation	Reagan-Udall Foundation for the FDA
SCDM	Sentinel Common Data Model (formerly Mini-Sentinel Common Data Model (MSCDM))
SDD	Sentinel Distributed Database

1. Introduction

1.1. Overview of IMEDS Program and the Reagan-Udall Foundation for the FDA

The Innovation in Medical Evidence Development and Surveillance (IMEDS) program is offered by the Reagan-Udall Foundation for the FDA (the Foundation), a 501(c)(3) organization located in Washington, D.C. that was established by Congress through the FDA Amendments Act of 2007 (FDAAA) to help advance the regulatory science needs of the Food and Drug Administration (FDA). IMEDS is a public-private partnership within the Foundation that is designed to build upon the significant progress made on research by FDA's Sentinel Initiative, including its Mini-Sentinel pilot and Observational Medical Outcomes Partnership (OMOP) projects.

A core goal of IMEDS is to support the FDA's Sentinel System. IMEDS creates and fosters an inclusive environment that enhances continued engagement and participation by multiple stakeholders as Sentinel evolves. Accordingly, IMEDS is committed to ensuring the transparency of both process and findings. IMEDS serves to advance the science and tools necessary to support evidence generation on regulated products, including safety surveillance and evaluations, and to facilitate utilization of a robust electronic healthcare data platform for such activities.

1.2. Overview of IMEDS

Launched in May 2008 by FDA, the Sentinel Initiative developed and implemented a system which complements existing approaches the Agency has in place to track reports of adverse events linked to the use of its regulated products. As of 2016, Sentinel is a fully functioning active surveillance system that is used by FDA to routinely monitor the safety of FDA-regulated medical products. Sentinel uses pre-existing electronic healthcare data from multiple sources. Collaborating institutions provide access to data as well as scientific and organizational expertise.

As developed, the Sentinel system is enabled through contracts with the FDA, which limits the ability of others to access this important resource. However, the FDA's vision for Sentinel includes leveraging the tools and system capabilities for broader public health and safety uses by stakeholders other than FDA. IMEDS seeks to fill this need by providing access to those outside of FDA. The goal for IMEDS is to build collaborations among Sentinel data partners, investigators, FDA, and non-FDA entities to apply the tools and capabilities used by Sentinel, to conduct safety assessments of marketed medical products and other scientific inquiries of importance. On occasion these may be opportunities for groups of non-FDA stakeholders to collaborate on topics of common interest, for example, health outcomes of interest.

The large distributed network of electronic healthcare databases and associated modular analytic programs originally developed for the FDA's Sentinel system will provide other stakeholders with an opportunity to conduct rapid queries or protocol-based safety surveillance in an efficient manner. Access to this national resource will address many of the potential limitations of passive spontaneous reporting systems and studies performed using a single database. Through IMEDS, the medical products industry will have another resource which it can use to fulfill regulatory obligations and other activities that are part of a medical product's risk management. Such activities may include active surveillance programs, safety signal refinement, safety signal evaluations/required post-market safety studies, and

evaluations of the effectiveness of Risk Evaluation and Mitigation Strategy (REMS) program elements. Other stakeholders may also be interested in undertaking these activities or analyzing broader safety concerns.

IMEDS safety assessments will be completed by the IMEDS Operations Center (OC) using the IMEDS Distributed Database (IDD). The IDD is a virtual distributed data system that includes data maintained by network partners that have agreed to collaborate with the Foundation on a voluntary basis to complete work using the Sentinel Common Data Model (SCDM) and associated tools.

1.3. IMEDS Commitment to Transparency

With the ultimate goal of improving public health, the Foundation provides a unique opportunity to bring all stakeholders to the table to work together in a transparent way to inform the evolving area of regulatory science. Participation by non-FDA stakeholders, including regulated industry, is a fundamental part of the legislative scheme created by Congress when it established the Foundation, because important scientific work and knowledge resides within private sector companies, academia, and the advocacy community, as well as within government. Acting as a neutral party, the Foundation strives for balanced input from all stakeholders and operates with a high level of transparency to actively address actual and potential conflicts of interest through a variety of mechanisms, as described in Section 7. IMEDS Conflict of Interest Policy.

- To promote transparency, IMEDS adheres to the following principles and practice:
- IMEDS will make results, once considered final (see Section 4.4.3. Determination of Final Results) and approved by the IMEDS Scientific Director, available to the general public via the IMEDS web pages.
- IMEDS will disseminate information about its operations and study results through various communication vehicles.
- IMEDS will hold a group conference call prior to any finalization of queries in order to communicate the intent and nature of the queries, as well as garner alignment.

1.4. IMEDS Scope and Approach

IMEDS provides an opportunity for non-FDA public or private organizations to sponsor projects that utilize Sentinel tools and data to evaluate important medical product safety concerns. By using the same data and tools, and by completing the same types of assessments as the Sentinel system used by FDA, IMEDS helps expand the volume and improve consistency of safety surveillance activities in the United States.

Key Features of IMEDS:

Supporting the Vision of Sentinel: The FDA views Sentinel as a valuable national resource for other safety researchers, besides those at FDA.[1] IMEDS provides an opportunity for other public and private

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[1] Janet Woodcock, December 31, 2014. Available here:
http://blogs.fda.gov/fdavoice/index.php/2014/12/another-important-step-in-fdas-journey-towards-enhanced-safety-through-full-scale-active-surveillance/, Accessed February 5, 2018.

organizations to conduct active surveillance and other medical product safety evaluations using the same data infrastructure and methods as Sentinel.

Consistency in Active Surveillance: Sentinel monitors the safety of FDA-regulated medical products through assessment of routinely collected electronic healthcare data in response to FDA concerns. IMEDS provides an opportunity for additional organizations to leverage the tools and capabilities with the same data partners for additional safety assessments, ensuring consistency in data and methods.

Re-use of the Sentinel Distributed Data Network: Through close partnership with Sentinel partners, IMEDS facilitates additional projects aimed at safety assessments to be funded by sponsors and completed under the supervision of the IMEDS OC.

Transparency: Transparency is a fundamental principle of the operations of Sentinel and IMEDS. Data specifications Final results of IMEDS activities are placed in the public domain.

Privacy: All IMEDS activities adhere to applicable privacy-related laws and regulations governing public health practice and/or research. Whenever possible, aggregate data or individual level data without direct identifiers are used, and appropriate use is made of Institutional Review Boards for activities that qualify as human subject research.

Collaboration: IMEDS strives to ensure that the design, operation, and governance of the IMEDS program include input from IMEDS data partners, the Analytic Center, FDA, and other stakeholders, including patient and consumer groups, medical product manufacturers and providers.

2. IMEDS Governance and Organizational Structure

The OC is responsible for managing the IMEDS Program and is comprised of dedicated Foundation employees and contractors as needed. A number of governing bodies also provide strategic guidance to the OC. These governing bodies (the Foundation Board of Directors, including committees of the Board, and the IMEDS Steering Committee) are comprised of stakeholders from regulated industry, network partners, providers, academia, patient and consumer advocates, and FDA (as non-voting members) to ensure IMEDS remains an effective and transparent public-private partnership. The specific organizational structure and governance of the IMEDS program is depicted in **Figure 1**.

Figure 1. Organization Structure of IMEDS

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│  IMEDS Steering             │          │  Foundation Executive        │
│  Committee  (Advises IMEDS  │          │  Director                    │
│  Scientific Director)       │          │  (Oversight of IMEDS Program)│
└─────────────────────────────┘          └──────────────────────────────┘
                                                        │
                                          ┌──────────────────────────────┐
                                          │  IMEDS Scientific Director   │
                                          │  (Leads and Manages IMEDS    │
                                          │  Program)                    │
                                          └──────────────────────────────┘
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                          ┌─────────────────────────────┴──────────┐
           ┌──────────────────────────────┐          ┌──────────────────────────────┐
           │  Legal/Privacy Compliance    │          │  IMEDS Operations            │
           │  Officer                     │          │  Center (OC)                 │
           │  (Advises on data privacy    │          │  (Manages operations)        │
           │  and complaince)             │          └──────────────────────────────┘
           └──────────────────────────────┘                       │
                              ┌──────────────────────────────┐
                              │  IMEDS                       │
                              │  Data Analytic Center (AC)   │
                              │  (Data Analytics)            │
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2.1. Reagan-Udall Foundation for the FDA Executive Director

The Foundation Executive Director is appointed by the Foundation Board and serves as supervisor to the IMEDS Scientific Director, who has oversight of the IMEDS Program.

The Foundation Executive Director's roles and responsibilities are detailed in the Foundation's bylaws and governing statute, codified at 21 USC 379dd. The Foundation Executive Director oversees all Foundation projects approved by the Foundation Board, including IMEDS. The Foundation Executive Director's IMEDS-specific roles and responsibilities include, but are not limited to:

- Recruit, interview, and hire the IMEDS Scientific Director.
- Oversee the IMEDS Scientific Director's management of the IMEDS program.
- Present periodic IMEDS updates, with the IMEDS Scientific Director, to the Foundation Board and/or Board Liaison Committee.
- Ensure alignment between Foundation's mission and the missions of all IMEDS projects.
- Collaborate with the IMEDS Scientific Director, Foundation staff, and Foundation contractor(s) to create appropriate communication plans.
- Approve the IMEDS operating budget (subject to review by the Foundation Board).
- Coordinate IMEDS fundraising efforts in collaboration with the IMEDS Scientific Director.
- Provide strategic oversight and develop partner relationships.
- Serve as spokesperson as needed

2.2. IMEDS Scientific Director

The IMEDS Scientific Director provides scientific and operational leadership for the IMEDS program in general. For specific sponsored projects, the IMEDS Scientific Director serves as either lead or co-lead, depending on the nature of the project. As the program scales up, the IMEDS Scientific Director may delegate to additional IMEDS scientific staff which may serve as direct reports or as contractors. As such, this individual, and other individuals hired to accept delegated duties as a lead or co-lead on sponsored projects, should have a strong scientific background, preferably in epidemiology, with experience utilizing electronic health data for safety evaluations. From an operations perspective, this individual should also have the ability to direct the operational aspects of the program. The IMEDS Scientific Director should be an employee of the Foundation. The IMEDS Scientific Director reports to the Foundation Executive Director, and as a Foundation employee, the IMEDS Scientific Director is subject to the conflicts of interest disclosure and transparency rules set forth in the bylaws for Foundation employees.

The IMEDS Scientific Director's roles and responsibilities include, but are not limited to, the following (the IMEDS Scientific Director may also assign completion of tasks associated with his/her responsibilities to other members of the IMEDS program staff, as necessary):

Operational responsibilities:
- Lead operational aspects of the IMEDS program
- Serve as a spokesperson for IMEDS to internal and external stakeholders, including the Foundation Board, the Foundation Board Liaison Committee, IMEDS Steering Committee, IMEDS Analytic Center, IMEDS project sponsors, FDA and other regulators, and the public.
- Oversee completion of all IMEDS work, and all staff and external contractors hired to support the IMEDS program.

- Recruit, interview, and hire IMEDS program team members (including administrative staff, technical staff, contractors, and intramural investigators).
- Nominate individuals to supplement the knowledge of the IMEDS program team in areas such as use of data, protocol design, conflicts, privacy, and infrastructure. These nominations must be approved by the Foundation Executive Director, and will serve as contractors to the Foundation.
- Establish master and project-specific agreements with network partners associated with the IMEDS Distributed Database.
- Create and maintain the IMEDS operating budget (subject to approval by the Foundation Executive Director, and the Foundation Board).
- Oversee external communications on behalf of IMEDS to FDA and other stakeholders, with oversight and guidance from the Foundation Executive Director. Communications may be delivered through the Foundation website, public symposia, teleconferences, and other means, and should be in alignment with any IMEDS and Foundation communication strategy.
- Negotiate contracts and statements of work with the IMEDS Analytic Center, network partners, and sponsors.
- Ensure IMEDS's adherence to privacy and ethical standards, laws, and regulations.
- Ensure compliance among IMEDS participants with the policies outlined in this IMEDS Policies and Procedures document.
- Establish appropriate conflict of interest procedures.

<u>Scientific responsibilities</u>
- Lead (or co-lead) the projects, as described below. (This individual would have scientific credentials sufficient for leading an IMEDS project, including modular program assessments and may lead or co-lead protocol-based assessments).
- Collaborate with FDA and the Analytic Center to maintain up-to-date knowledge and understanding of the Sentinel tools and capabilities that are available for use in IMEDS activities

2.3. IMEDS Steering Committee

A multi-stakeholder IMEDS Steering Committee (SC) provides guidance on the operation of IMEDS.

IMEDS Steering Committee Responsibilities Specific to IMEDS:
- Reviews, guides, and provides input to the overall management and operations of the IMEDS Program.
- Forms temporary sub-committees as necessary to support its decision-making. These sub-committees may cover technical issues, data issues, privacy/legal and ethical issues, policy issues, communications, and other program issues as deemed necessary.
- Forms an executive/rapid-response committee, as necessary, which could be convened expeditiously to make critical, time-sensitive decisions between formal IMEDS Steering Committee meetings.
- This committee does not have responsibilities on individual IMEDS sponsored projects.

2.5. IMEDS Operations Center (OC)

The OC, managed by and located at the Foundation, leads all scientific and management operations of the IMEDS program and reports to the IMEDS Scientific Director. The OC manages and coordinates the administrative and project management aspects of the IMEDS Program, including managing and supporting the activities of the IMEDS Analytic Center (AC) and individual projects sponsored by external organizations. The OC is the central point of contact for the IMEDS project sponsors, network partners, FDA, and all other collaborating organizations regarding operational aspects of IMEDS.

Responsibilities

- Develop operational policies and procedures.
- Develop IMEDS project programming work plans.
- Organize and manage all committees and workgroups.
- Negotiate and manage contracts and subcontracts.
- Manage finances.
- Engage legal counsel to advise compliance with state and federal regulations on patient privacy and data security.

2.6. IMEDS Collaborating Organizations

The IMEDS collaborating organizations include network partners, individual project sponsors, and other organizations that fulfill the needs of the OC. In addition, other organizations or individuals who bring specific expertise needed for individual sponsored projects may be invited to participate on projects and therefore would be considered collaborating organizations during the time they are participating on individual sponsored projects. Collaborating organizations bring to the IMEDS program one or more of the following characteristics to meet the requirements of projects: opportunities to run queries against healthcare data, data and technical expertise, scientific and methodologic expertise, therapeutic area-specific clinical expertise, and/or organizational expertise. Representatives of the collaborating organizations participate in various capacities, including as members of specific study groups.

The IMEDS Scientific Director, with oversight from the Foundation Executive Director, is responsible for determining the organizations considered to be collaborating organizations. Any collaborating organizations that knowingly conducts its participation in a manner that contradicts policies established in this document may be subject to review and consideration by the IMEDS Steering Committee and/or the Foundation Board of Directors for potential termination of partnership with the IMEDS program.

2.6.1. IMEDS Analytic Center

The IMEDS Analytic Center (AC) is responsible for providing data coordinating services, results reporting, and report generation services for IMEDS sponsored projects. The AC will provide Sentinel tools and procedures to facilitate the use of the IMEDS Distributed Database (IDD) by external stakeholders in a manner which mirrors FDA's use of Sentinel. The AC will provide technical support, guidance, and consulting on the strengths and limitations of the Sentinel resources. The AC will also work with the OC and the study sponsor to develop protocol based or other customized assessments for IMEDS project

sponsors. Harvard Pilgrim Healthcare Institute is the current Sentinel Analytic Center and will serve as the AC.

<u>Responsibilities</u>
- Coordinate and support programming and analytic activities for individual projects, as necessary.
- Coordinate and oversee implementation of the distributed data approach and common data model on individual projects, as necessary.
- Document data sources and characteristics.
- Assess data quality of IDD when used for individual sponsored projects.
- Lead programming to support workgroups and analyses.
- Review data-related workgroup proposals and develop statements of work for each study.
- Provide methodologic expertise (in collaboration with the IMEDS Scientific Director, study sponsor, and network partners if needed).
- Facilitate reuse, with modification if necessary, of tools, programs, and other capabilities for individual sponsored projects.
- Implementation of epidemiological and biostatistical methods of Sentinel and other scientifically appropriate methods for individual sponsored projects.
- Identify available Sentinel analytic tools, other tools if appropriate, and data structures to address specific medical product questions as part of individual sponsored projects.
- Provide interpretation of data from the IDD.
- Preparation of deliverable reports.
- Ensure all data used for IMEDS projects have completed Sentinel SOPs for data quality.

2.6.2. IMEDS Network Partners

The IMEDS network partners include organizations that have the capability and have agreed to participate in planned IMEDS activities; partners can choose to participate on a project-by-project basis prior to the initiation of a project. Organizations that are fully operational Sentinel data partners, with an operational SDD, will be invited to become IMEDS network partners. For participation in individual projects, the IMEDS network partner must pass the most recent data quality checking algorithms established within Sentinel. The AC will work with the IMEDS Scientific Director to ensure this requirement is met.

The current Sentinel data partners that are IMEDS network partners include:

- Aetna
- Harvard Pilgrim Health Care Institute
- HealthCore
- HealthPartners
- CMS data can also be utilized for certain studies
- Humana

- Marshfield Clinic
- Meyers Primary Care Institute
- Vanderbilt University Medical Center
- Kaiser Permanente Washington Health Research Institute

2.6.3. IMEDS Project Sponsors

IMEDS projects can be sponsored by either public or private organizations. Examples of such organizations include pharmaceutical, biologic, or medical device manufacturers, foundations, academic institutions, disease-specific associations, patient advocacy organizations, payers, trade associations, other (non-FDA) Agencies of the US Department of Health and Human Services, and foreign regulators (e.g., European Medicines Agency).

Project sponsors initiate studies with the OC via completion of an IMEDS Intake Form, informal discussions, or by other communications. Project sponsors collaborate with the OC and the AC to complete rapid queries and modular program-based assessments and can add investigators to projects with formal workgroups.

3. Data

3.1. Use of Sentinel System Data for IMEDS

IMEDS sponsored projects utilize the IDD, which represents a carbon-copy or permissible portion[2] of the SDD created through a partnership between IMEDS and the Sentinel data partners that agree to participate in IMEDS. Appendix A summarizes the SDD and the SCDM. Under this partnership, IMEDS data partners agree to utilize a copy of the most up-to-date version of the original source and, if permitted, external source production data used in the SDD. Existing SDD external source data collected for Sentinel purposes cannot be re-used by IMEDS 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 authorization. Likewise, IDD external source data collected for IMEDS project purposes cannot be re-used by Sentinel without authorization by the external source in keeping with all applicable data privacy regulations. Only data contained in the SDD that are permissible for non-Sentinel use will be included in IMEDS projects. Data partners currently participate in data checking procedures and adjustments with the AC.

This arrangement is intended to allow for "new uses" of the Sentinel data and infrastructure without disruption for alteration of the underlying data used for Sentinel activities by FDA. Accordingly, data partners also agree to keep the SCDM formatting on the data when used for IMEDS sponsored projects.

Within Sentinel, the Sentinel collaborating organizations, the Sentinel Analytic Center, and the FDA are each responsible for the stewardship of data in their possession and adhere to strict data governance principles. The IMEDS program and its participants, including the OC, AC and data partners must also

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[2]Data partners may choose to create an actual carbon-copy of the production data used in the MSDD, the permissible portion of the MSCDM, or may utilize the same database, depending on the data partner's preference. All attention is made to ensure that IMEDS activities are using the same data as the Sentinel activities, unless otherwise noted, without allowing any IMEDS activity to disrupt or alter Sentinel production data in any way.

adhere to the same data stewardship principles, where applicable. The OC leads all activities related to the use of the IDD for IMEDS activities. When necessary, the OC will delegate specific data activities to the AC.

In response to specific queries, data partners do not share direct patient identifiers with the AC and adhere to the HIPAA minimum necessary standard.[3] Data are provided AC 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 demographics, medical product exposures, health outcomes, days between exposure and outcomes, co-morbidities, and dates when such information is required based on the methodology and study design of the specific project. Provision of person-level data is contingent on receipt of appropriate internal approvals by the data partners.

The AC shares de-identified summary results with the OC. IMEDS data partners can review the summary results. These results are then shared with the individual project sponsor, led by the OC, aggregated across all data partners and potentially at the individual data partner level (masked), when necessary and to illustrate the between data partner variability on key results. When required for analysis and interpretation of results, the project sponsor or OC can request to review results stratified by data partner. Stratified results will be summary measures presented by masked data partner (e.g., DP1, DP2, etc.) such as rates or proportions per 1000 eligible members. For count variables that may unintentionally identify specific data partners (e.g., if it was known that a specific health plan allows an unusual days supply to be dispensed) an overall mean, median, standard deviation, min, max may be presented but not by each data partner. Data partners will approve the method of presenting variability prior to finalizing analytic query results. All results will be presented with appropriate caveats regarding the results being only one piece of information that contribute to risk management decisions. Access to the non-summarized data is limited to authorized individuals within the AC or others authorized by the AC to act on its behalf upon data partner approval.

Data transfer between data partners and the AC and between the AC and the OC and project sponsors is done by means of a secure web-based file sharing system. The AC complies with standards established by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Federal Information Security Management Act of 2002 (FISMA).

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[3] 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)).

3.2. Data Use Limitations

3.2.1. Original Source Data

The IMEDS program recognizes that according to the Sentinel Principle Policies, data partners may use their own original source data transformed into MSCDM 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. For original sourced data, data partners will adhere to the same data retention parameters as with Sentinel.

3.3.2. External Source Data

The AC and data partners may only use data obtained from sources other than their own institution in the conduct of specific IMEDS sponsored projects if authorized by the external source in keeping with all applicable data privacy regulations. Such external data obtained for IMEDS may not be reused, re-disclosed, altered, or sold for any purposes other than those defined in the IMEDS project contract without specific authorization. Examples include data from the Social Security Administration Death Master file, data from state immunization registries, etc.

Unauthorized disclosure and/or use will be reported to the OC. The user will be allowed an opportunity to remedy the situation on terms that are satisfactory to the IMEDS Scientific Director 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 the IMEDS program. For externally sourced data, data partners will adhere to the same data retention parameters as with Sentinel.

3.3.3. Use of Data by IMEDS

For the purposes of data used for IMEDS activities, the OC, including the AC, obtains specific rights to use query result information securely shared by data partners with the AC in accordance with data partner agreements with IMEDS for the performance of IMEDS sponsored projects. In keeping with the confidentiality sections of the sponsor contract and this statement of IMEDS Policies and Procedures, 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. Use of the data is governed by relevant laws and regulations and data partner authorization.

3.3.4. Use of Data by Project Sponsors

Individual project sponsor use of query result information for IMEDS sponsored projects will be limited to de-identified aggregate summary level data (i.e., tabular results). **Person-level data will not be transferred to project sponsors.** However, de-identified person-level data may be accessed by work group members (including those engaged/employed by the sponsor) through a secure web portal if necessary to conduct a protocol based assessment. Data partners will be provided table shells prior to result generation that depict how the data will be presented so that appropriate approvals can be obtained. Modifications to the way results are presented based on actual results will not be permitted, with the exception of aggregation of table cells with small numbers to maintain compliance with de-identification standards.

4. Sponsored Project Operations

4.1. Minimum Criteria for an IMEDS Sponsored Project

To fulfill its mission of expanding the opportunities for using the same tools and capabilities as FDA for conducting safety assessments by interested organizations other than the FDA, the IMEDS program has established a set of minimum criteria that must be met for an individual project to be considered. The IMEDS Scientific Director will be responsible for determining that such criteria are met before proceeding with a project.

The following items represent the minimum criteria:

1. The IDD is considered an appropriate data source[4] for completing the objectives of the project (disagreements will be handled by the Foundation Executive Director through the dispute resolution process involving review and advice from IMEDS Steering Committee).
2. The proposed objectives of the project consist of a safety assessment, and the project sponsor provides the public health importance and context for the safety concerns of interest. Safety assessments may examine exposures to medical products, exposure-outcome relationships, or the impact of risk mitigation activities (e.g., REMS or other educational or behavioral actions intended to mitigate the risks of medical products).

4.2. Process for Project Sponsors to Engage with IMEDS

Organizations wishing to sponsor studies utilizing the IDD can make their request to the OC by submitting a completed IMEDS Intake Form. The IMEDS Scientific Director, using the minimum criteria for an IMEDS sponsored project as a guide, will determine if a potential project is appropriate for the IMEDS program. The IMEDS Scientific Director will work with the sponsor's representatives and the AC to develop a project scope of work and budget and invite data partners. Once the sponsor agrees to the proposal and commits the funds and staff, if applicable, the project will be initiated.

4.3. Types of Projects

Table 1: Summary of the Types of Projects Available for IMEDS Sponsored Projects

Project Type	Description
Modular Programs	Modular programs facilitate rapid querying of the data to glean information such as counts of enrollment, diagnoses, procedures, drug, device, and biologic utilization, and other cohort size measures. Newly released tools (e.g., propensity score matched and self-controlled risk interval) can adjust for confounding as part of a one-time assessment.

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[4] The IDD will be considered an "appropriate data source" if the currently available data represented by the IDD provide sufficient ability to ascertain medical product exposures and outcomes of interest with some ability to reduce systematic bias, if needed, and the distributed nature of the data allow for appropriate analytic techniques.

Protocol-Based Assessments	Protocols are detailed plans for customized pharmacoepidemiologic studies.
Validation Studies	Studies that evaluate the validity of the algorithms used to identify individuals with specific health outcomes or exposures, or who belong to a specific cohort

4.4. Project Operations for Rapid Queries with Modular Programs and/or Summary Tables

4.4.1. Initiation and Conduct of Sponsored Project

The initiation of sponsored projects using modular programs is summarized in **Figure 2**. The OC, AC, and project sponsor collaborate to determine the necessary existing non-customizable modular programs; numbers of queries to run etc., prior to soliciting network partner participation. When IMEDS projects rely solely on non-customizeable modular programs and where the scope of the project does not include significant scientific or methodological input into program modification, project workgroups will not be formed in an effort to ensure that IMEDS projects are efficient and cost-effective. In this case the OC, AC, and the project sponsor will work to develop the rapid descriptive and comparative analyses to ensure speed and efficiency. Participating network partners will have an opportunity to review and provide input to the rapid query assessments prior to executing them on their data and resulting reports.

Network partners and other experts, if needed, will be invited to participate via a notification to participate in an IMEDS sponsored project. The notification will contain the following information:

- Name of project sponsor organization
- Project title (if there is one)
- Objectives of the queries
- Public health importance of the objectives and rationale, including but not limited to explanation if this is part of a regulatory mandate, potential safety concern identified from spontaneous report data, etc.
- Scope of work, including types of queries.

Network partners interested in participating will obtain necessary internal approvals and submit a budget for data management, analytic support, and project management support as needed. Note: Opportunities for advanced commitment for a pre-specified volume of queries by project sponsors will increase predictability of the volume of work, allowing for more efficient budgeting, contracting, staffing, and internal approval steps.

Prior to commencing of the sponsored project, the Sentinel Lead at the FDA will be notified that queries will be run. This notification is for informational purposes only and should not be construed to imply that IMEDS is seeking permission from FDA or that FDA is serving as a "gatekeeper" for IMEDS. Project sponsors can review related FDA Sentinel activity by consulting the Sentinel website.

4.4.2. General Activities and Timelines

A goal of the IMEDS program is to provide broader stakeholders the opportunity to sponsor safety assessments for important potential safety concerns. The IMEDS program strives to enable rapid evaluations of potential safety concerns using modular programs. It is essential that the analytic programs and data used are of high quality that have been tested with appropriate QA/data checking procedures.

Further, in an effort to promote transparency and inclusiveness of the network partners, a group conference call will be held prior to any finalization of queries in order to communicate the intent and nature of the queries. Network partner input and feedback will be welcomed.

Table 2 provides a summary of the activities and timing of major steps in conducting IMEDS Sponsor-initiated studies and activities. These timelines are an estimate only, and can vary depending on the timing and complexity of the study.

IMEDS Sponsor-initiated Study Timeline

Activity	Details / Comments	Time Estimation
Sponsor / IMEDS Initial Call	Potential sponsor contacts IMEDS regarding details and goals of study	1 week
Sponsor completed and submits IMEDS intake form	Intake form provides details on study, public health justification	2-3 weeks
Master Services Agreement and Non-Disclosure Agreement	"Opens the door" between RUF and Sponsor, establishes legalities (includes legal review and execution)	4-5 weeks
Sponsor Webinar Presentation to IMEDS Network Partners (NPs)	Explains study goals, allows stakeholders to meet, determine NP interest in study participation	2 weeks
Receive study synopsis from Sponsor	If applicable/completed	In parallel with above tasks
Development of Statements of Work for Sponsor, IMEDS OC, IMEDS AC, and/or lead NP	Includes legal review, determination of activity scope, timelines, deliverables	6 - 8 weeks
Statements of Work developed with participating NPs	Initiated once the IMEDS AC/Lead NP statement of work and general study timeline have been established	3 - 5 weeks
Budget development and execution of SOWs	Initiated once scope and deliverables are finalized	In parallel with SOW development
IRB submission (if necessary)	Initiated for projects that involve data use outside the blanket IMEDS IRB protocol	2-3 weeks
Data Use Agreements (if necessary)	Initiated for projects that include ad hoc data sources or do not use the distributed network.	In parallel with IRB

Note: Total of ~ 24 weeks to contract execution. Many tasks may be completed in parallel. Timelines are subject to change based on Sponsor legal requirements and scoped activities, and activities may be added or removed based on necessity for the required deliverables.

IMEDS Project Implementation Timeline: Protocol Development or "Phase 1"

Activity	Details / Comments	Time Estimation
IMEDS study team formed	(comprised of Sponsor, IMEDS AC, IMEDS OC, NPs)	2-3 weeks
Project kickoff call	Sets up next steps and recurring call schedule	Included in above task
Protocol development	• Can also include development of study synopsis, SAP, and plans for feasibility analysis if requested by Sponsor • Typically includes 3-4 weeks each for two drafts developed and shared with Sponsor	15 weeks
Review of draft protocol (and additional deliverables) by NPs		1 week
Submission to regulatory body and inclusion of regulatory comments	Depends on regulatory comment return	2-3 weeks to receive and incorporate comments
Posting of protocol or protocol synopsis	Depends on regulatory status of product (only for approved products and indications)	Within 30 days of protocol approval

Note: Many tasks may be completed in parallel. Timelines are subject to change based on Sponsor legal requirements and scoped activities, and activities may be added or removed based on necessity for the required deliverables.

IMEDS Project Timeline –Study Implementation or "Phase 2", "Phase 3"

Activity	Details / Comments	Time Estimation
FDA informed of study commencement and queries to be run		Upon SOW execution.
Kickoff meeting	Includes all stakeholders; goal is to set up next steps and recurring call schedule	1 week
Draft specifications for Modular Program (MP)		1 week
Finalize specifications for Modular Program (MP)		2 weeks
Develop and test MP package (including any ad-hoc programming)	Includes beta testing of MP package at single NP site	4 weeks
Network Partner execution and development of standard tables / summary report for Sponsor		6-8 weeks
NPs review report / deliverables		7 work days to review after draft report provided by IMEDS AC
Development of final report / deliverables	Analysis and quality check by IMEDS AC Includes Sponsor reviews of report/deliverable	Estimated 6-8 weeks but can change based on Sponsor/NP/IMEDS rounds of review requested
Deliverables delivered to Sponsor by IMEDS OC		
Dissemination of final results	To occur after 'completion' of project/study is determined by study team and in collaboration with Sponsor Could take the form of study results posted on RUF website, publication, report, etc	30 days after project determined 'complete'

Table 2. Activities and Timelines for IMEDS Sponsor-Initiated Studies and Activities [SAMPLE TABLE]

Time allotted for finalizing analytic programs is highly dependent upon sponsor familiarity with the available programs and time needed for agreeing on program inputs (e.g., set of diagnostic/procedure codes for inclusion/exclusion, exposures, and outcomes; specified observation times). Data partners will

notify the AC if results are not compliant with Privacy/PHI regulation, or if release of data is not approved following data partner internal approvals process. This will allow for appropriate data handling and reporting to be completed. Time allotment is generalized – these times will be adjusted based on the specific study.

4.4.3. Determination of Final Results

The IMEDS Scientific Director, will be responsible for determining when the results of IMEDS projects are final, after all pre-specified analyses are complete. In some instances post-hoc analyses may be completed if budget allows and partners agree. The IMEDS Scientific Director may consult with the participating data partners and the project sponsor, if needed. In the event of a written disagreement (that cannot be resolved through discussion) between any members of the project team regarding the IMEDS Scientific Director's determination or any other scientific issue, the SC or their designees will provide independent review of the issue and will provide formal non-binding advice to the Foundation Executive Director. The Foundation Executive Director will make the final determination.

4.5. Project Operations for Protocol-Based Assessments (PBA)

The IMEDS team has the ability to create and implement protocol-based assessments. These would be customized studies with a unique statement of work and budget. PBAs would be collaborative projects that may allow our network partners to assume a lead role on the study.

5. Privacy

Collaborators must observe all applicable federal and state privacy-related laws and regulations.

5.1. Human Subjects Protection

The Foundation has received an NE IRB exemption for a protocol submitted for the Innovation in Medical Evidence Development and Surveillance (IMEDS) Program (NEIRB Work Order #: 1-8738-1), indicating that these studies are not human subjects research. Prior to the performance of any analyses, the network partner seeks approval from their respective Institutional Review Boards (IRBs) and/or Privacy Boards, or obtain waivers of authorization under HIPAA, to participate in studies covered under the Blanket IRB named above (45 CFR §164.512(b)). For efficiency, network partners and the AC may use the exempt decision from the NE IRB. Further, as the HIPAA requirements for research differ for those data partners that are covered entities from those that are insurers, all necessary internal approvals will be obtained prior to any use of data for the project.

5.2. Individual Health Information

The structure of IMEDS protects the privacy and confidentiality of individual health information. Network partners maintain physical and operational control over the data in their possession and execute analysis programs distributed by the AC behind their own firewalls. In most cases, the output of these programs is provided to the AC in summary format. The AC aggregates IMEDS Data Partner responses to queries and sends results from the individual data partner level and aggregated across all data partners to the OC. When person-level information is requested for analyses, and contingent upon

receipt of appropriate data partner approvals, data partners remove direct patient identifiers from the information conveyed to the AC (removal of direct identifiers will be part of the SAS package and will not require manual programming by the IMEDS Data Partner). If the AC inadvertently receives direct patient identifiers, it will return or destroy the data immediately. The project sponsor does not receive or possess personally identifiable information (PII), as defined by the Privacy Act of 1974, in the conduct of IMEDS activities.

Direct patient identifiers may be used by data partners when necessary, and after obtaining all necessary approvals, 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 AC, direct patient identifiers are stripped.

5.4. Minimum Necessary Standard

Only the minimum amount of data necessary to respond to specific queries, as determined by the AC or specific project workgroups, will be requested by collaborators.

5.5. Security

Sentinel data (and therefore the data comprising the IDD) are managed in accordance with the national standards established by the HIPAA Security Rule. The secure networking software and implementation used by the AC/Sentinel Operations Center are also managed in accordance with the Federal Information Security Management Act of 2002 (FISMA). Administrative, physical, and technical safeguards are employed to ensure the confidentiality, integrity, and security of electronic health information (45 CFR Part 160 and Subparts A and C of Part 164; 44 U.S.C. § 3541, *et seq*). Study results will be communicated between the AC, the OC, and the sponsor using a secure FTP technology.

5.6. Specially Protected Health Information

It is the responsibility of IMEDS data partners to determine whether state laws regulate the use and disclosure of health information for IMEDS purposes and to comply with any such laws. The OC, with input from the IMEDS Privacy Compliance Officer and in consultation with data partners, may provide additional guidance to assist data partners in assessing whether state law applies to a particular IMEDS 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.

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 information from a federally-assisted substance abuse treatment program to confirm a drug 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.

6. Communications

6.1. Review Period for the IMEDS Project Sponsor

Upon delivery of a final report to a project sponsor, the Foundation will not publicly disseminate results for a period of 30 days*. In the case of a PMR, PASS study or peer-reviewed publication, the waiting period may be extended pending receipt of results by the regulator or publication date of a journal article. This period of temporary confidentiality is necessary to permit the sponsor to conduct internal assessment activities, including but not limited to evaluating the impact of the results to the benefit/risk profile of the product(s) under examination. Once this period of temporary confidentiality has expired, the OC will post the final report on its website and notify the FDA Sentinel Lead.

*The Foundation will cooperate with the FDA in the event that FDA requests a delay due to regulatory action.

6.2. Dissemination to the Public

All project results will be made available to the public through posting to the IMEDS public website after the study has concluded. Additionally, the OC and project sponsor may submit manuscripts based on the final report to peer-reviewed journals. The publication plan for each project will be decided prior to project commencement by the IMEDS Scientific Director and based on discussions with project participants, including the project sponsor.

As described above, results from modular programs are aggregated across data partner sites (presented in overall form only). However to illustrate the between data partner variability on key results, summary measures will be presented by masked data partner (e.g., DP1, DP2, etc.) such as rates or proportions per 1000 eligible members. For count variables that may unintentionally identify specific data partners (e.g., if it was known that a specific health plan allows an unusual days supply to be dispensed) an overall mean, median, standard deviation, min, max may be presented but not by each data partner. Data partners will approve the method of presenting variability prior to finalizing analytic query results. All results will be presented with appropriate caveats regarding the results being only one piece of information that contribute to risk management decisions.

6.3. Publications and Presentations

Project participants will identify potential publications and presentations and assign authorship roles among themselves. Ideally, this will occur early during the course of collaboration before analyses occur. IMEDS adopts the authorship guidelines established by the International Committee of Medical Journal Editors (ICMJE). Authorship credit is based only on substantial contribution to:

- Concept and design, or acquisition of data, or analysis and interpretation of data; and
- Drafting or revising the manuscript for important intellectual content; and
- Approval of the final version to be published.

The determination of who obtains authorship credit lies with the potential authors, in accordance with ICMJE guidelines. The IMEDS Scientific Director will adjudicate authorship disputes. For all sponsored

project publications, authors must ensure that the sponsor's support of the project and the relationship of any author with the sponsor are disclosed in the publication. All publications describing work that made use of the IMEDS Distributed Database should include an acknowledgement of the IMEDS program and be submitted to the OC for prior review.

7. Conflict of Interest

7.1. IMEDS Conflict of Interest Policy

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

In the IMEDS Program, conflicts of interest (COI) are determined in the context of specific project activities. In general, COI exist when:

- 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

Conflicts of interest 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 IMEDS activities.

Individuals are required to disclose financial, business, or professional interests that might introduce actual or apparent conflicts during the period of their engagement in that IMEDS activity.

Appendix A

Sentinel System Data Structure and Common Data Model

Sentinel uses a distributed data approach in which Sentinel 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 Sentinel Analytic Center and then share the output of these queries, typically in summary form, with the Sentinel Analytic Center.

The SCDM is a data structure that standardizes administrative and clinical information across data partners. Data partners maintain and access data in common data model format. The SCDM makes it possible to execute standardized programs developed by the Sentinel Analytic Center in collaboration with the data partners. The SCDM relies on existing standardized coding schema (e.g., ICD-9-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 Data Core leaders coordinate and facilitate active participation by the data partners in the creation, implementation, updating, maintenance, enhancement, and use of the Common Data Model. The Data Core works closely with the Methods and Active Surveillance Cores to ensure that members of those Cores fully understand the characteristics and capabilities of the data and that the Common Data Model is designed to meet their needs. Data partners provide knowledge and expertise to ensure appropriate use and interpretation of data in the Common Data Model format.

The Sentinel Analytic Center, in collaboration with FDA, may also work with data partners to incorporate other data sources into the SCDM. These additional data sources may represent "original source data" or "external source data", as necessary.

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 dispensing, and registry data. Data partners retain stewardship and possession of both original source data and data transformed into SCDM format. Sentinel data partners manage and store the data in accordance with their own institutional policies.

As necessary, data partners may be asked to collect information from sources other than their own institution (referred to as "external source data") for purposes such as identifying or confirming exposures or outcomes of interest. Healthcare data registries for particular diseases or medical procedures 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.