Reagan-Udall Foundation for the FDA
Standard Operating Procedure

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Revision History

Date	Version No.	Section(s) Affected	Description of Revision
August 2016	1	NA	NA
February 2018	2		
September 2020	3		
April 2023	4	All	Updated the policies and procedures and formatted per the SOP template.

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

Contents

Table of Abbreviations

Abbreviations	
AC	Analytic Center
FTP	Secure File Transport Protocol
FDA Foundation	Reagan-Udall Foundation for the FDA
IDD	IMEDS Distributed Database
IMEDS	Innovation in Medical Evidence Development and Surveillance
OC	Operations Center
PMR	Post-marketing Requirements Study
PASS	Post-authorization Safety Study
SC	Real-world Evidence (RWE) Steering Committee
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 FDA Foundation), a 501(c)(3) organization located in Washington, D.C. that was established by Congress through the FDA Amendments Act of 2007 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 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 has been 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 organizations outside of FDA. The goal for IMEDS is to build collaborations among Sentinel initiative collaborators and 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 largely 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) where appropriate. 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 contractual basis to complete work using the Sentinel Common Data Model (SCDM) and associated tools. Additionally, data and data sources that are not routinely populated in the SCDM or necessarily network partners, including those vetted by Sentinel, may also be included if required to answer the research question and proper quality assurance can be established.

1.3. IMEDS Commitment to Transparency

With the ultimate goal of improving public health, the FDA 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 FDA 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 FDA 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 practices:

- IMEDS will make results, once considered final (see Section 4.4.3. Determination of Final Results) and approved by the FDA Foundation Director of Research, available to the general public. The format of dissemination may vary, including peer-reviewed publication, white-paper, etc. Results will be presented in aggregate across all partners to protect patient privacy.
- IMEDS will disseminate information about its operations and study resultsthrough various communication vehicles.

- IMEDS will hold a group conference call prior to any finalization of distributed 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/or data to evaluate important medical product safety concerns. By using the same tools (and often the same data) to complete 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 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 similar tools and capabilities, often with the same Sentinel initiative collaborators and 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. 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. Dependent on the type of project, when appropriate aggregate data or individual level data without direct identifiers are used, an appropriate use is made of Institutional Review Boards (IRB) 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 Network Partners, the IMEDS Analytic Center (AC), FDA, and other stakeholders, including patient and consumer groups, medical product manufacturers and providers.

[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.

2. IMEDS Governance and Organizational Structure

The OC is responsible for managing the IMEDS Program and is comprised of dedicated Foundation research staff. 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 – specifically the Research Committee, and the Real-World Evidence (RWE) 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**.

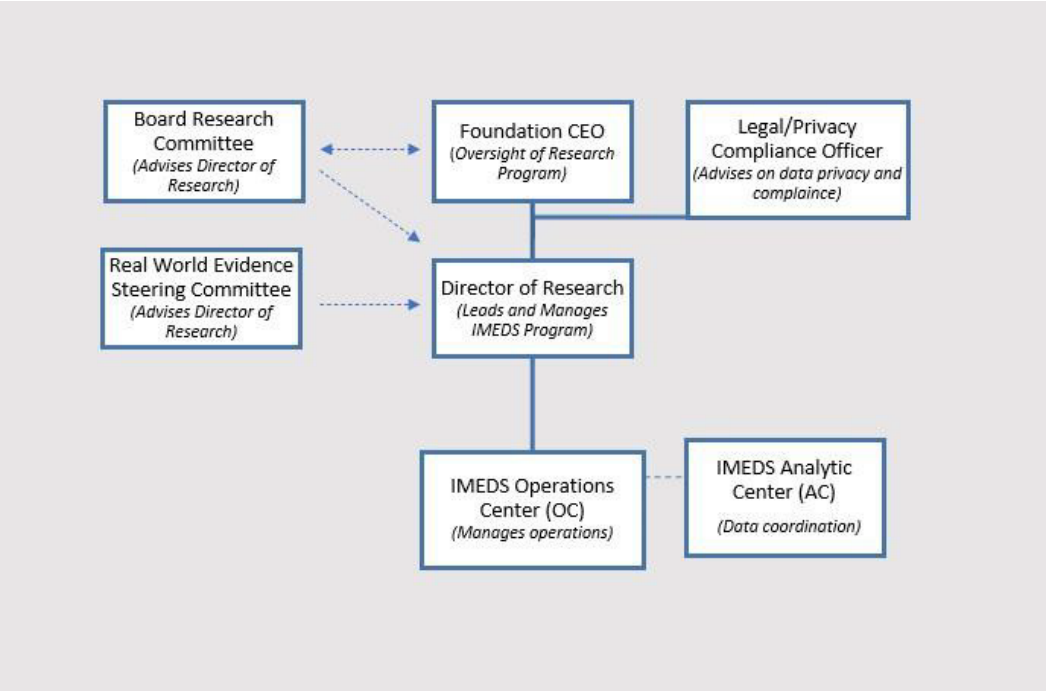

Figure 1. Organizational Structure of IMEDS

2.1. Reagan-Udall Foundation for the FDA Chief Executive Officer

The FDA Foundation Chief Executive Officer (CEO) is appointed by the FDA Foundation Board and serves as supervisor to the FDA Foundation Director of Research, who has oversight of the IMEDS Program.

The FDA Foundation CEO's roles and responsibilities are detailed in the Foundation's bylaws and governing statute, codified at 21 USC 379dd. The FDA Foundation CEO oversees all FDA Foundation projects approved by the FDA Foundation Board, including IMEDS. The FDA Foundation CEO's IMEDS-specific roles and responsibilities include:

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

2.2. FDA Foundation Director of Research

The FDA Foundation Director of Research provides scientific and operational leadership for the IMEDS program in general. For specific sponsored projects, the FDA Foundation Director of Research serves as either lead or co-lead, depending on the nature of the project. As the program scales up, the FDA Foundation Director of Research may delegate tasks to additional IMEDS scientific staff who 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 FDA Foundation Director of Research should be an employee of the Foundation. The FDA Foundation Director of Research reports to the Foundation CEO, and as an FDA Foundation employee, the FDA Foundation Director of Research is subject to the conflicts of interest disclosure and transparency rules set forth in the bylaws for FDA Foundation employees.

The FDA Foundation Director of Research's roles and responsibilities include the following. The FDA Foundation Director of Research may also assign completion of tasks associated with his/her responsibilities to other members of the IMEDS program staff and contractors:

Operational responsibilities:

- Lead operational aspects of the IMEDS program

- Serve as a spokesperson for IMEDS to internal and external stakeholders, including the FDA Foundation Board, the FDA Foundation Board Research Committee, RWE Steering Committee, IMEDS AC, 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.
    - Nominees must be approved by the FDA Foundation CEO 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 CEO, and the FDA Foundation Board).
- Oversee external communications on behalf of IMEDS to FDA and other stakeholders, with oversight and guidance from the Foundation CEO.
    - Communications may be delivered through the FDA 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 AC, 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.

Scientific responsibilities

- Lead (or co-lead) the projects, as described below.
    - This individual must 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 IMEDS AC to maintain up-to-date knowledge and understanding of the Sentinel tools and capabilities that are available for use in IMEDS activities.

2.3. RWE Steering Committee (SC)

A multi-stakeholder RWE SC provides strategic guidance on the operation of IMEDS, among other topics. This committee does not have responsibilities for individual IMEDS-sponsored projects. The SC will conduct their work as outlined in the SC Charter.

RWE SC Responsibilities Specific to IMEDS:

- Provides strategic guidance to the IMEDS Program.
- Form temporary sub-committees as necessary to support IMEDS activities.
    a. Sub-committees may cover technical issues, data issues, privacy/legal and ethical issues, policy issues, communications, and other program issues as deemed necessary.
- Form an executive/rapid-response committee, as necessary, which can be convened expeditiously to provide input on critical, time-sensitive topics between formal RWE SC meetings.

2.4. IMEDS Operations Center (OC)

The IMEDS OC, managed by and located at the FDA Foundation, leads all scientific and management operations of the IMEDS program and is led by the FDA Foundation Director of Research. The OC manages and coordinates the administrative and project management aspects of the IMEDS Program, including managing and supporting the activities of the IMEDS 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.

2.5. IMEDS Analytic Center (AC)

The IMEDS 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 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 IMEDS AC and also serves as the Sentinel Operational Center.

Responsibilities

- 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.
- Provide methodologic expertise.
    - As needed this should occur in collaboration with the FDA Foundation Director of Research, study sponsor, and network partners.
- Facilitate reuse, with modification if necessary, of tools, programs, and other capabilities for individual sponsored projects.
- Implement epidemiological and biostatistical methods of Sentinel and other scientifically appropriate methods for individual sponsored projects.
- Identify available Sentinel analytic tools and other tools as appropriate, and data structures to address specific medical product questions as part of individual sponsored projects.
- Provide interpretation of data from the IDD.
- Prepare deliverable reports.
- Ensure all Sentinel Common Data Model (SCDM) data used for IMEDS projects have completed Sentinel SOPs for data quality.

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 those individual sponsored projects. Representatives of the collaborating organizations may participate in various capacities, including as members of specific study groups. 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.

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

2.6.1. 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 Sentinel Initiative collaborators, including fully operational Sentinel data partners, with an operational Sentinel Distributed Database (SDD), can 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 Network Partner will work with the FDA Foundation Director of Research to ensure this requirement is met.

The current Sentinel initiative collaborators that are IMEDS Network Partners include:

- CVS Health Clinical Trial Services LLC, a CVS Health company
- Harvard Pilgrim Health Care Institute
- Carelon Research (fka HealthCore, Inc)
- HealthPartners Institute
- Humana/Humana Healthcare Research

- Kaiser Permanente Washington Health Research Institute
- Marshfield Clinic Health System
- University of Massachusetts Chan Medical School Division of Health Systems Science
- Vanderbilt University Medical Center

Additional data sources may also be included as required to meet study requirements.

2.6.2. 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 where appropriate. The IDD represents a carbon-copy or permissible portion[2] of the SDD created through a partnership between IMEDS and the Sentinel initiative collaborators that agree to participate in IMEDS. Appendix A summarizes the SDD and the SCDM. Under this partnership, IMEDS Network 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. Network 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, network partners also agree to keep the SCDM formatting on the data when used for IMEDS sponsored projects.

[2]Network 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 network 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.

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 Network Partners must also adhere to the same data stewardship principles. 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, Network Partners do not share direct patient identifiers with the AC and adhere to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) minimum necessary standard.[3] Data are provided to the AC by network 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 Network Partners.

The AC shares de-identified summary results with the OC. IMEDS Network Partners can review the summary results. These results are then shared with the individual project sponsor, led by the OC, aggregated across all Network Partners and potentially at the individual Network Partner level (masked), when necessary and to illustrate the between Network 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 Network Partner. Stratified results will be summary measures presented by masked Network Partner (e.g., NP1, NP2, etc.) such as rates or proportions per 1000 eligible members. For count variables that may unintentionally identify specific network partners (e.g., if it was known that a specific health plan allows an unusual day's supply to be dispensed) an overall mean, median, standard deviation, min, max may be presented but not by each Network Partner. Network 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

[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)).

authorized individuals within the AC or others authorized by the AC to act on its behalf upon Network Partner approval.

Data transfer between Network 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 HIPAA and the Federal Information Security Management Act of 2002 (FISMA).

3.2. Data Use Limitations

3.2.1. Original Source Data

The IMEDS program recognizes that according to the Sentinel Principle Policies, Sentinel 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, IMEDS Network Partners will adhere to the same data retention parameters as with Sentinel.

3.3.2. External Source Data

The AC and Network 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 and 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 per SOP PGM-06 Quality Issue Management. The user will be allowed an opportunity to remedy the situation on terms that are satisfactory to the FDA Foundation Director of Research 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, IMEDS Network 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 Network Partners with the AC in accordance with Network 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 by Network 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. Network 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 FDA Foundation Director of Research 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 or other Sentinel data sources are considered an appropriate data source[4] for completing the objectives of the project (disagreements will be handled by the Foundation CEO through the dispute resolution process involving review and advice from RWE Steering Committee).
2. The proposed study objectives should include those that advance public health and/or be of high public health importance. Such studies 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 FDA Foundation Director of Research, using

[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.

the minimum criteria for an IMEDS sponsored project as a guide, will determine if a potential project is appropriate for the IMEDS program. The FDA Foundation Director of Research will work with the sponsor's representatives and the AC to develop a project scope of work and budget and invite Network Partners. Once the sponsor agrees to the proposal and commits the funds and staff the project can be initiated.

4.3. Types of Projects

Table 1: Summary of the Types of ProjectsAvailable 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.
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-customizable 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. While initial outreach will be most inclusive, the OC

will articulate very specific expectations regarding the data availability and timeframe needed to fulfil study aims, which may vary by Network Partner. The notification will contain the following information:

- Name of project sponsor organization
- Project title (if there is one)
- Objectives of the query(ies)
- 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.
- Brief description of anticipated 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 a 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.

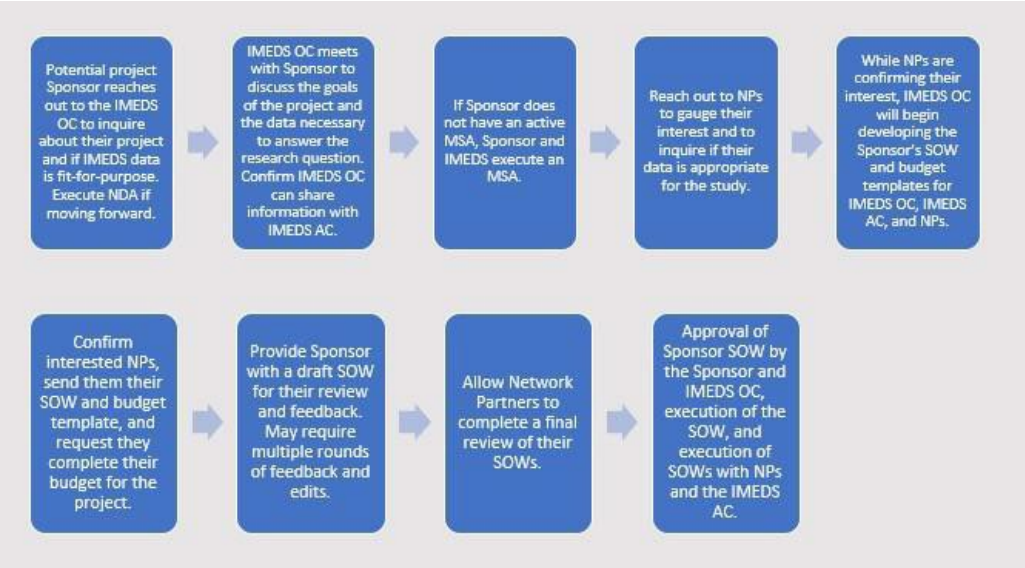

Figure 2. Initiating Sponsor Contracts and Subsequent Phases of Work

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

4.4.3. Determination of Final Results

The FDA Foundation Director of Research will be responsible for determining when the results of IMEDS projects meet current sponsor MSA definitions for “final” after all pre-specified analyses are complete. In some instances, post-hoc analyses may be completed if budget allows and partners agree. The FDA Foundation Director of Research may consult with the participating Network Partners and the project sponsor as needed. In the event of a written disagreement between any members of the project team regarding the FDA Foundation Director of Research’s determination or any other scientific issue that cannot be resolved through discussion, the RWE Steering Committee or their designees will provide independent review of the issue and will provide formal non-binding advice to the FDA Foundation CEO. The FDA Foundation CEO 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 are collaborative projects that may allow 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 and remain up to date with IMEDS program training and education requirements (ADM-23-03 Employee Training and Education Requirements and PGM-23-005 Vendor Qualification and Management).

5.1. Human Subjects Protection

The Foundation has received an Institutional Review Board (IRB) exemption for a blanket protocol submitted for the Innovation in Medical Evidence Development and Surveillance (IMEDS) Program (NEIRB Work Order #:1-1541016-1) from WCG IRB (formerly New England IRB), indicating that these studies are not human subjects research. This protocol can be updated and provided to the IRB for approval as needed. Additionally, project specific IRB protocols may be initiated if the data or procedures necessary to address the research question are not covered by the Blanket IRB.

Prior to the performance of any analyses, Network Partners seek approval from their respective IRB and/or Privacy Boards and obtain waivers of authorization under HIPAA; or must rely on the WCG IRB determination to participate in sponsored IMEDS studies. For efficiency, Network Partners and the AC may use the exempt decision from the WCG IRB. Further, as the HIPAA requirements for research differ for those Network 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 Network Partner responses to queries. Individual and Aggregated Network Partner results are sent to the OC. When person-level information is requested for analyses, contingent upon receipt of appropriate Network Partner approvals, Network 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 Network Partner. If the AC inadvertently receives direct patient identifiers, it will return or destroythe

data immediately. The project sponsor should not receive or possess personally identifiable information (PII), as defined by the Privacy Act of 1974, in the conduct of IMEDS activities.

As required by specific projects, direct patient identifiers may be used by Network Partners after obtaining all necessary approvals, including Business Associate Agreements, in order to gather additional clinical and demographic information or to link their data to data from other sources. 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 secure file transfer protocol (FTP) technology.

5.6. Specially Protected Health Information

It is the responsibility of IMEDS Network 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 Network Partners, may provide additional guidance to assist Network 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 Network 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 IMEDS Blanket IRB exemption letter (dated April 25, 2022) specifically includes “alcoholand substance use related diagnosis and medication.” Notable to IMEDS, the Part 2 regulations do not apply to information that does not identify an individual. If Network 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 FDA Foundation will not publicly disseminate results for a minimum period of 30 days*. In the case of a post-marketing requirements study (PMR), post-authorization safety study (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 facilitate final network reviews in accordance with existing network partner MSAs, then 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 (About IMEDS | Reagan-Udall Foundation (reaganudall.org)) 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 FDA Foundation Director of Research and will be based on discussions with project participants, including the project sponsor.

As described above, results from modular programs are aggregated across Network Partner sites (presented in overall format only). However, when scientifically appropriate to illustrate between Network Partner variability on key results, summary measures may be presented by a masked Network Partner (e.g., NP1, NP2, etc.) such as rates or proportions per 1000 eligible members. For count variables that may unintentionally identify specific Network Partners (e.g., if it was known that a specific health plan allows an unusual day's supply to be dispensed) an overall mean, median, standard deviation, and min/max may be presented, but not by each network partner. Network 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 FDA Foundation Director of Research 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 FDA 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.

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Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

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Envelope Summary Events	Status	Timestamps
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