Scientific Achievements of the IMEDS-Methods Program, 2015 (Q1-Q3)

Executive Summary

The Innovation in Medical Evidence Development and Surveillance (IMEDS)-Methods program of the Reagan-Udall Foundation for the FDA continued to make significant progress in 2015 with a number of important projects proceeding according to the Research Agenda developed in collaboration with FDA, industry, academia, and the IMEDS team. In the coming weeks, work will begin on the design of the 2016 Research Agenda.

IMEDS-Methods serves public health needs by initiating and facilitating research into methods of safety evaluation in large observational databases. The program also promotes communication across broad stakeholder groups to facilitate greater collaboration for the conduct of methods research. Core focus areas of the IMEDS-Methods Research Agenda for 2015 are:

1. addressing challenges to unbiased estimation of risks associated with the use of regulated medical products;
2. applying lessons learned from the suite of Observational Medical Outcomes Partnership (OMOP) experiments to FDA surveillance activities;
3. better understanding the uses and limitations of large administrate databases for conducting safety surveillance; and
4. expanding surveillance to risk/benefit assessment.

IMEDS-Methods established a Center of Excellence for Monitoring Bias in Research using Electronic Health Data at the University of Illinois, Chicago, beginning Fall 2015. The Center will identify important trends and discoveries across a range of disciplines that impact the ability to monitor post-market drug safety. The Center's mission includes disseminating these findings to a broad research community.

IMEDS-Methods also initiated a project to evaluate the FDA's Prospective Routine Observational Monitoring Program Tools (PROMPT). PROMPT provides semi-automated procedures for initiating and performing studies using Mini-Sentinel's network of distributed data partners. This external evaluation of PROMPT increases transparency through independent assessment of this important toolkit. Project findings will increase the utility of PROMPT within Mini-Sentinel, and will also support non-FDA sponsored surveillance activities carried out through the IMEDS-Evaluation program.

A joint IMEDS/FDA/Mini-Sentinel workgroup focused its work in 2015 on exploring characteristics of design and study elements that challenge large-scale observational studies using administrative data. In addition to a technical publication, the group is

addressing a broad audience through a Commentary highlighting the importance of combining sound clinical and epidemiologic judgment with appropriate computational and statistical technology.

The IMEDS Research Laboratory continues to play a key role in providing access to a centralized data repository, and software for methods research and development in a cloud computing environment. In addition, throughout 2015 IMEDS-Methods actively promoted and disseminated scientific advancements through organized webinars, conference presentations, and publishing.

1. Introduction

IMEDS-Methods projects carried out in the first three quarters of 2015 are described in Sections 2 through 6 below:

- Section 2 describes the establishment of a Center of Excellence for Monitoring Bias in Research using Electronic Health Data at the University of Illinois, Chicago, beginning Fall 2015.
- Section 3 outlines progress on evaluating the FDA's Prospective Routine Observational Monitoring Program Tools (PROMPT) for safety surveillance.
- Section 4 describes ongoing work of a joint IMEDS-FDA-Mini-Sentinel collaboration working to understand solutions to challenges inherent in large-scale studies of observational data.
- Section 5 summarizes 2015 activities in the IMEDS Research Laboratory in support of public health needs.
- Section 6 summarizes IMEDS-Methods outreach and communication strategies in 2015.

2. Center of Excellence for Monitoring Bias in Research using Electronic Health Data

Developments in the evaluation of real world data are moving quickly, even as the sources of data from health systems are themselves becoming more diverse and more complex. Transformative advances in pharmacoepidemiology, statistics, computer science, and medicine have implications for improving our ability to monitor post-market drug safety. IMEDS-Methods has entered into a collaboration with the University of Illinois at Chicago to establish a Center of Excellence that will integrate efforts of junior and senior researchers to follow important cross-disciplinary research and synthesize findings for the community at large. The Center will create an open access web-based repository of curated content. It will also offer a graduate-level seminar. Center operations begin Fall 2015.

> ***Value to researchers, manufacturers, and regulators.*** By synthesizing and disseminating findings to the community at large, Center activities will spur

advancements and promote interdisciplinary collaborations. Presentation of unifying themes and discussion boards will help investigators digest learnings in fields outside their own areas of expertise, and understand their relevance in drug development, testing, and safety. The Center's seminar offerings at UIC will provide a nuanced overview to junior researchers poised to enter the workplace.

3. Assessment of FDA's PROMPT System

The FDA's Prospective Routine Observational Monitoring Program Tools provide guidance and partial automation of tasks needed to carry out a study in the Mini-Sentinel Distributed Data Network. IMEDS-Methods is providing the FDA with an external assessment that complements internal FDA efforts. The project is being carried out by researchers at The Gillings School of Public Health at the University of North Carolina. The goals of the project are two-fold. First, to document and validate the use of PROMPT's semi-automated modules for performing safety studies. A second goal is to provide feedback that helps guide the FDA in refining existing tools, and in the development of future tools.

The assessment will include a usability study of the PROMPT request form and the PROMPT Taxonomy Tool. Investigators will also use PROMPT level II modular programs to perform drug safety studies. In order to assess performance, test cases for these studies consist of drug-outcome pairs whose associations have previously been established. The groundwork for carrying out these analyses in the IMEDS Research Lab was initiated in 2015. Three existing datasets in the Lab were formatted to adhere to the Mini-Sentinel Common Data Model (CDM), and subjected to quality control testing. (Datasets in the lab also remain available in the OMOP CDM format.)

Value to patients, clinicians, researchers, manufacturers, and regulators. PROMPT offers robust semi-automated methods for safety surveillance enhance early detection of safety concerns. This project promotes transparency between the FDA, the public, and regulated industry. Feedback on usability and reliability of the tools can inform future modifications to PROMPT. Investigators from institutions already using these publicly available tools within their own internal lab environments will directly benefit from findings produced by this work. These benefits will also enhance the IMEDS-Evaluation program.

4. Characteristics of study design and elements that may facilitate or challenge electronic safety monitoring systems

Obtaining unbiased causal effect estimates from large-scale observational studies is a challenging task. Nevertheless, electronic health databases are a valuable component of the Mini-Sentinel safety surveillance system. In order to make the best use of Mini-

Sentinel resources, in 2014 a joint work group of IMEDS, FDA, and Mini-Sentinel investigators took on the task of characterizing elements of the scientific question, data, and study design that contribute to producing robust study findings. The workgroup extended its work into 2015 to focus on characteristics of design and study elements that challenge large-scale observational studies using administrative data. Technical findings document pitfalls of a fully-automated approach to safety surveillance. The group is also drafting a Commentary addressed to a broad audience to highlight the importance of combining sound clinical and epidemiologic judgment with appropriate computational and statistical technology. The Commentary also highlights the growing need for education and awareness of cross-disciplinary activities among rising scientists.

> ***Value to regulators and manufacturers.*** The design and interpretation of large-scale observational studies requires sound judgment. Characterizing examples of assessments that appear to be wrong will inform general guidelines for routine Mini-Sentinel studies and research-style assessments.

5. Advancing technology in the IMEDS Research Laboratory

The IMEDS Research Lab continues to provide an accessible, integrated environment for conducting research into improved methods and tools for exploiting electronic healthcare data. In 2015 the lab welcomed new user groups from academia (Stanford University, Brown University, University College London, University of Miami), industry (IBM Watson Research Center), the FDA (CDER), and the Mini-Sentinel Operations Center (MSOC) at Harvard Pilgrim.

In 2015 the Lab began offering datasets formatted in both the OMOP CDM and the Mini-Sentinel CDM. Dual availability is needed for IMEDS 2014 Research Agenda projects, and also facilitates FDA activities. The MSOC is investigating the use of the IMEDS Lab to conduct experiments into computational and hardware improvements to the Mini-Sentinel Distributed Data Network. The MSOC is also experimenting to find ways in which the IMEDS Research Lab can be used to streamline Mini-Sentinel querying activities across the distributed data network. These efforts will also inform IMEDS-Evaluation program activities.

> ***Value to patients, doctors, manufacturers, and regulators.*** In addition to helping the nation create a cadre of investigators with technical skills, the IMEDS Research Laboratory is contributing to the success of post-market safety studies carried out by the FDA. This advantage will extend to externally sponsored research conducted through the IMEDS-Evaluation program.

6. Outreach and Communication

IMEDS fosters communication with stakeholder groups over multiple channels. IMEDS **e-blasts** disseminate news and announcements to over 2,100 recipients. The **IMEDS**

Community Call Webinar Series features talks on topics that inform the uses of large observational datasets for medical products research. Presenters in 2015 have included investigators from the FDA, HealthCore, Astrazeneca, Meyers Primary Care Institute, and more, who discussed the latest statistical, clinical, data, and computational advances. Attendance doubled within the past year. Presentations are available for download on our website at http://www.imeds.reaganudall.org/presentations, and posted on YouTube, https://www.youtube.com/user/RUFoundation/videos.

Scientific content created through the IMEDS-Methods program was disseminated in numerous publications and presentations at conferences throughout 2015 (listed below). RUF was a proud sponsor of the 2015 International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE), Boston, August 2015. In addition, RUF will sponsor the 2nd Seattle Symposium on Health Care Data Analytics, Fall 2016.

Publications (2015)

- Gruber S. A Causal Perspective on OSIM2 Data Generation, with Implications for Simulation Study Design and Interpretation. *Journal of Causal Inference*. ISSN (Online) 2193-3685, ISSN (Print) 2193-3677, DOI: 10.1515/jci-2014-0008, April 2015.
- Lanes S, Brown JS, Haynes K, Pollack MF, Walker AM. Identifying Health Outcomes in Healthcare Databases. *Pharmacoepidemiology and Drug Safety* (in press, 2015).

Manuscripts submitted and in preparation (2015)

- Weiner M, Embi P, Kahn M. OMOP and Mini-Sentinel Data Models: Form Fits Functions
- Gruber S and Tchetgen Tchetgen E. Limitations of empirical calibration of p-values using observational data.
- Joint FDA/MS/IMEDS Workgroup. An examination of anomalous findings using automated safety surveillance methods.

Presentations (2015)

- *Novel Computational Approaches in Safety Surveillance,* an IMEDS-organized session at the Joint Statistical Meetings, 2015 in Seattle.
    - *Exploratory Data Analysis in Observational Data Utilizing Machine Learning--Based Approaches.* Andrew Bate, Pfizer Inc.
    - *Which Needles Are Not in the Haystack? Linking Evidence to Support the Establishment of a Reference Standard of Negative Controls for Pharmacovigilance.* Richard D. Boyce, University of Pittsburgh ; Erica Voss, Janssen R&D ; Christian Reich, AstraZeneca ; Nicholas Tatonetti, Columbia University ; Patrick Ryan, Observational Health Data Sciences and Informatics
    - *Bayesian Assessment of Safety Profiles in Clinical Trial Studies.* Judy Li, FDA ; Wei-Chen Chen, FDA ; John Scott, FDA ; Paul Mintz, FDA

  - *Use of Design-Driven Automated Drug Safety Monitoring Systems to Obtain Causal, Multidatabase Estimates of Safety Risks*. Jeremy Rassen, Aetion, Inc.
  - *Monstrous MCMC: Fully Bayesian Inference in Cyclops for Massive Observational Data Sets*. Trevor Shaddox, UCLA ; Marc A. Suchard, UCLA
- *Big Data and Safety Surveillance*. Susan Gruber, DIA 2015, Washington, DC.
- *Computer Power and Human Reason,* keynote address by Alec Walker (WHISCON, IMEDS). Panelists include Susan Gruber and Robert Ball (FDA, IMEDS SAC). 2015 International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE), 2015, Boston.
- *Computation and Big Healthcare Data.* BigDiP USA 2015, Boston.