Real World Data and Evidence for Regulatory Decision Making

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Office of Medical Policy
Center for Drug Evaluation and Research
FDA

Disclaimer

The views and opinions expressed in the following slides are those of the individual presenter and should not be attributed to the FDA.

No relevant financial relationship exists

Laying the Groundwork

A Framework for Regulatory Use of Real-World Evidence

September 13, 2017

The National Academies of SCIENCES ENGINEERING MEDICINE

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l World Evidence

Real World Evidence

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Real world data (RWD) and real world evidence (RWE) are playing an increasing role in health care decisions.

- FDA uses RWD and RWE to monitor postmarket safety and adverse events and to make regulatory decisions.
- The health care community is using these data to support coverage decisions and to develop guidelines and decision support to
- Medical product de pragmatic clinical tr

rge simple trials, roaches.

The 21st Century Cure regulatory decision ma

of data to support

Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry

Electronic Source Data in Clinical Investigations

Use of Electronic Informed Consent

Questions and Answers

Guidance for Industry and ood and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

estions about this document regarding CDRH-regulated devices, contact the Office of llance and Biometrics (OSB) at 301-796-5997 or CDRHClinicalEvidence@fda.hhs.gov. estions about this document regarding CBER-regulated devices, contact the Office of unication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

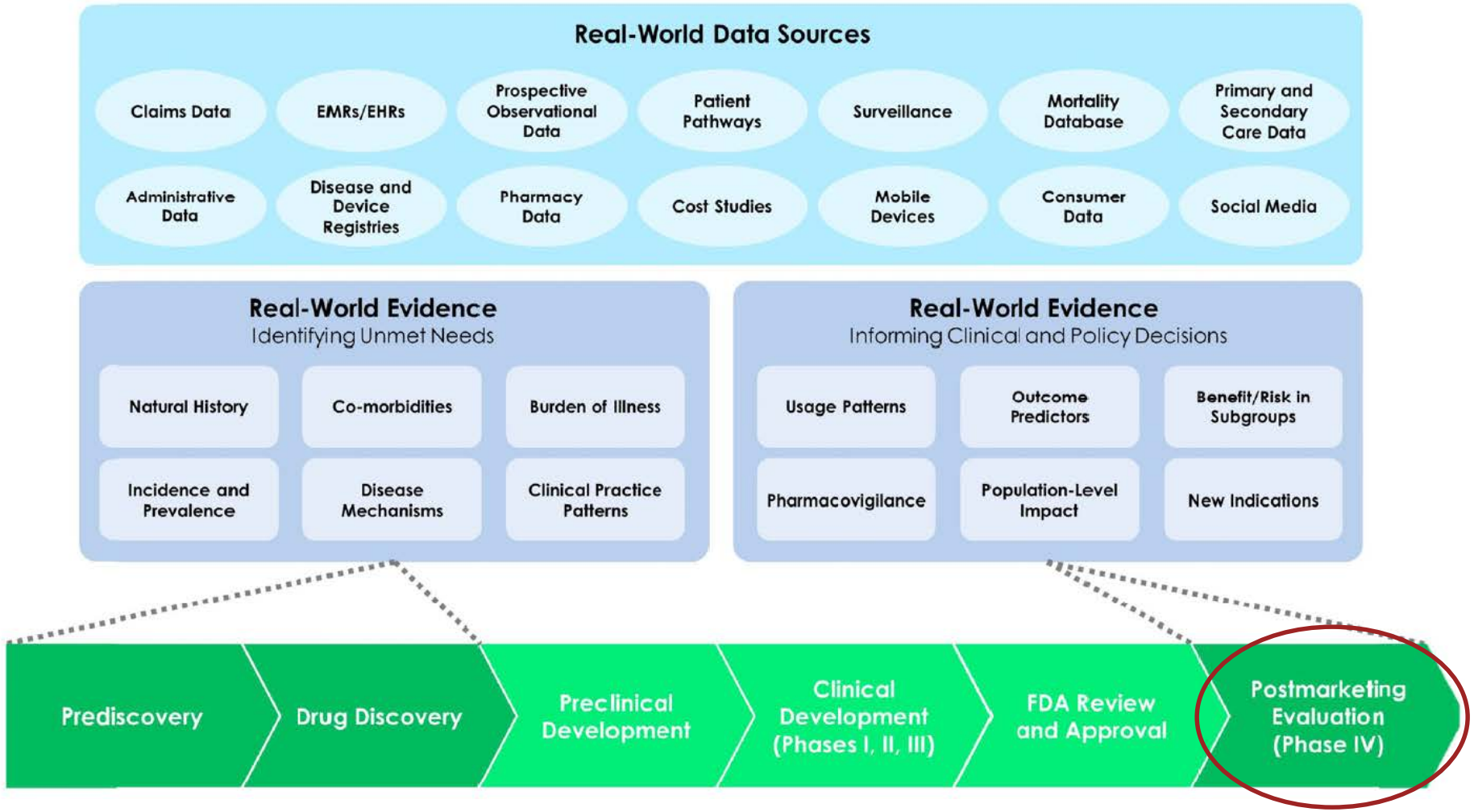
Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

DRAFT GUIDANCE

What will be Sufficient?

Real World Data vs Evidence



National Academies of Sciences, Engineering, and Medicine. 2017. *Realworld evidence generation and evaluation of therapeutics: Proceedings of a workshop*. Washington, DC: The National Academies Press. doi: 10.17226/24685

5

Use of RWD in Evaluation of Drugs for Rare Diseases

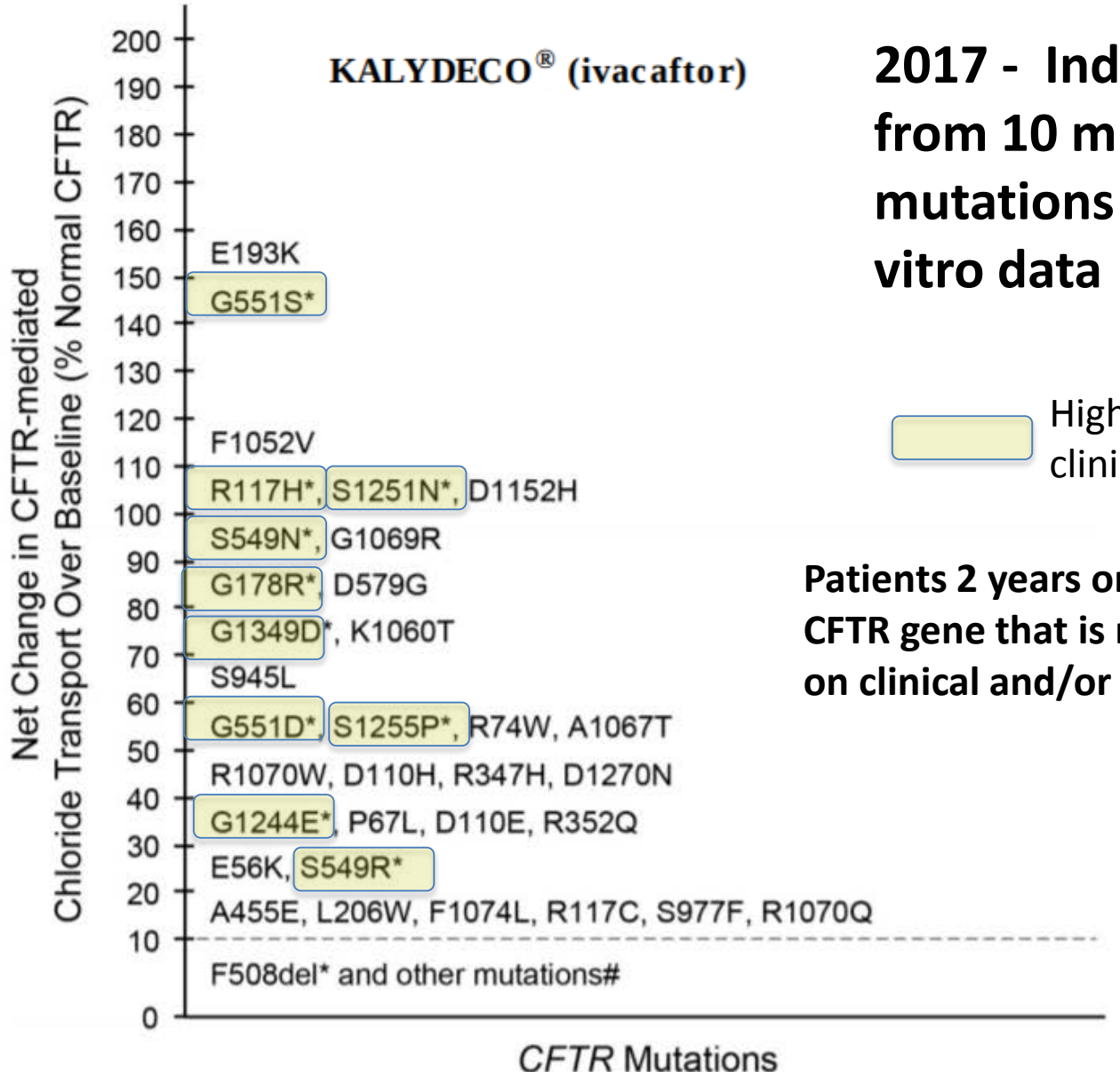
Drug	Indication	Status	Data
Lutathera *(lutetium 177 dotate)*	GEP-NET Gastropanc. Neuroendo tumors	Approved 2017	▪ Open label clinical trial ▪ **Analysis of 360 patients in an investigator sponsored, expanded access protocol** of 1214 patients*
Voraxaze *(glucarpidase)*	Treatment of MTX toxicity	Approved 2012	▪ Approval based on open-label, NIH **compassionate Use Protocol**
Uridine Triacetate	Treatment of 5 FU overdose	Approved 2015	▪ Two single-arm, open label expanded access trial of **135 patients compared to case history control**
Blincyto (Blinatumomab)	Treatment of Acute Lymphoblastic Leukemia	Approved 2014	▪ Single arm trial ▪ Reference for effect weighted analysis of patient level **data on chart review of 694 patients at EU and US study sites***
Carbaglu® (carglumic acid) Tablets	Treatment of NAGS deficiency	Approved 2010	▪ Retrospective, non-random, un-blinded **case series of 23 patients** compared to **historical control group**
Myozyme® (alglucosidase alfa)	Treatment of Pompe disease	Approved 2004	▪ Open-label, non-randomized study of 18 patients compared to **historical control group of 62 untreated patients**
Refludan®	Anti-coagulation in heparin-induced thrombocytopenia	Approved 1998	▪ Two non-randomized, open-label multicenter trials using **historical control comparator group from HIT Registry**

NOT EXHAUSTIVE

Bold = RWE

*https://www.nature.com/bcj/journal/v6/n9/full/bcj201684a.html

Figure 1: Net Change Over Baseline (% of Normal) in CFTR-Mediated Chloride Transport Following Addition of Ivacaftor in FRT Cells Expressing Mutant CFTR (Ussing Chamber Electrophysiology Data)



2017 - Indication expanded from 10 mutations to 33 mutations based in part on in-vitro data

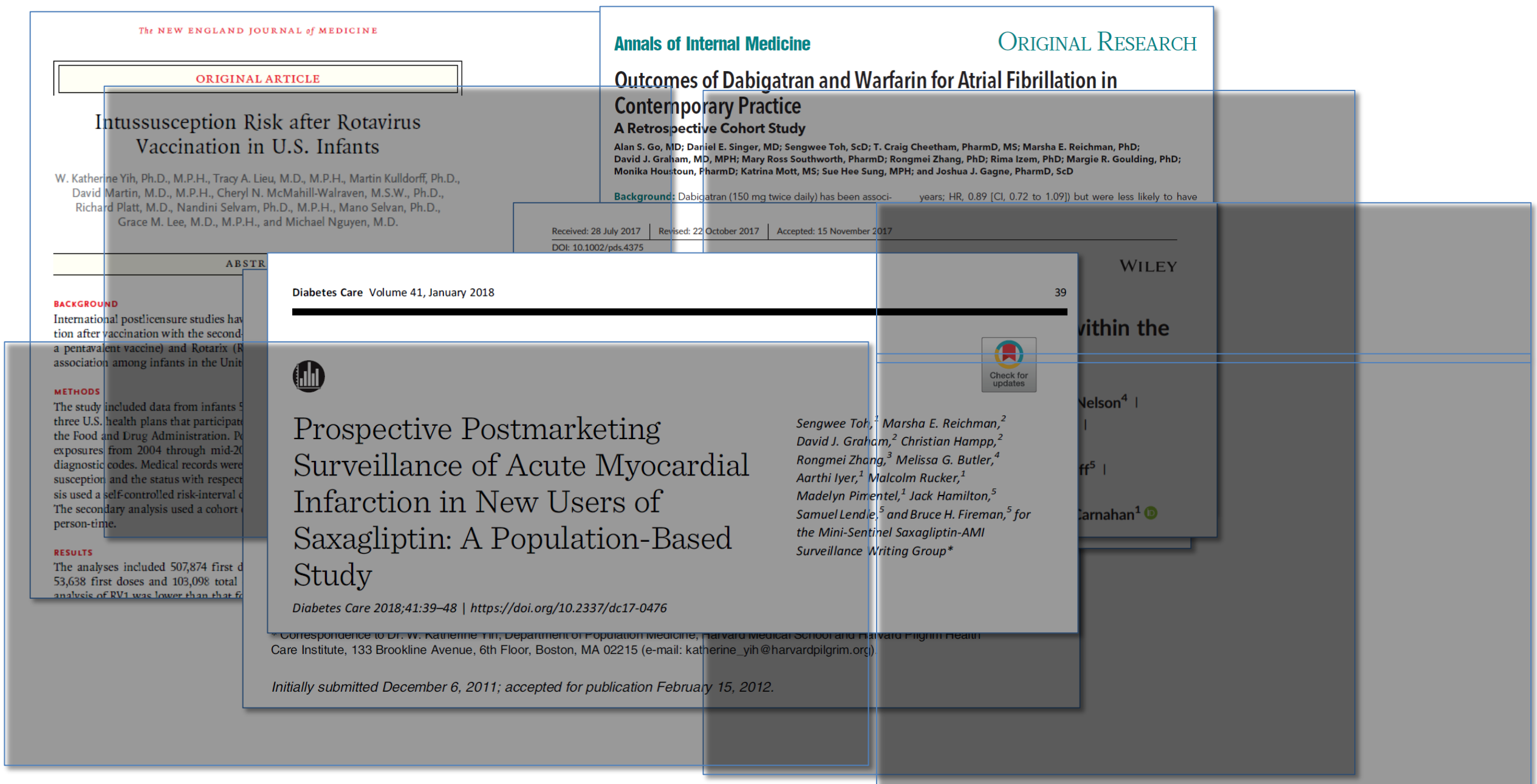
Highlighted mutations had clinical data as well

Patients 2 years or older with one mutation in CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data

Kalydeco Post Marketing Commitment

- **3-year, single arm, observational study**
- Various subgroups of CF patients with CFTR mutations deemed responsive to ivacaftor based on **in vitro evidence**
- Include all patients registered in the U.S. Cystic Fibrosis Foundation Patient Registry who have a newly designated CFTR mutation shown to be responsive to ivacaftor who initiate ivacaftor therapy following the date of approval of this supplement.
- Patients will be followed for at least 3 years on ivacaftor after ivacaftor initiation.
- The key outcomes of interest will include lung function measurements (FEV1), nutritional parameters (e.g., BMI), pulmonary exacerbations, hospitalizations, select CF complications (e.g., symptomatic sinus disease, CFRD, distal intestinal obstruction), and the presence of select pulmonary microorganisms (e.g., P aeruginosa).

Experience with Evidence Generation



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intussusception Risk after Rotavirus Vaccination in U.S. Infants

W. Katherine Yih, Ph.D., M.P.H., Tracy A. Lieu, M.D., M.P.H., Martin Kulldorff, Ph.D., David Martin, M.D., M.P.H., Cheryl N. McMahill-Walraven, M.S.W., Ph.D., Richard Platt, M.D., Nandini Selvam, Ph.D., M.P.H., Mano Selvan, Ph.D., Grace M. Lee, M.D., M.P.H., and Michael Nguyen, M.D.

ABSTR

BACKGROUND

International postlicensure studies hav
tion after vaccination with the second
a pentavalent vaccine) and Rotarix (R
association among infants in the Unit

METHODS

The study included data from infants
three U.S. health plans that participat
the Food and Drug Administration. P
exposures from 2004 through mid-20
diagnostic codes. Medical records were
susception and the status with respect
sis used a self-controlled risk-interval
The secondary analysis used a cohort
person-time.

RESULTS

The analyses included 507,874 first d
53,638 first doses and 103,098 total
analysis of RV1 was lower than that fo

Annals of Internal Medicine

ORIGINAL RESEARCH

Outcomes of Dabigatran and Warfarin for Atrial Fibrillation in Contemporary Practice

A Retrospective Cohort Study

Alan S. Go, MD; Daniel E. Singer, MD; Sengwee Toh, ScD; T. Craig Cheetham, PharmD, MS; Marsha E. Reichman, PhD; David J. Graham, MD, MPH; Mary Ross Southworth, PharmD; Rongmei Zhang, PhD; Rima Izem, PhD; Margie R. Goulding, PhD; Monika Houstoun, PharmD; Katrina Mott, MS; Sue Hee Sung, MPH; and Joshua J. Gagne, PharmD, ScD

Background: Dabigatran (150 mg twice daily) has been associ- years; HR, 0.89 [CI, 0.72 to 1.09]) but were less likely to have

Received: 28 July 2017 | Revised: 22 October 2017 | Accepted: 15 November 2017

DOI: 10.1002/pds.4375

WILEY

within the

Nelson[4] |

ff[5] |

Carnahan[1]

Diabetes Care Volume 41, January 2018 39

Check for updates

Prospective Postmarketing Surveillance of Acute Myocardial Infarction in New Users of Saxagliptin: A Population-Based Study

*Sengwee Toh,[1] Marsha E. Reichman,[2] David J. Graham,[2] Christian Hampp,[2] Rongmei Zhang,[3] Melissa G. Butler,[4] Aarthi Iyer,[1] Malcolm Rucker,[1] Madelyn Pimentel,[1] Jack Hamilton,[5] Samuel Lendle,[5] and Bruce H. Fireman,[5] for the Mini-Sentinel Saxagliptin-AMI Surveillance Writing Group**

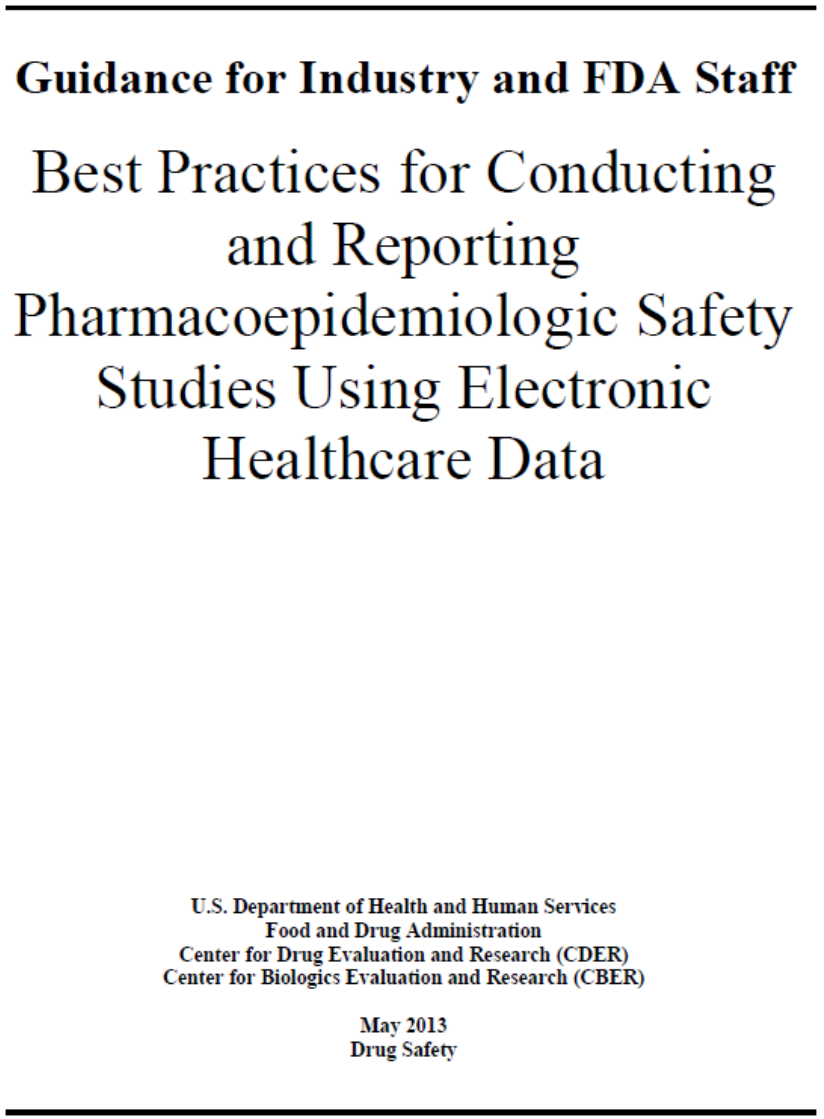
Diabetes Care 2018;41:39–48 | https://doi.org/10.2337/dc17-0476

* Correspondence to Dr. W. Katherine Yih, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 133 Brookline Avenue, 6th Floor, Boston, MA 02215 (e-mail: katherine_yih@harvardpilgrim.org).

Initially submitted December 6, 2011; accepted for publication February 15, 2012.

FDA Guidance

- **Purpose is to ensure that patients whose records have the code-based operational outcome definition actually experienced that event**
- **Basic approach:**
  - **Select all or a sample of cases with the codes of interest**
  - **Review the medical charts to determine if the patient experience the event of interest**
  - **Calculate the positive predictive value of the code**
- **If the code or algorithm has been previously validated:**
  - **Cite the specific literature reference**
  - **Describe the validation algorithm in detail, including the population studied and the database used, time frame, and performance characteristics**
- **Need also to describe the sensitivity of the outcome definition:**
  - **Within the database**
  - **Within the population**
- **Other considerations:**
  - **Primary versus secondary positions**
  - **Inpatient versus outpatient**
  - **Diagnostic codes and procedure codes**



July 10, 2018

Transition to the *ICD-10* in the United States
An Emerging Data Chasm

Rohan Khera, MD[1]; Karen B. Dorsey, MD, PhD[2,3]; Harlan M. Krumholz, MD, SM[3,4]

» Author Affiliations | Article Information

JAMA. 2018;320(2):133-134. doi:10.1001/jama.2018.6823

JAMA. 2018;320(2):133-134. doi:10.1001/jama.2018.6823

Transition occurred in October 2015. The *ICD-9*, which was in place for nearly 4 decades in the United States, included unique codes for 14 000 diagnoses and 4000 procedures. The *ICD-10* expanded to include nearly 70 000 diagnoses and 72 000 procedures

a surveillance of hospitalizations with a diagnosis of opioid use disorder across the transition from the *ICD-9* to the *ICD-10* found an abrupt 14% increase in the *ICD-10*-coded period relative to the preceding *ICD-9*-coded period

An assessment of a 20% sample of all patients in the Veterans Affairs system found that *ICD-10*-coded data had a 2-fold higher odds of identifying Alzheimer disease and less than half the odds of accurately identifying patients with HIV/AIDS and those with alcohol and tobacco dependence.

Claims Data – Validating Endpoints

An Automated Database Case Definition for Serious Bleeding Related to Oral Anticoagulant Use

Andrew Cunningham, M.D., C. Michael Stein, MB, ChB, Cecilia P. Chung, M.D., MPH, James R. Daugherty, M.S., Walter E. Smalley, MD, MPH, and Wayne A. Ray, Ph.D.

Pharmacoepidemiol Drug Saf. 2011 June ; 20(6): 560–566. doi:10.1002/pds.2109.

The case definition utilized information from an in-progress retrospective cohort study of warfarin-related bleeding in Tennessee Medicaid enrollees 30 years of age or older. It identified inpatient stays during the study period of January 1990 through December 2005 with diagnoses and/or procedures that indicated a current episode of bleeding

Of the 186 hospitalizations adjudicated, there were 165 (88.7% [95% CI, 83.4%-92.5%]) clinically confirmed bleeding-related hospitalizations, of which 133 were definite (71.5% [64.6%-77.5%]) or and 32 were probable (17.2% [12.5%-23.3%]) (Table 2). An additional 19 hospitalizations (10.2% [6.6%-15.4%]) were adjudicated as possibly bleeding-related, with a clinical history consistent with bleeding, but no objective evidence noted in the hospital record.

A case definition for bleeding-related hospitalizations suitable for automated databases had a positive predictive value of between 89% and 99% and could distinguish specific bleeding sites

Claims Data – Validating Endpoints

JAMA Cardiology | Original Investigation

Accuracy of Medical Claims for Identifying Cardiovascular and Bleeding Events After Myocardial Infarction
A Secondary Analysis of the TRANSLATE-ACS Study

Patricia O. Guimarães, MD; Arun Krishnamoorthy, MD; Lisa A. Kaltenbach, MS; Kevin J. Anstrom, PhD; Mark B. Effron, MD; Daniel B. Mark, MD, MPH; Patrick L. McCollam, PharmD; Linda Davidson-Ray, MA; Eric D. Peterson, MD, MPH; Tracy Y. Wang, MD, MHS, MSc

Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome(TRANSLATE-ACS) was a multicenter, longitudinal study of 12 365 patients with acute myocardial infarction (MI) enrolled at 233US hospitals. Medical claims forms for all rehospitalizations of TRANSLATE-ACS participants during the study follow-up period (April 1, 2010, to May 13, 2014) were collected. Medical records were collected to perform independent physician adjudication of MI, stroke, and bleeding events. Our objectives were to (1) compare medical claims–identified vs physician-adjudicated cumulative incidence of recurrent MI, stroke ,and bleeding events within 1 year after MI and (2) assess the accuracy of claims identified events using physician adjudication as the criterion standard.

Agreement between medical claims–identified and physician- adjudicated events was modest, with a κ of 0.76 (95% CI, 0.73 to 0.79) for MI and 0.55 (95%CI, 0.41 to 0.68) for stroke events. In contrast, agreement between medical claims–identified and physician -adjudicated bleeding events was poor, with a κ of 0.24 (95% CI,0.19 to 0.30) for any hospitalized bleeding event and 0.15 (95%CI, 0.11 to 0.20) for moderate or severe bleeding on the GUSTO scale

RWD and Endpoints

- **Review of 138 new indications added to FDA labeling found that 108 (78.3%) of the pivotal clinical trials had a primary outcome that was not identifiable in US longitudinal databases (e.g. pathology results, changes in clinical scores and radiologic tumor responses).**

* JAMA Internal Medicine doi:10.1001 (Nov. 2017)

EHRs are the Key to Completing the Picture, but….

EHR data have advantages of:

- A more complete and granular clinical picture
- Include labs/imaging/pathology reports

IDEAS AND OPINIONS

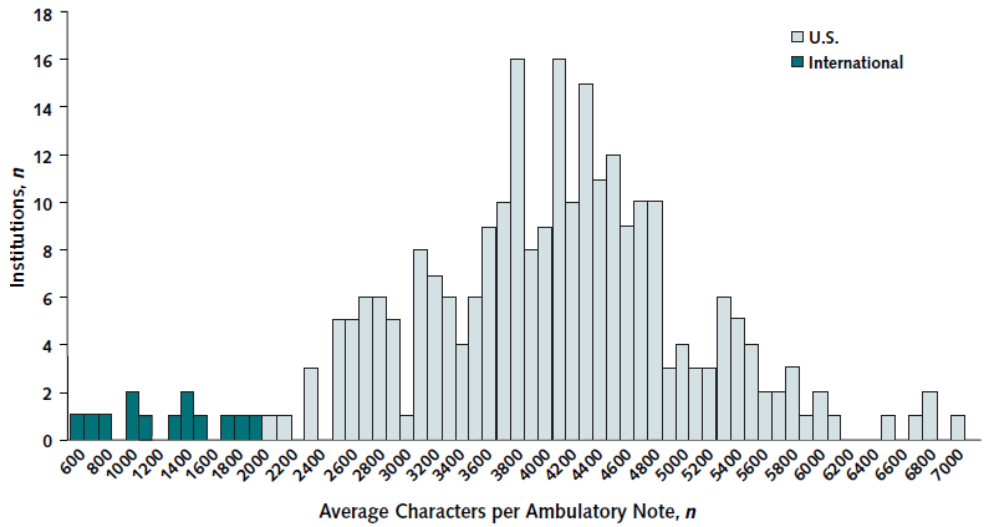
Annals of Internal Medicine

Metrics May 24, 2018

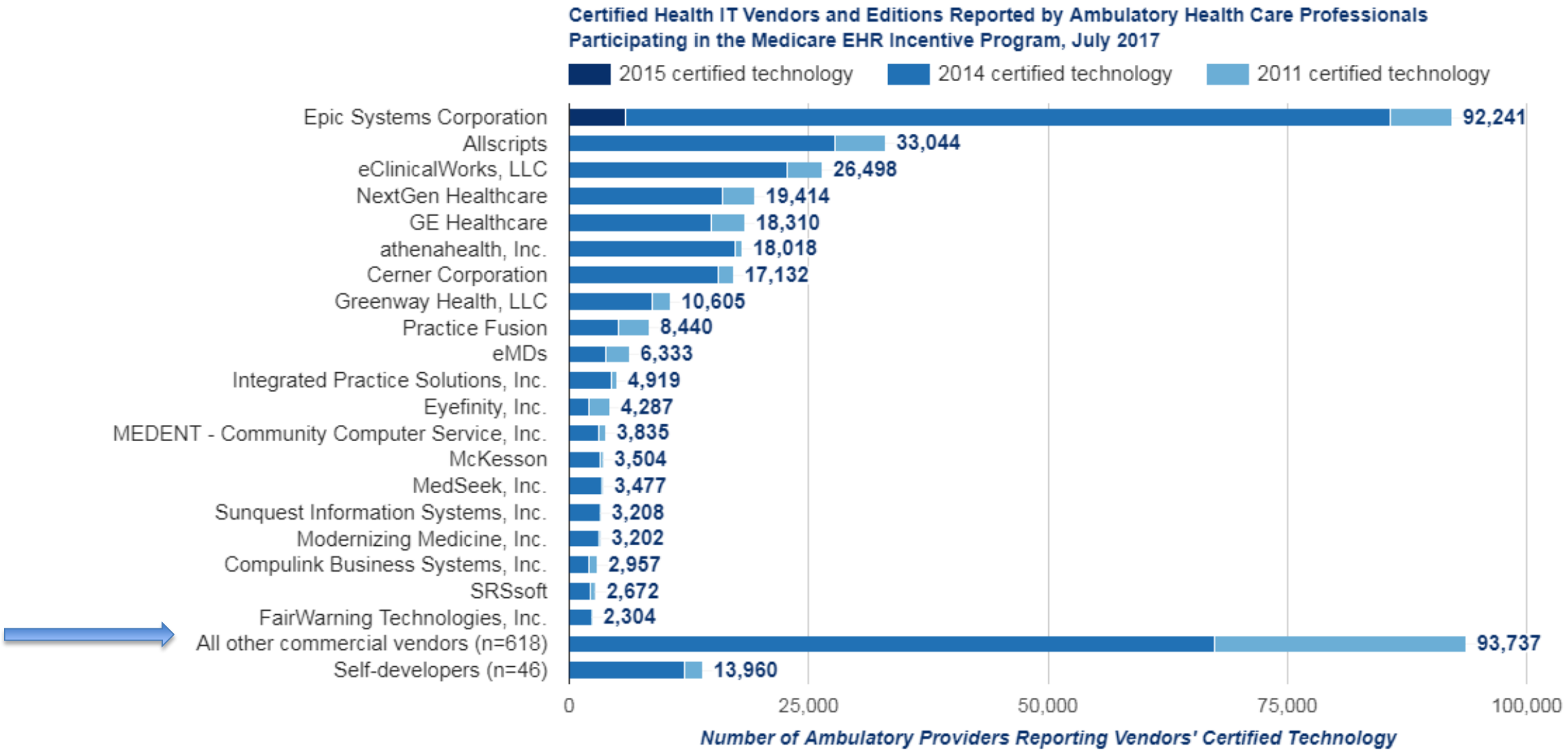
Physician Burnout in the Electronic Health Record Era: Are We Ignoring the Real Cause?

N. Lance Downing, MD; David W. Bates, MD, MSc; and Christopher A. Longhurst, MD, MS

Since the Health Information Technology for Economic and Clinical Health (HITECH) Act was enacted, U.S. clinical notes have doubled in length (Epic Systems. Unpublished data.). Meaningful use incentives have unintentionally created requirements for substantial, low-value documentation



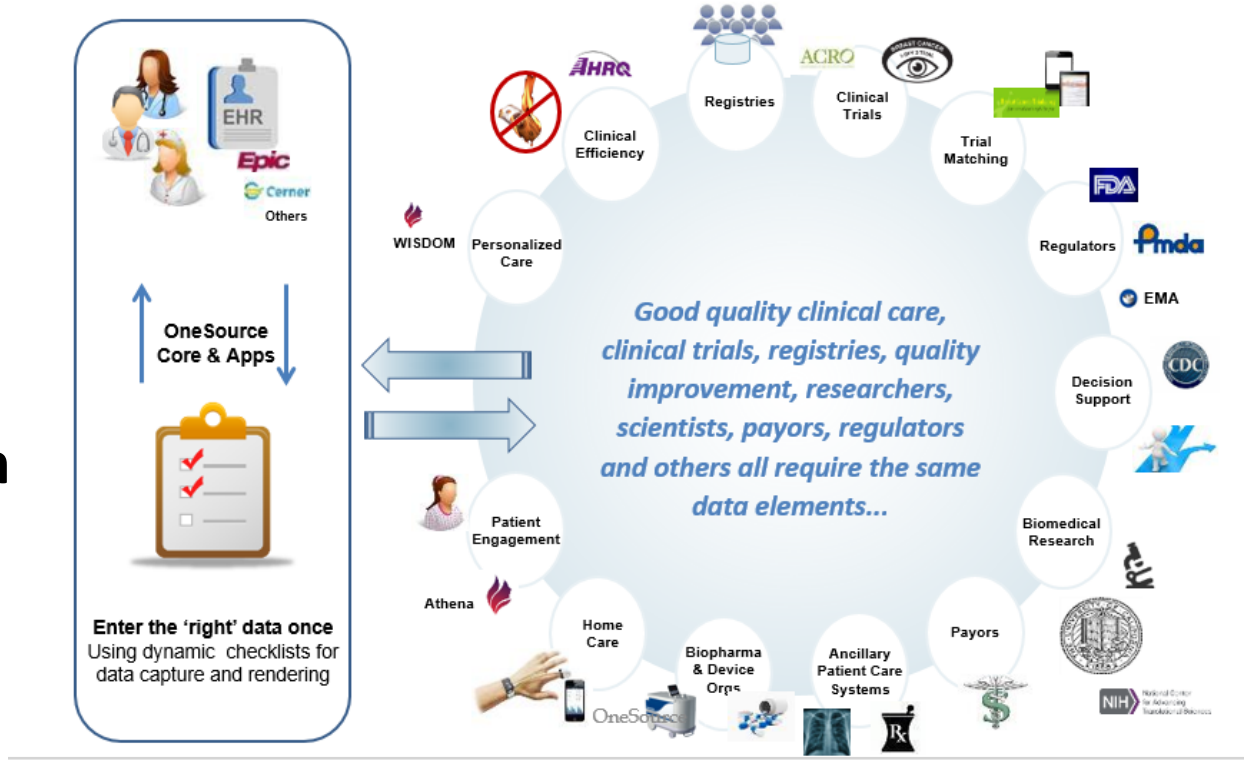
Many systems/configurations: Fragmentation



Certified Health IT Developers and Editions Reported by Ambulatory Primary Care Physicians, Medical and Surgical Specialists, Podiatrists, Optometrists, Dentists,

Demonstration Projects- Assessing Data Fitness /Standards

- **OneSource: “enter the right clinical data once, use many times”**
- **FDA collaboration with Dr. Laura Esserman, UCSF**
- **Integration of standards based tools into the EHR to bring together health care and research**
- **Demonstration in breast cancer clinical trials**



Courtesy of Dr. Laura Esserman and Susan Dubman

Networks of Data Exist

Sentinel

Largely Claims data

- **66.9 million members currently accruing new data**
- **292.5 million cumulative patient identifiers between 2000 and 2017**
- **14.4 billion pharmacy dispensings**
- **13.3 billion unique medical encounters**
- **45.6 million members with at least one laboratory test result**

Data at a Glance

The Sentinel Distributed Database is comprised of quality-checked electronic data held by 18 partner organizations.

pcornet® The National Patient-Centered Clinical Research Network

Largely EHR data

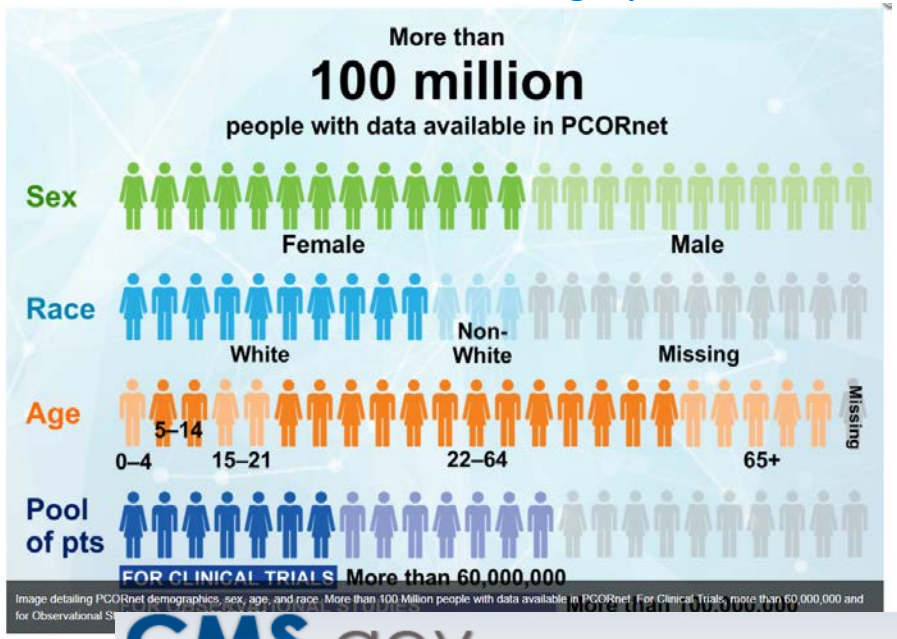


Image detailing PCORnet demographics, sex, age, and race. More than 100 Million people with data available in PCORnet. For Clinical Trials, more than 60,000,000 and for Observational S

Wade *Health Information Science and Systems* 2014, **2**:4
http://www.hissjournal.com/content/2/1/4

HEALTH INFORMATION SCIENCE AND SYSTEMS

REVIEW Open Access

Traits and types of health data repositories

Ted D Wade

Abstract

We review traits of reusable clinical data and offer a typology of clinical repositories with a range of known examples. Sources of clinical data suitable for research can be classified into types reflecting the data's institutional origin, original purpose, level of integration and governance. Primary data nearly always come from research studies and electronic medical records. Registries collect data on focused populations primarily to track outcomes, often using observational research methods. Warehouses are institutional information utilities repackaging clinical care data. Collections organize data from more organizations than a data warehouse, and more original data sources than a registry. Therefore even if they are heavily curated, their level of internal integration, and thus ease of use, can be less than other types. Federations are like collections except that physical control over data is distributed among donor organizations. Federations sometimes federate, giving a second level of organization. While the size, in number of patients, varies widely within each type of data source, populations over 10 K are relatively numerous, and much larger populations can be seen in warehouses and federations. One imagined ideal structure for research progress has been called an "Information Commons". It would have longitudinal, multi-leveled (environmental through molecular) data on a large population of identified, consenting individuals. These are qualities whose achievement would require long term commitment on the part of many data donors, including a willingness to make their data public.

Keywords: Registry, Observational research, Big data, Information commons, Data warehouse, Federated database

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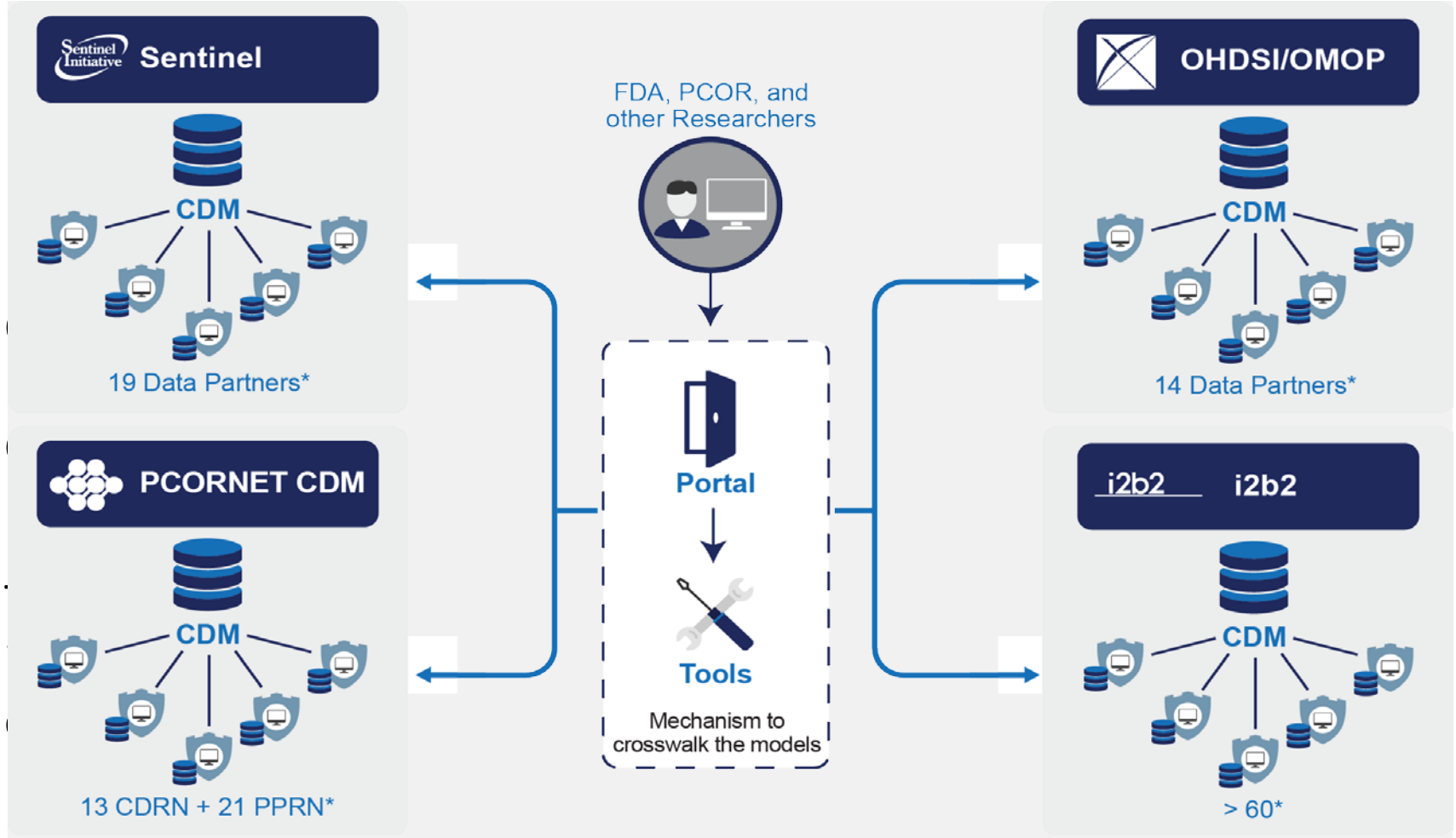
Integrated Data Repository (IDR)

Integrated Data Repository (IDR)

The Integrated Data Repository (IDR) is a high-volume data warehouse integrating Parts A, B, C, D, and DME claims, beneficiary and provider data sources, along with ancillary data such as contract information, risk scores, and many others. Access to this robust integrated data supports much needed analytics across CMS.

Data Standards Demonstration

FUTURE State

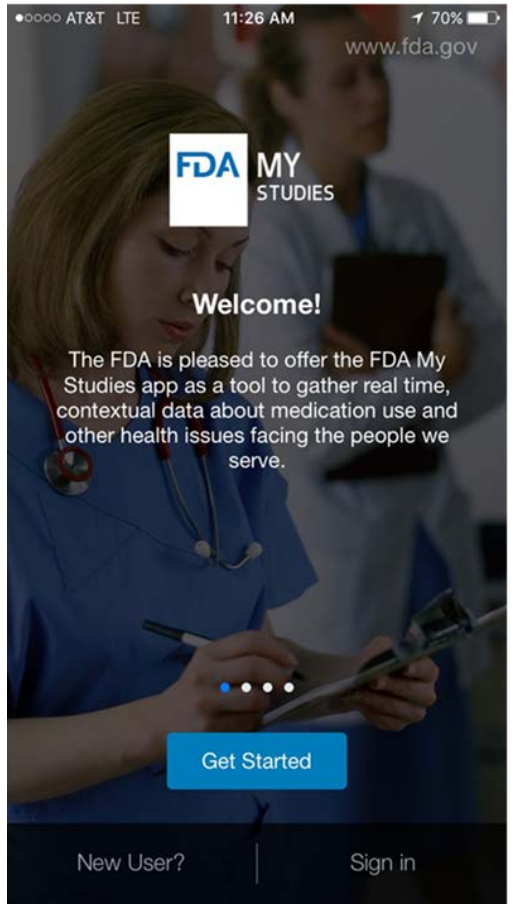


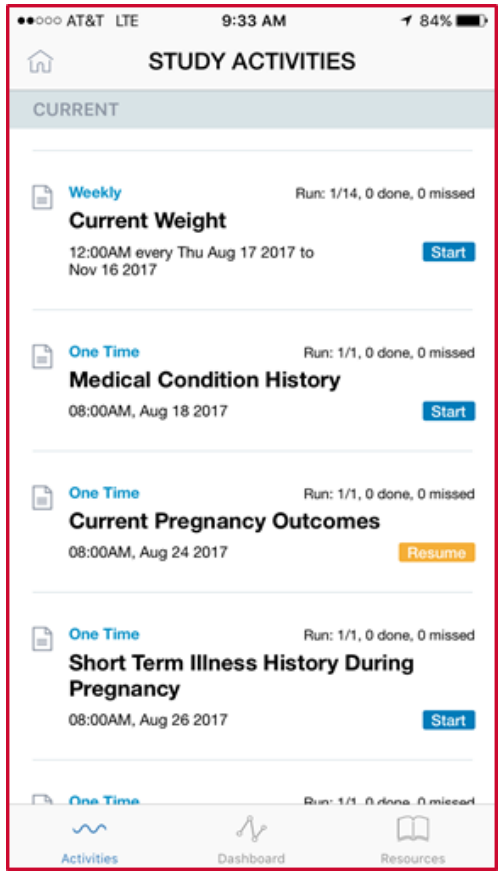
FDA Budget Matters: A Cross-Cutting Data Enterprise for Real World Evidence

Posted on **July 10, 2018** by **FDA Voice**

- To these ends, as part of the President's Fiscal Year 2019 Budget, we've put forward a $100M medical data enterprise proposal to build a modern system that would rely on the electronic health records from about 10 million lives. This system would expand the data enterprise that we already maintain by incorporating new information from electronic health records, and other sources that would allow us to more fully evaluate medical products in the post-market setting.
- This is the next evolution in the Agency's development of a comprehensive data enterprise to improve medical product regulation and better inform us on the safety and benefits of new innovations.

Patient Centric RWE may require more than Health Care Records



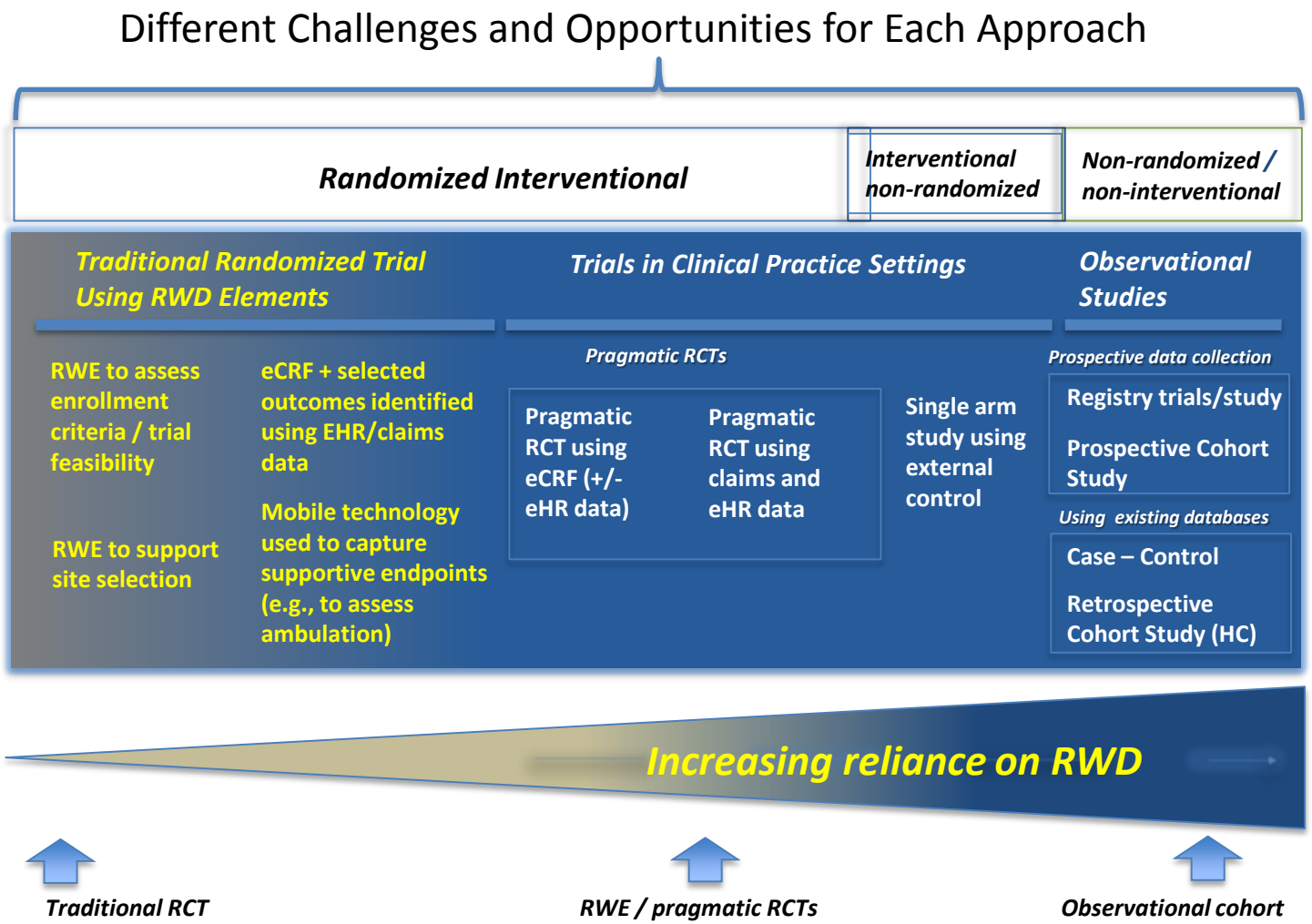


JAMA Cardiology | Original Investigation

Passive Detection of Atrial Fibrillation Using a Commercially Available Smartwatch

Geoffrey H. Tison, MD, MPH; José M. Sanchez, MD; Brandon Ballinger, BS; Avesh Singh, MS; Jeffrey E. Olgin, MD; Mark J. Pletcher, MD, MPH; Eric Vittinghoff, PhD; Emily S. Lee, BA; Shannon M. Fan, BA; Rachel A. Gladstone, BA; Carlos Mikell, BS; Nimit Sohoni, BS; Johnson Hsieh, MS; Gregory M. Marcus, MD, MAS

Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies



Courtesy of Peter Stein, FDA

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

As we adapt the tools and methods of traditional trials to real-world settings, we must consider the components of such trials that are critical to obtaining valid results and minimizing bias.

We All Need Confidence and Experience in Using New Data Streams, Technologies, and Analytical Methodologies for RWE

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OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Evaluating authentication options for mobile health applications in younger and older adults

Kelly Grindrod, Hassan Khan, Urs Hengartner, Stephanie Ong, Alexander G. Logan, Daniel Vogel, Robert Gebotys, Jilan Yang

Published: January 4, 2018 • https://doi.org/10.1371/journal.pone.0189048

eGEMs The Journal for Electronic Health Data and Methods

Reading: Data Cleaning in the Evaluation of a Multi-Site Intervention Project

Share:

Case study

Data Cleaning in the Evaluation of a Multi-Site Intervention Project

Authors:

Sav

NCBI Resources How To

PubMed.gov

US National Library of Medicine
National Institutes of Health

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Advanced

Format: Abstract

Int J Nurs Stud. 2017 Nov;76:36-44. doi: 10.1016/j.ijnurstu.2017.06.017. Epub 2017 Jul 20.

Methodological approaches in analysing observational data: A practical example on how to address clustering and selection bias.

Trutschel D[1], Palm R[2], Holle B[3], Simon M[4].

techemergence

Search Companies , Industries Use Cases & More ...

INDUSTRIES COMPANIES INTERVIEWS RESEARCH

Machine Learning Healthcare Applications 2018 and Beyond

Risk-Based Source Data Verification Approaches: Pros and Cons

Article (PDF Available) *in* Therapeutic Innovation and Regulatory Science
44(6):745-756 · November 2010 *with* 975 Reads

DOI: 10.1177/009286151004400611

All Expertise are Needed

U.S. FOOD & DRUG ADMINISTRATION

What questions can be answered using available data and current data sources?

Lessons learned (Pilots. Real-world studies, demonstration projects, etc.)

INFORMING THE FUTURE

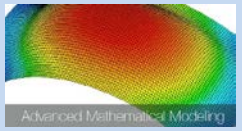
How can we improve and establish new systems and data sources to better answer key questions?

Future

- Research fully embedded in care settings (no data is wasted).
- Integrated/connected systems throughout the entire health care continuum with feedback loops.
- Seamless and integrated auditing and quality control mechanisms
- Flexible and linkable on-demand data aggregation from databases/registries.
- All stakeholders engaged (including patients)
- Secured and traceable access and management of data (blockchain)
- RWE continuously utilized to support decision making processes.

ALL EXPERTISE NEEDED

Data Analytics
Data linkage
Quality control and validations
Database design, maintenance, and quality assurance
Data security and confidentiality
Study designs
Statistics



RCTs or P[redacted]studies or…???

Convergence of all relevant evidence
FIT FOR PURPOSE

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- Khair ElZarrad
- Dianne Paraoan
- David Martin
- Peter Stein

Questions/ Comments

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov


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