Highlights and Key Findings from IMEDS-Methods Research Activities in 2014

Overview

IMEDS-Methods is a program within the Reagan-Udall Foundation (RUF) that supports the FDA's scientific mission of serving public health needs through research into methods for safety evaluation. IMEDS-Methods aims to improve the tools for post-marketing safety surveillance using automated healthcare data and to foster their adoption. IMEDS-Methods also adds to the general body of knowledge about the use of such data for generating evidence about marketed regulated products.[1]

This report reviews the achievements of the IMEDS-Methods program in 2014. These accomplishments include progress on projects on the 2014 IMEDS-Methods Research Agenda, and activities to broaden awareness and facilitate collaboration and communication among all key stakeholder groups.

Projects on the 2014 IMEDS-Methods Research Agenda

The 12 projects on the 2014 IMEDS-Methods Research Agenda focused on improving our ability to use electronic healthcare data to inform regulatory decision-making. Synthesis of the implications of this work for the FDA's Sentinel Program is ongoing.

Project 1: The IMEDS Research Laboratory

The IMEDS Research Lab is a cloud configuration of five commercially available data sets, software to access and analyze the data, and data characterization and visualization tools. All five of the datasets have been formatted in the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). In addition, in 2014 IMEDS mapped two of these to the Mini-Sentinel CDM format. The availability of common data sets in multiple CDMs allows full use of tools developed for use in each. It also permits both Agenda-based and investigator-initiated research in characterizing and comparing the results, given identical data and similar epidemiologic designs. RUF supported the ongoing development of the IMEDS Standard Vocabulary to facilitate use of OMOP CDM-formatted data.

Over 28 investigator groups from industry, government, and academic research institutions used the IMEDS Research Lab in 2014. In addition, FDA Sentinel Program investigators are exploring ways to use the Lab for evaluating components of the

[1] Innovation in Medical Evidence Development and Surveillance (IMEDS) Charter. http://www.reaganudall.org/our-work/safety-and%20better-evidence/imeds-program/imeds-charter/ accessed September 30. First Draft Completed: April 2013 Proposed Revised Draft: August 2013; Section 3.1

system, and testing and refining queries before executing them in the Sentinel distributed data network.

Projects 2 – 6 comprise a suite of projects aimed at understanding the implications of the OMOP Experiments for the FDA's Sentinel Program.

Project 2: Mini-Sentinel and IMEDS Discussion of Overlapping Work

A joint work group with members from FDA, Sentinel data partners, and IMEDS built on the earlier congruent findings on angioedema and ACE inhibitors from OMOP and Mini-Sentinel to exemplify a setting in which results in observational drug safety studies appear to have been replicable. This work culminated in a peer-reviewed publication in *Pharmacoepidemiology and Drug Safety* and describes characteristics of study design and elements that may contribute to the success of electronic safety monitoring systems.[2] Work on a companion project to understand characteristics that present challenges to electronic safety monitoring systems is underway. The goals of this second task are to better understand factors that can contribute to anomalous study findings, and to gain insight into how to detect and mitigate these factors.

Taken together, these tasks increase our understanding of the uses and limitations of currently available electronic health data for conducting safety surveillance. The findings will provide guidance on design and priority for studies within the Sentinel distributed data network. They will inform criteria to predict and assess the reliability of study results.

Project 3: Comparative Presentation of Mini-Sentinel and OMOP CDMs

This project addresses the impact of differing data models on study results. Mark Weiner and co-authors Michael Kahn and Peter Embi are preparing a white paper that describes the history of the Mini-Sentinel and OMOP CDMs, and which details the structures, standard vocabularies and algorithms that underlie each CDM. Weiner, Kahn and Embi lay out research implications of choosing either model as the starting point for research or surveillance activities.

This report sheds light on whether the choice of CDM is likely to be a meaningful source of disparities in study results from databases and it will weigh the relative advantages of each CDM for internal data storage and management. The paper will be posted on the IMEDS website after completion (expected February 2015).

Project 4: Methods for Creating Health Outcome Definitions

A common step of most database studies of drug safety is the identification health outcomes as study endpoints. Health outcomes are identified in electronic healthcare

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[2] C Bell, A Chakravarty, S Gruber, S Heckbert, M Levenson, D Martin, J Nelson, S Pinheiro, B Psaty, C Reich, S Schneeweiss, A Shoaibi, S Toh, A Walker. Commentary - When can electronic drug safety succeed. Pharmacoepidemiology and Drug Safety 2014 Nov; 23(11):1223-5.

databases by specifying certain database criteria such as diagnosis codes or combinations of codes. HealthCore is leading the development of a journal article that describes best practices for developing case definitions. The paper provides researchers with a framework for incorporating database, clinical, and methodologic factors into their creation or application of case definitions. Lead authors are Stephen Lanes (HealthCore), Alec Walker (WHISCON), and Jeff Brown (Harvard Pilgrim). The manuscript is on track for submission to a peer-reviewed journal in February 2015.

Project 5: Recreate Mini-Sentinel Protocol-Based Findings

This project is aims to elucidate discrepancies between results obtained from Mini-Sentinel and OMOP studies. A request-for-proposal (RFP) was issued to recreate three Mini-Sentinel protocols that had already been conducted using Mini-Sentinel data, but now using IMEDS data sources formatted in the OMOP CDM. Qualified investigators were asked to describe a plan for comparing results of the OMOP and Mini-Sentinel-based studies to identify and assess any differences in findings. Proposals were evaluated by the IMEDS Scientific Advisory Committee, and a funding recommendation was sent to the IMEDS Steering Committee. Final approval by the Reagan-Udall Foundation Board of Directors resulted in awarding a two-year contract to a team headed by Dr. Joshua Gagne at Harvard Medical School and Brigham & Women's Hospital. Work will commence in 2015.

Project 6: Mini-Sentinel Cross-Check of OMOP Findings

This project assesses unresolved findings of the OMOP experiment using Mini-Sentinel data formatted in the Mini-Sentinel CDM. During 2014 it became clear that Project 2 investigators plan to perform studies in the Sentinel distributed data network, as well as within the IMEDS Research Lab. Project 5 investigators plan to compare results obtained from a single dataset formatted in both CDMs. These activities sufficiently address the goals of Project 6. Additional funding will not be allocated.

Project 8: New Data Sources

IMEDS is in discussion with PatientsLikeMe (PLM) to bring de-identified structured patient-reported data into the IMEDS lab. PLM develops and validates instruments for timely, customized data collection, and uses a structured vocabulary to represent concepts. These data provide complementary information to that available in claims and electronic medical records datasets. How to best incorporate this information into studies is not well understood. Researchers will be able to access PLM data formatted in the OMOP CDM to develop methods for exploiting information in patient-generated data to enhance post-market monitoring of medical products.

Project 9: PROMPT Assessment

Evaluate the FDA's PROMPT (Prospective Routine Observational Monitoring Program Tools) system in the IMEDS Lab. This project was placed on hold pending completion of the coding of PROMPT modules. It is a high priority for the FDA, and is described in detail in the upcoming 2015 IMEDS-Methods Research Agenda.

Projects 7, 10, 11, and 12 had lower priority in 2014, and were placed on hold pending additional resources. FDA input into the annual review and update of the IMEDS-Methods research agenda signaled continued interest in Project 12, and de-emphasized projects 7, 10, and 11 for 2015.

Project 7: Mini-Sentinel New Outcomes (HOLD)

Evaluate previously unstudied drug-outcome pairs with presumed known associations to assess learning from the previous projects.

Project 10: Non-Pre-Specified Adverse Events (HOLD)

Propose and evaluate methods for detecting non-pre-specified adverse events in large databases.

Project 11: Methods to Conduct "Experiments" in Distributed Data (HOLD)

Develop and demonstrate efficient methods to conduct sophisticated variants on analyses in a distributed data environment.

Project 12: Performance Standards (HOLD)

Develop standards for evaluating research systems for drug safety. This project has been carried over to the 2015 Research Agenda.

Activities to Facilitate Collaboration and Communication

Throughout 2014 IMEDS has participated in and helped organize scientific meetings designed to disseminate findings and improved techniques across sectors. In addition to their scientific impact, these activities also increased awareness of the IMEDS-Methods Program and increased participation.

- IMEDS Community Call hosted monthly webinars presented by industry, academic, and FDA speakers.
- IMEDS convened a roundtable at the 2014 FDA-Industry Statistics Workshop, led by Patrick Ryan (Janssen Research and Development) and Susan Gruber (IMEDS). The session title was *Extracting information from observational electronic health and claims data to enhance post-approval medical product safety surveillance*.
- The IMEDS-Methods team was invited to speak at the *First Seattle Symposium on HealthCare Data Analytics*, organized by GroupHealth (October, 2014), and the *Mini-Sentinel Investigator Meeting,* held at the FDA, Silver Spring, MD (November, 2014).

These activities cultivated active collaborations among investigators, and increased interest in carrying out projects in the IMEDS Laboratory. Recent inquiries have been made by researchers at Oracle, FDA, Harvard School of Public Health, and the Canadian Network for Observational Drug Effect Studies (CNODES).

Upcoming activities include a session at the Joint Statistical Meetings, (JSM, 2015), titled *Novel Computational Approaches in Safety Surveillance*. IMEDS-affiliated industry and

academic researchers will present state-of-the-art work aimed at solving real world challenges inherent in using electronic health data to conduct safety surveillance. At the next annual meeting of the Drug Information Association (DIA, 2015), IMEDS staff will address the "more is always better" myth of Big Data. Speakers for the monthly webinar series have been scheduled through May, 2015.

Jan 15 Christian Reich, Global Head of Discovery Informatics, AstraZeneca
Feb 19 Greg Daniel, Engelberg Center for Health Care Reform, Brookings Institution
Mar 19 Richard Boyce, Dept. of Biomedical Informatics, University of Pittsburgh
Apr 16 Susan Andrade, Meyers Primary Care Institute, UMass Medical School
May 21 Jennifer Nelson, Director of Biostatistics, Group Health Research Institute

Concluding Remarks

The IMEDS-Methods Program offers a common ground for representatives with diverse perspectives to collectively address challenges in post-market safety surveillance. The accomplishments of the IMEDS-Methods program were made possible through collaborative work of individuals from the FDA, data providers, health care providers, academic institutions, the pharmaceutical industry, and patient representatives. IMEDS Scientific Advisory Committee and Steering Committee members are drawn from these stakeholder groups. 2014 committee members articulated goals for the IMEDS-Methods Program, and provided ongoing expertise and guidance. Entering 2015, IMEDS is finalizing an updated Research Agenda that capitalizes on progress made in 2014. IMEDS continues to provide a meeting place where all stakeholders contribute to defining concrete steps towards achieving our shared goal of improved public health.

A Look Ahead: IMEDS-Evaluation (Pilot Project)

Overview

In order for regulated industry to respond rapidly to concerns about product safety, and to meet its regulatory obligations, high quality and validated data resources must be available and accessible. The development of electronic medical record and insurance claims databases, including in-patient databases, over the past 25 years has provided several advantages for conducting active surveillance programs and post approval safety studies. Additionally, these data sources are now being used to evaluate the effectiveness of risk minimization measures, such as patient or physician educational materials or physician adherence to product label changes. Furthermore, in some of these data sources it is possible to study pregnancy outcomes and the safety of medicines used by pediatric patients. These databases are usually large and include many years of observation. They enable more rapid analysis than do primary prospective observational studies and they are truly observational, as physician and

patient behavior in health care systems occurs without knowledge of which exposures and outcomes may eventually be studied.

A common research limitation of automated data sources is that a sufficient number of users may not yet be recorded in any one resource, particularly early in marketing. Rarity of some safety outcomes interest can accentuate the problem of insufficient size. Medication use patterns may vary regionally, and results from some covered populations (e.g., only the government insured, Veterans, or the privately insured) may not generalize to other group. Most of these data collection systems have been designed for administrative purposes rather than epidemiologic research studies. As a result, information needed to assess a specific safety issue may be unavailable or inadequate without prior validation studies or access to at least a subset of medical records.

The ability of regulated industry to access large distributed networks of electronic healthcare databases and associated modular analytic programs, such as those included in Sentinel, provides an opportunity to conduct rapid query or research protocol-based safety surveillance more efficiently and rapidly than is possible currently. These distributed networks may offer an important advantage to studies conducted across a small number of databases through their use of common data models, as endpoint and variable definitions are shared across the network facilitating direct comparisons. If granted access, regulated industry would use the system, through partnership with IMEDS and its data partners, to fulfill regulatory obligations and other activities that are part of a medicine's risk management, such as post approval safety studies, active surveillance programs or evaluations of the effectiveness of Risk Evaluation and Mitigation Strategy (REMS) program elements.

The goal for IMEDS-Evaluation, a core component of IMEDS, is to build collaboration among Sentinel data partners, investigators, and non-FDA entities such as the regulated industry to apply lessons learned from IMEDS-Methods and the tools and capabilities used by Sentinel, to conduct safety assessments of marketed medical products.

Once IMEDS-Evaluation is operational, safety assessments would be completed in partnership with and using the "IMEDS distributed database" and facilitated by an IMEDS operations center. The IMEDS Distributed Database is intended to describe a partnership between Mini Sentinel (MS) Data Partners and RUF whereby data partners agree to partner with RUF on a voluntary basis to complete work (either through IMEDS-Methods or IMEDS-Evaluation) using the MS CDM and associated tools using the distributed approach.

The IMEDS-Evaluation Pilot Project will use demonstration cases in the development of governance and process for the IMEDS-Evaluation program. It will explore how, and when, regulated industry may engage and collaborate with the Sentinel network through partnership with IMEDS. This pilot project invites full participation from current

MS data partners, Harvard Pilgrim, and the industry sponsor. The final deliverable will include a draft IMEDS-Evaluation Policies and Procedures as well as summary results of the demonstration cases.

Pilot Goals

The primary goal is to define governance and processes for the IMEDS-Evaluation program using two demonstration cases. To accomplish this goal, the following objectives will be met:

- Describe and test which elements of existing IMEDS governance and operations are applicable to regulated industry's participation in safety queries within the IMEDS Distributed Database.
- Identify gaps in existing governance or process relevant to a Sponsor's interaction with IMEDS/Sentinel when implementing the demonstration cases.
- Make recommendations regarding governance and research team composition/roles.
- Create simple end-to-end process steps that are repeatable and scalable.
- Explore the establishment of standard timelines for Modular and non-Modular based queries and protocol-based assessments.
- Delineate policies and timelines for public dissemination and publication of Sponsor-initiated queries taking into account Sponsors' legal obligations for regulatory notification and Sponsor actions required prior to dissemination to ensure adherence to securities laws (i.e., information is material).

The IMEDS-Evaluation Pilot Project was initiated in 4Q2014 and is currently estimated to conclude in 3Q2015.