FDA U.S. FOOD & DRUG ADMINISTRATION

Real World Evidence
A Path Forward

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Office of Medical Policy
Center for Drug Evaluation and Research
FDA
September 13, 2017

Presenter Disclosure Information

Jacqueline Corrigan-Curay, JD MD

FINANCIAL DISCLOSURE:

No relevant financial relationship exists

The views expressed herein are those of the author and should not be construed as FDA's views or policies

Overview

- **Definitions**
- **Goals and expectations**
- **FDA experience with Real World Data (RWD)/Real World Evidence (RWE)**
- **Foundational activities**
- **Looking forward**

Definitions

- **Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.**
- **Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.**

RWD include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices.

RWE: What are the Goals?

- **Maximize the opportunities to have regulatory decisions incorporate data/evidence from settings that more closely reflect clinical practice**
  - **Increase the diversity of populations**
  - **Improve efficiencies**
    - **Population identification/selection**
    - **Reduce duplicative capture of data**

RWE: What are the Expectations?

21St Century Cures

- **FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to support:**
  - **approval of new indication for a drug approved under section 505(c)**
  - **satisfy post-approval study requirements**

Real world evidence means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than *traditional clinical trials*

21st Century Cures

- **Program will be based on a framework that:**
  - **Categorizes sources of RWE and gaps in data collection activities**
  - **Identifies standards and methodologies for collection and analysis**
  - **Describes the priority areas, remaining challenges and potential pilot opportunities that the program will address**

Framework will be developed in consultation with stakeholders

PDUFA VI Commitments

- **Enhance use of RWE in regulatory decision making**
  - **Conduct a public workshop to gather input into topics related to the use of RWE for regulatory decision-making**
  - **Initiate appropriate activities (e.g. pilot studies or methodology development projects) to address key issues in the use of RWE for regulatory decision making purposes**
  - **Publish draft guidance on how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions (e.g. supplemental applications, post-marketing applications)**

FDA Experience with RWD/RWE

425 million person years of observation time
43 million people currently accruing new data
5.9 billion pharmacy dispensings
7.2 billion unique medical encounters
42 million people with at least one laboratory test result

Sentinel Initiative

Network of Collaborators

Sentinel brings together public, academic and private organizations that provide access to healthcare data and expertise.

Data at a Glance

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

Statistical Methods

Sentinel explores the application of a wide range of methods to enhance medical product safety assessment.

https://www.sentinelinitiative.org/

Making Informed Decisions

"…large numbers of reported cases of bleeding with dabigatran is an example of stimulated reporting. The Mini-Sentinel assessment suggests that bleeding rates with dabigatran are not higher than those with warfarin, a finding that is consistent with the results of RE-LY"

-April 2013

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

N Engl J Med 2013; 368:1272-1274 | April 4, 2013 | DOI: 10.1056/NEJMp1302834

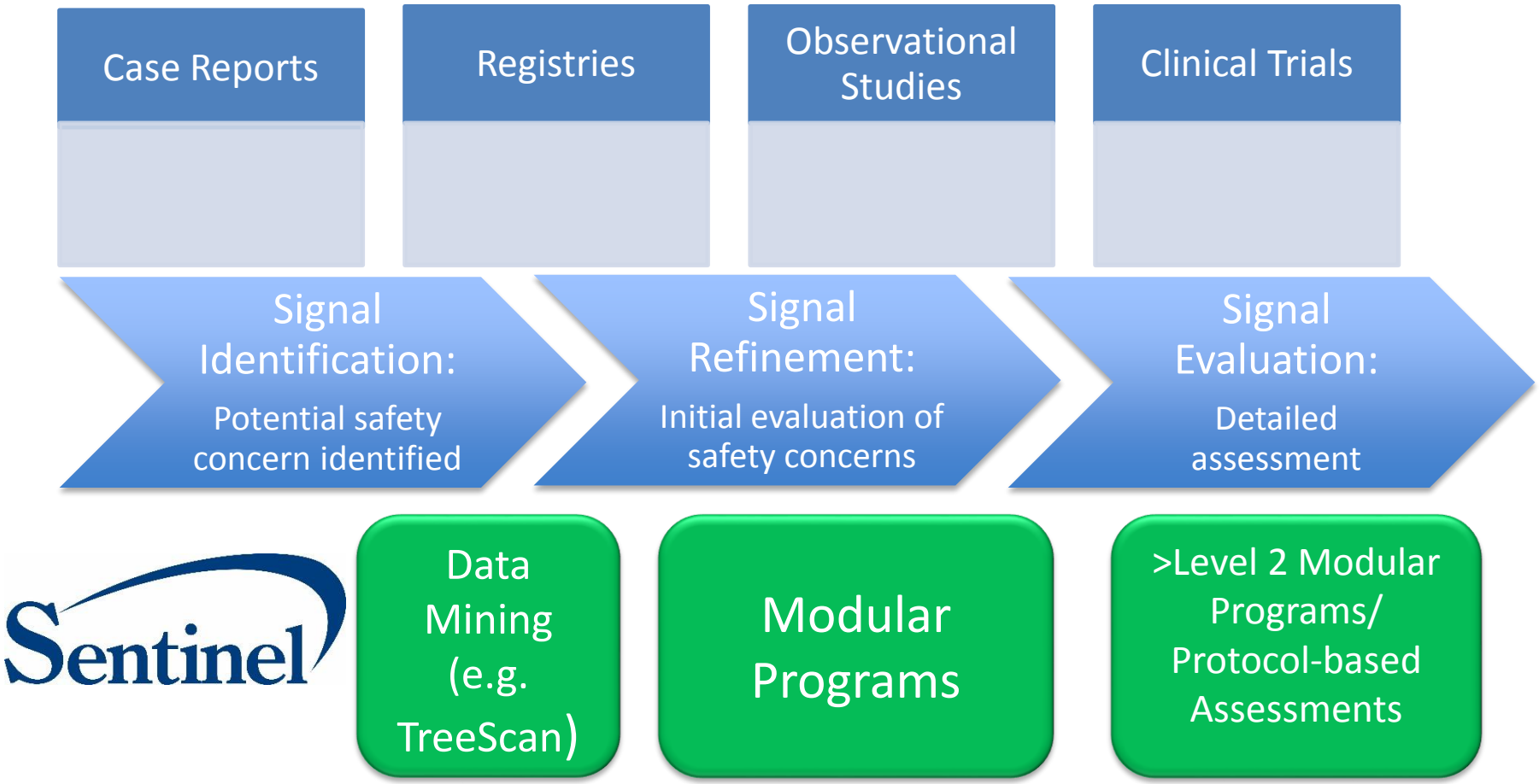
Share:

Article

In the months following the approval of the oral anticoagulant dabigatran (Pradaxa, Boehringer Ingelheim) in October 2010, the Food and Drug Administration (FDA) received through the FDA Adverse Event Reporting System (FAERS) many reports of serious and fatal bleeding events associated with use of the drug. Because dabigatran is an anticoagulant, reports of bleeding were anticipated, but the rate of reported incidents was unusually high and was greater than the concurrent rate of reported bleeding incidents with warfarin, which had been the anticoagulant of choice for nearly 60 years before dabigatran was approved. In contrast, the controlled trial that supported the approval of dabigatran (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY]), which compared warfarin with dabigatran in patients with nonvalvular atrial fibrillation,[1] showed that the two drugs conferred a similar risk of bleeding.

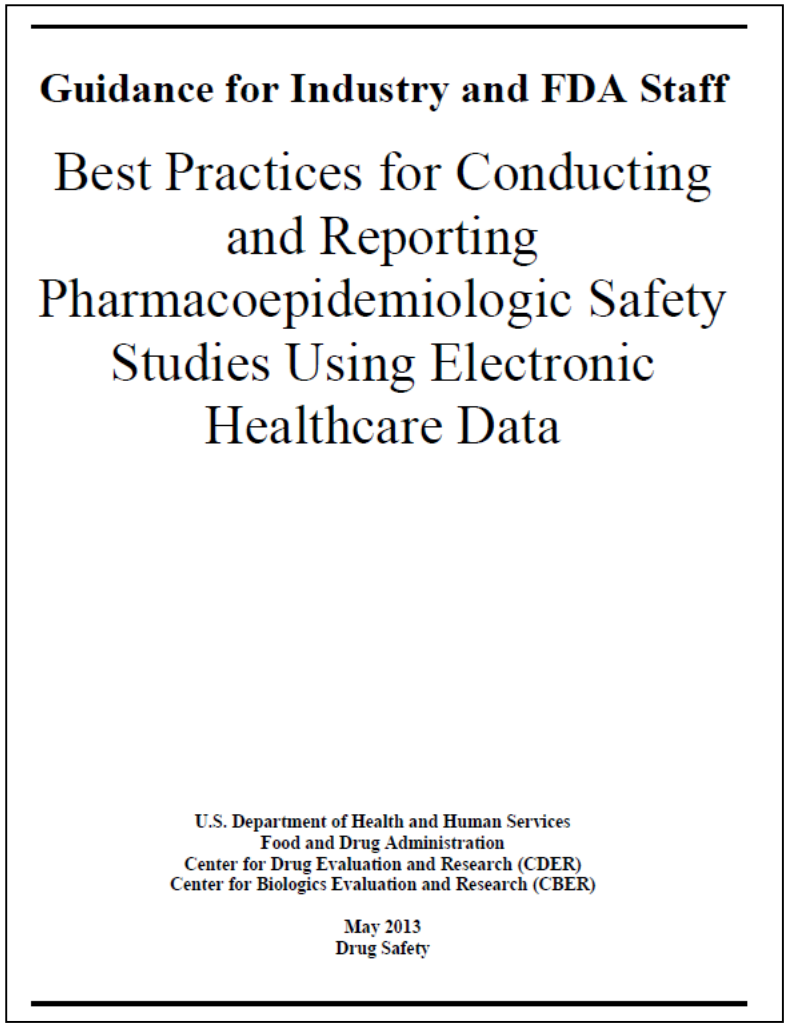
The postmarketing reports of bleeding with dabigatran led to discussions in medical publications as well as the mainstream media about the agency's approval of the drug. Many of these discussions cited the large numbers of reports of bleeding events in FAERS as a reason to question the benefit–risk profile of dabigatran as described in its labeling. But important factors that could have affected reporting rates, such as the novelty of dabigatran (relative to the well-established warfarin) and the coverage of novel drugs in the media, which can greatly influence how and when adverse events are reported, were not generally considered.

Post-Market Safety Assessment



Epidemiology – Final Guidance

- Pertains to pharmacoepidemiology safety studies using electronic healthcare data
- Final guidance was issued May 14, 2013



Guidance for Industry and FDA Staff

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2013
Drug Safety

The NEW ENGLAND JOURNAL of MEDICINE

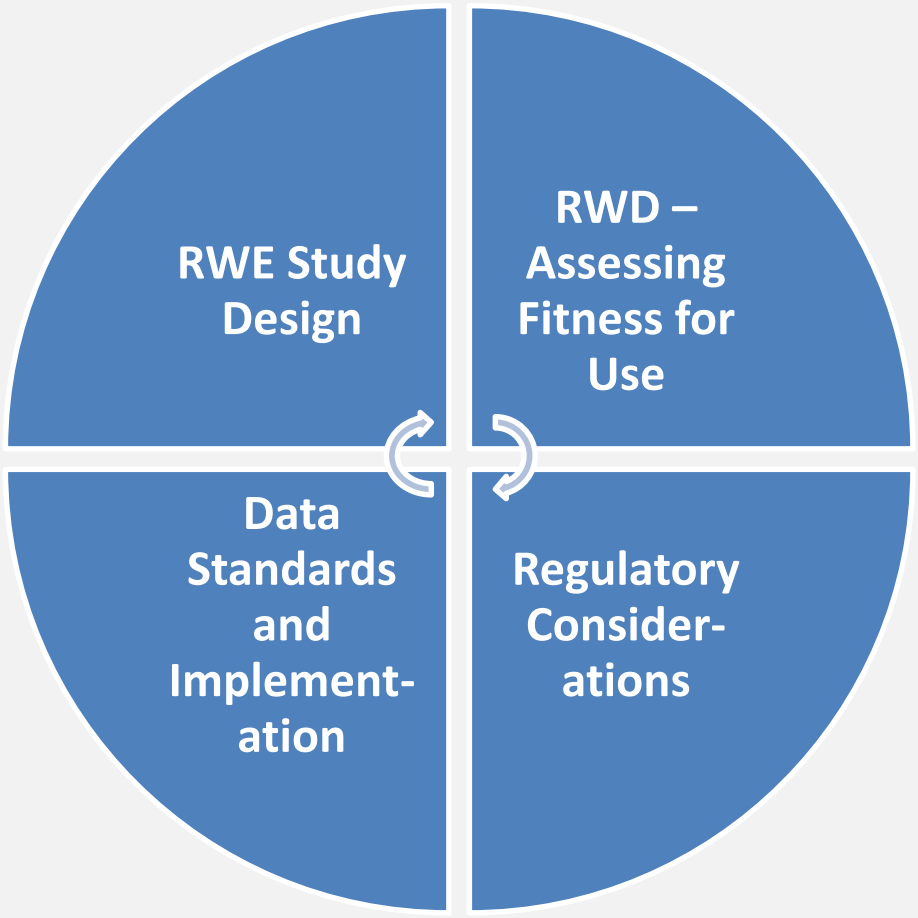
SOUNDING BOARD

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.

N ENGL J MED 375;23 December 8, 2016

Turning RWD into RWE



Engage with FDA early on this journey

Laying the Foundation

FDA

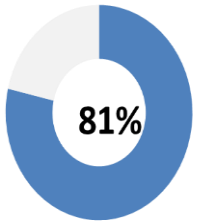
Data Standards

Stakeholder Engagement

Duke | MARGOLIS CENTER *for* Health Policy

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

FDA'S THERAPEUTIC AREA STANDARDS PROJECT



Of the 54 TAs prioritized, 44 have started with 21 of those completed as of Feb 2017

Guidances

Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers

Draft

Draft

Use of Electronic Health Record Data in Clinical Investigations

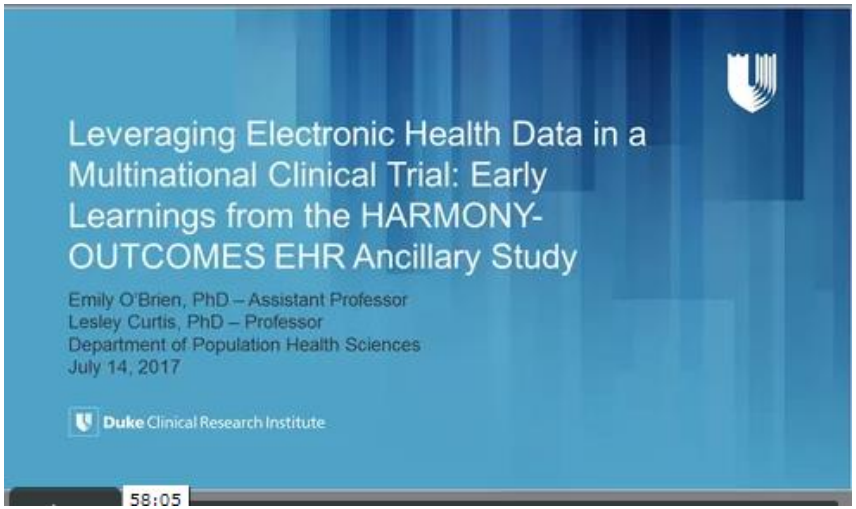
Demonstration Projects

Electronic Source Data in Clinical Investigations

Use of Electronic Informed Consent

Demonstration Projects- Assessing Data Fitness

- **Collaboration Duke Clinical Research Institute and GlaxoSmithKline**
- **Supported by FDA**
- **Assess EHR ability to:**
  - **Facilitate recruitment**
  - **Populate baseline characteristics**
  - **Identify clinical endpoints**



July 14, 2017: Leveraging Electronic Health Data in a Multinational Clinical Trial: Early Learnings from the HARMONY-Outcomes EHR Ancillary Study

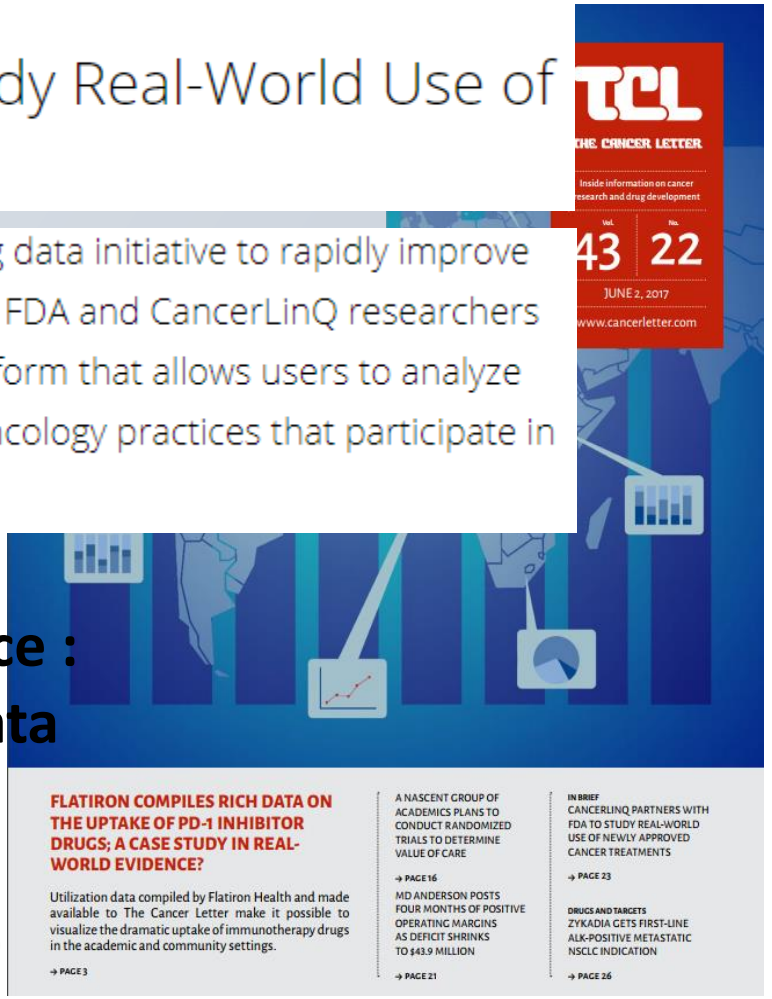
http://www.rethinkingclinicaltrials.org/grand-rounds-7-14-17/

Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus NCT02465515

Demonstration Projects- Assessing Data Fitness

CancerLinQ Partners with FDA to Study Real-World Use of Newly Approved Cancer Treatments

CancerLinQ® is the American Society of Clinical Oncology's big data initiative to rapidly improve the quality of cancer patient care. Under the new partnership, FDA and CancerLinQ researchers will use CancerLinQ Discovery™, a research and analytics platform that allows users to analyze real-world, aggregated, de-identified patient care data from oncology practices that participate in the CancerLinQ data-sharing program.



Oncology Center for Excellence : Information Exchange and Data Transformation (INFORMED)

Contact: Sean Khozin, MD

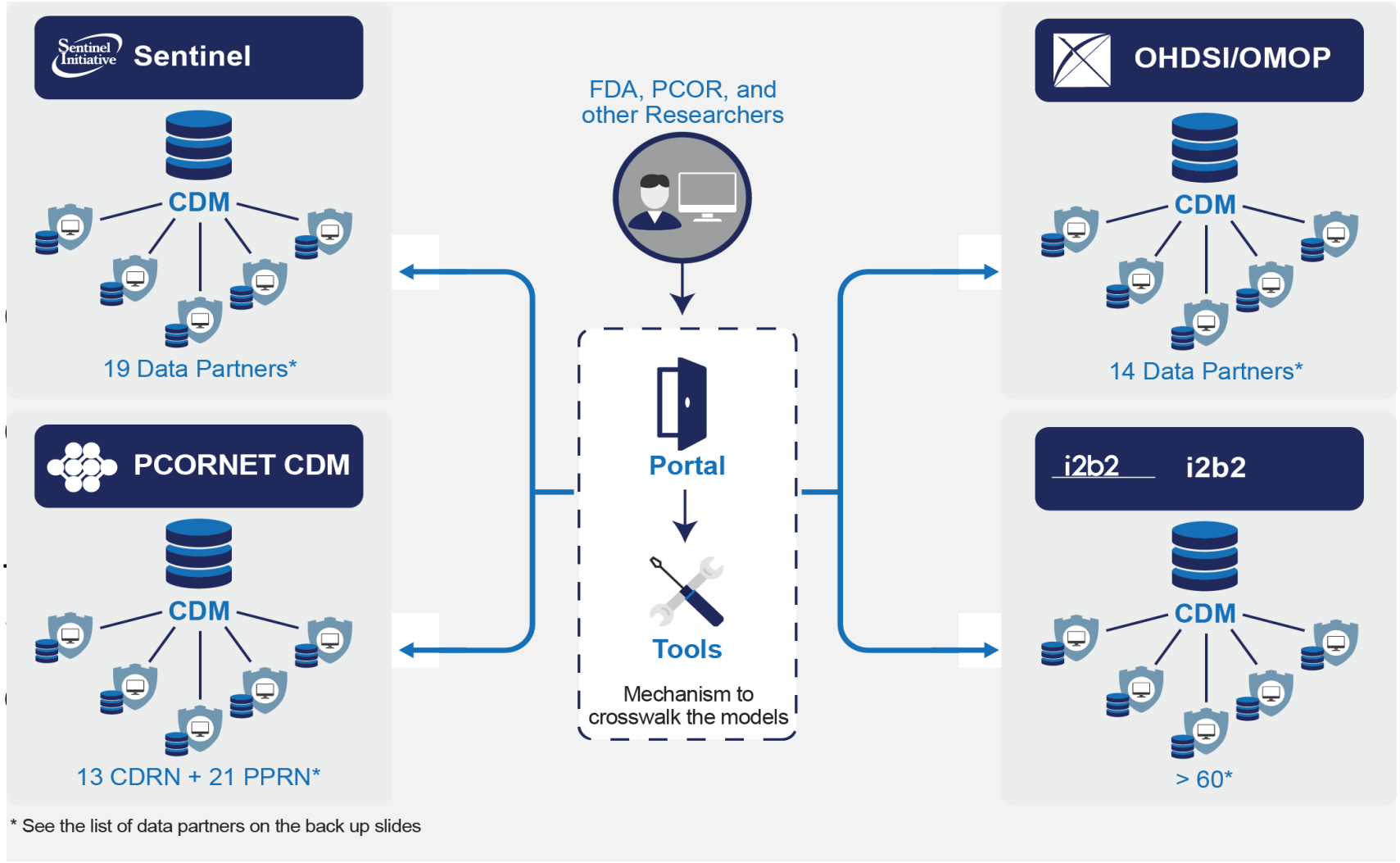
Demonstration Projects- Assessing Data Fitness /Standards

- **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

Data Standards Demonstration

FUTURE State



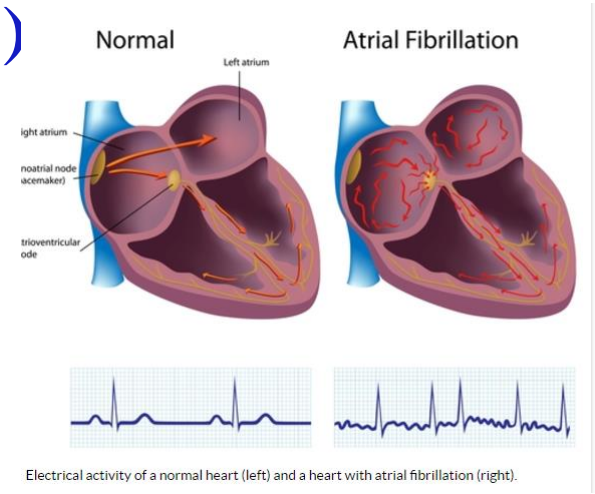
* See the list of data partners on the back up slides

Demonstration Projects- Evidence Generation

IMPLEMENTATION OF A RANDOMIZED CONTROLLED TRIAL TO IMPROVE TREATMENT WITH ORAL ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION (IMPACT-AFib)

An individually randomized trial of a practice and patient level educational intervention to increase anticoagulant use for individuals with atrial fibrillation and increased risk of stroke (i.e. CHA2DS2-VASc score ≥2). This project is a proof of concept effort, the first trial conducted using Sentinel Infrastructure, and will inform future interventional studies that are designed to utilize existing healthcare data as part of their design.

https://www.sentinelinitiative.org/sites/default/files/About/IMPACT-AFib_Protocol_Public_Comment_03012017.pdf



Electrical activity of a normal heart (left) and a heart with atrial fibrillation (right).

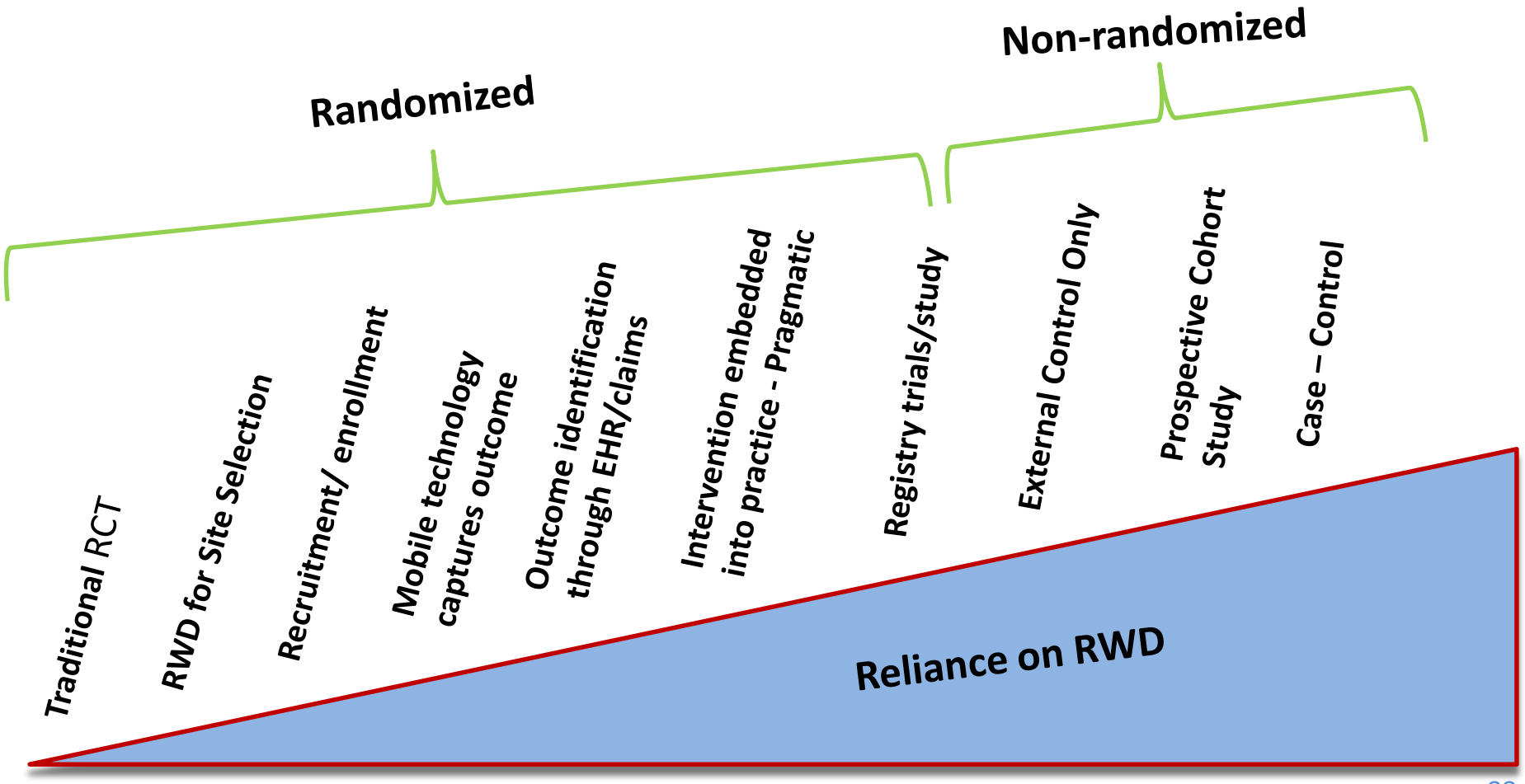
~9% of people >65 years have Afib

AFib increases stroke risk by 4-5x

Oral anticoagulants significantly decrease risk of stroke

Source -- CDC Atrial Fibrillation Fact Sheet

Spectrum of Reliance on RWD



Looking Forward

- **Continued engagement with stakeholders to identify the key questions that FDA needs to answer to facilitate sponsor use of RWD and RWE for regulatory decisions**
  - **Provide appropriate guidance(s)**
- **Identify knowledge gaps and support appropriate demonstration projects to facilitate development of RWE for regulatory decisions**
- **Develop a framework and program**

Acknowledgments

- Melissa Robb
- Dianne Paraoan
- Robert Ball
- Michael Blum
- Laura Esserman
- Leslie Curtis
- Sean Khozin
- Mitra Rocca
- Mary Ann Slack
- Vaishali Popot

Questions/ Comments

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov


FDA
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ADMINISTRATION

Turning RWD into RWE

Defining the scientific question

Identify suitable trial design

Selection of RWD Sources that are "Fit for Purpose"

Data standards/ analytics

Ensure compliance with FDA Regs

e.g. Part 11 and GCP

Submission of RWE for regulatory action

Decision

Public Meeting: A Framework for Regulatory Use of Real-World Evidence

September 13, 2017

Margolis.RWE@Duke.edu

@DukeMargolis #RWE

Clarifying the Real-World Data and Evidence Landscape

Gregory Daniel

September 13, 2017

Historically, traditional RCTs have been the gold standard for drug evidence development

- However, randomized controlled trials:
  - Are increasingly time- and resource-intensive to conduct, with some estimates attributing the bulk of 10-year development programs to trails themselves
  - Suffer from one-off design and infrastructure issues
  - Are not broadly representative of the patients seen in actual clinical care
  - May not be generating actionable evidence on endpoints that are truly useful to patients, providers, or payers
  - May be unethical or infeasible to perform given small patient population sizes
- While many efforts are underway to address RCT inefficiency, better use of RWD/RWE can fill remaining downstream evidence gaps

Data and methods for generating RWE are rapidly maturing

- RWD is increasingly available through a variety of sources:
  - Electronic health records
  - Payer claims data
  - New technologies for patient generated data
  - Dedicated registries
- Methods for generating RWE are improving
- Applications for RWE are either well-established or growing:
  - More relevant to patient and provider decision-making
  - Supportive of payment and reimbursement decisions
  - Fit for regulatory purposes

FDA has mandates for exploring the use of RWE within the regulatory framework

Prescription Drug User Fee Act VI

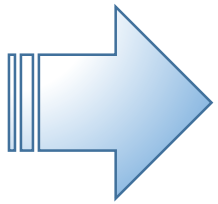
- Requires FDA to enhance use of RWE for use in regulatory decision-making
- FDA must:
  - Hold a public workshop with key stakeholders (e.g., patients, industry, academia) by the end of 2018
  - Initiate (or fund) activities (e.g., pilot studies or methodology development projects) aimed at addressing key concerns and considerations in the use of RWE by the end of 2019
  - Issue draft guidance by the end of 2021

21st Century Cures Act

- Requires FDA to establish a program to evaluate the potential use of RWE to:
  - Help support the approval of new indications for an approved drug
  - Help support or satisfy post approval study requirements
- FDA must issue:
  - A draft framework for this program by the end of 2018
  - Draft guidance by the end of 2021

Still, stakeholders need clarity on key terms

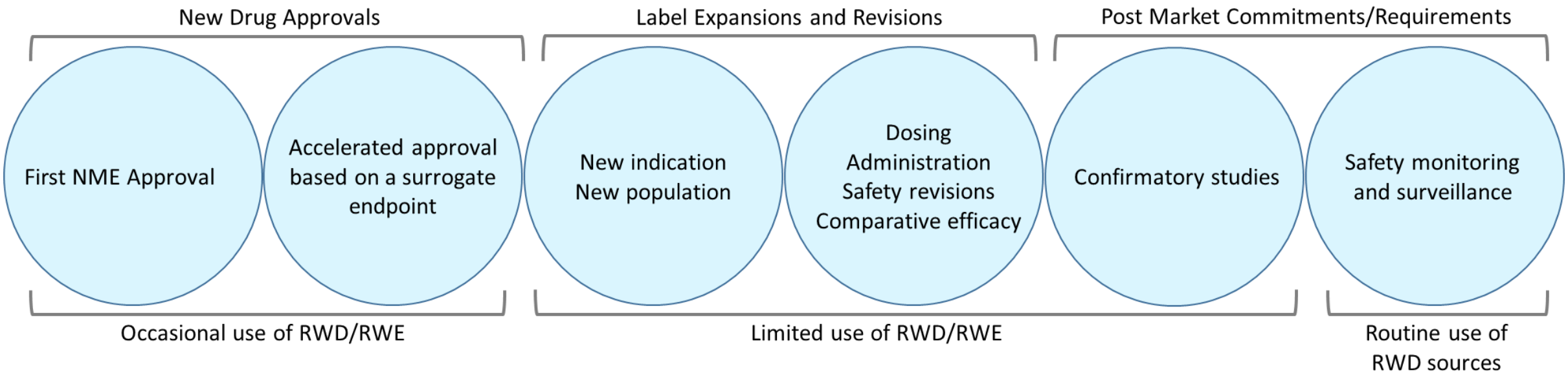
- **Real world data (RWD)** is data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources



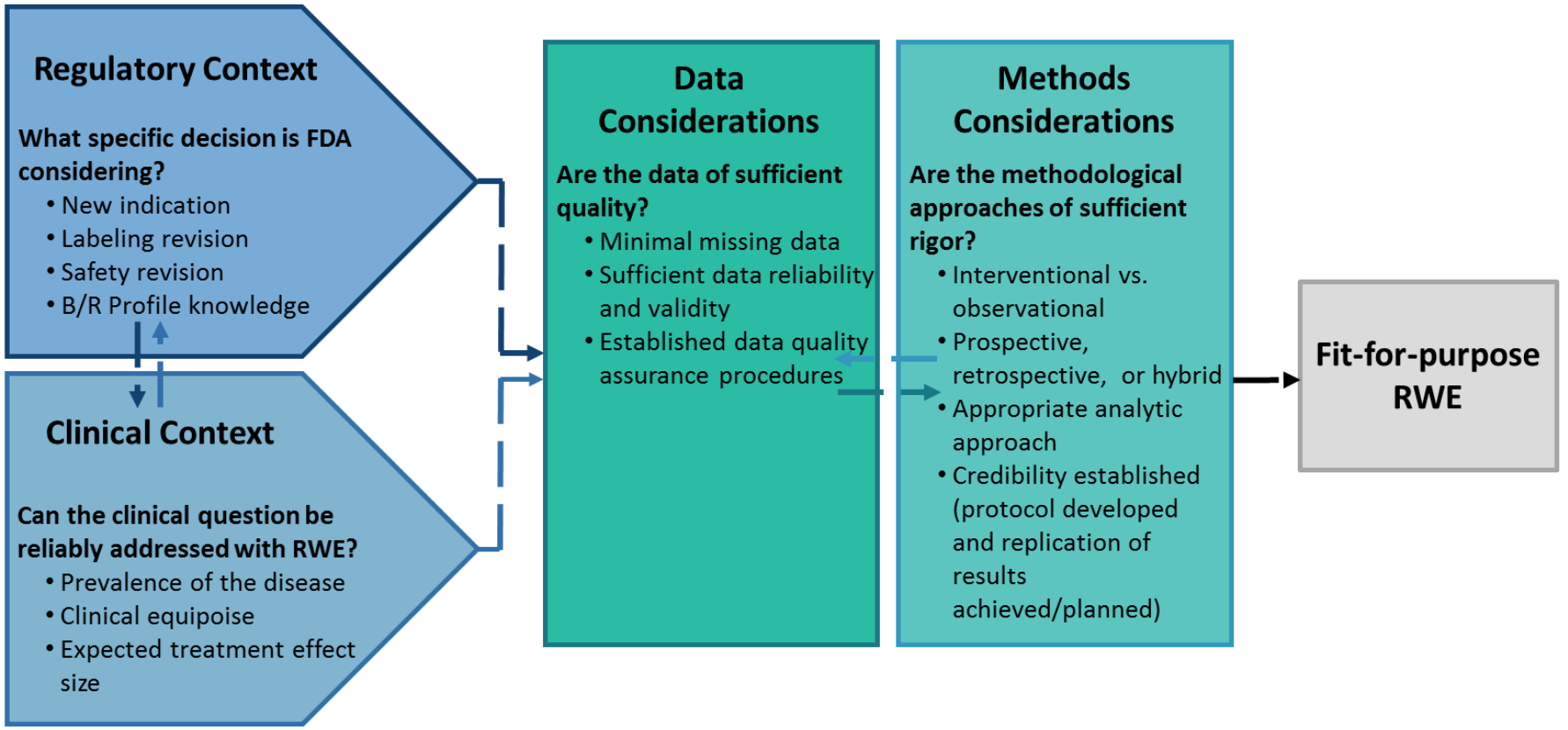
- **Real-world evidence (RWE)** is evidence derived from RWD through the application of research methods.
- For regulatory applications, RWE can further be defined as clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of RWD.

How we define RWD/RWE has follow-on implications for discussing how to develop and use both within stakeholder decision making processes

There has been varying experience utilizing RWD and RWE for regulatory purposes



Considerations for Generating RWE Fit for Regulatory Purposes



Matching data sources and methods to answer specific clinical and regulatory questions will dictate vary inappropriate g applicability of RWE for different regulatory use cases

Developing Fit for Purpose Real World Data

We need to close the gaps in data necessary to close the gaps in evidence and ultimately the gaps in care.

Kevin Haynes, HealthCore

Developing Fit for Purpose Real World Data

Amalgamated longitudinal real world stories put data into context and set the stage for real world learning.

Amy Abernethy, Flatiron Health

Developing Fit for Purpose Real World Data

Crossing the river by feeling the stones....

Sally Okun, PatientsLikeMe

Developing Fit for Purpose Real World Data

“We are refocusing clinical practice on high quality data collection- to transform the point of care into a patient centric datahub- where learning and improvement are part of the routine of care.”

Laura Esserman, UCSF School of Medicine

CLINICAL TRIALS TRANSFORMATION INITIATIVE

September 13, 2017

Real World Evidence Project

David Thompson, PhD
Senior Vice President, Real-World & Late Phase
INC Research / inVentiv Health

CTTI Introduction

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Public-Private Partnership
Co-founded by Duke University & FDA
Involves all stakeholders
80+ members

MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

CTTI

Real World Evidence Project Team

Team Leads

- Lesley Curtis (Duke Univ)
- Scott Evans (SCT)
- Jane Perlmutter (Individual Patient)
- Jack Sheehan (Janssen/J&J)
- Juli Tomaino (FDA CDER)

CTTI Project Manager

- Gerrit Hamre

gerrit.hamre@duke.edu

CTTI Social Scientists

- Amy Corneli
- Brian Perry

Team Members

- Kathrena Aljallad (Life Raft Group)
- Naomi Aronson (BCBS)
- Ken Carson (Flatiron)
- Cathy Critchlow (Amgen)
- Ruthie Davi (Medidata)
- Ryan Ferguson (Dept of Veterans Affairs)
- Jerry Heatley (Abbott)
- Ani John (Genentech)
- Jessie Juusola (Evidation Health)
- Martin Landray (Univ of Oxford)
- John Laschinger (FDA CDRH)
- Sara Leatherman (Dept of Veterans Affairs)
- Amanda Niskar (Individual Patient)
- Eric Peterson (Duke Univ)
- Sudha Raman (Duke Univ)
- David Thompson (INC Research/inVentiv Health)

CTTI

Use-Cases for RWD in Early Development

- To date, focus on use of the data …
  - Historical controls in rare diseases ➔ Accepted by FDA in instances in which a control group in a trial is infeasible and/or unethical
  - Assessment of treatment patterns & adherence ➔ How are drugs being used in actual practice? Is there an "efficacy-effectiveness gap?"
  - Patient segmentation & assessment of heterogeneity of treatment effects ➔ Are there differential benefits/harms? Is there an unmet medical need?

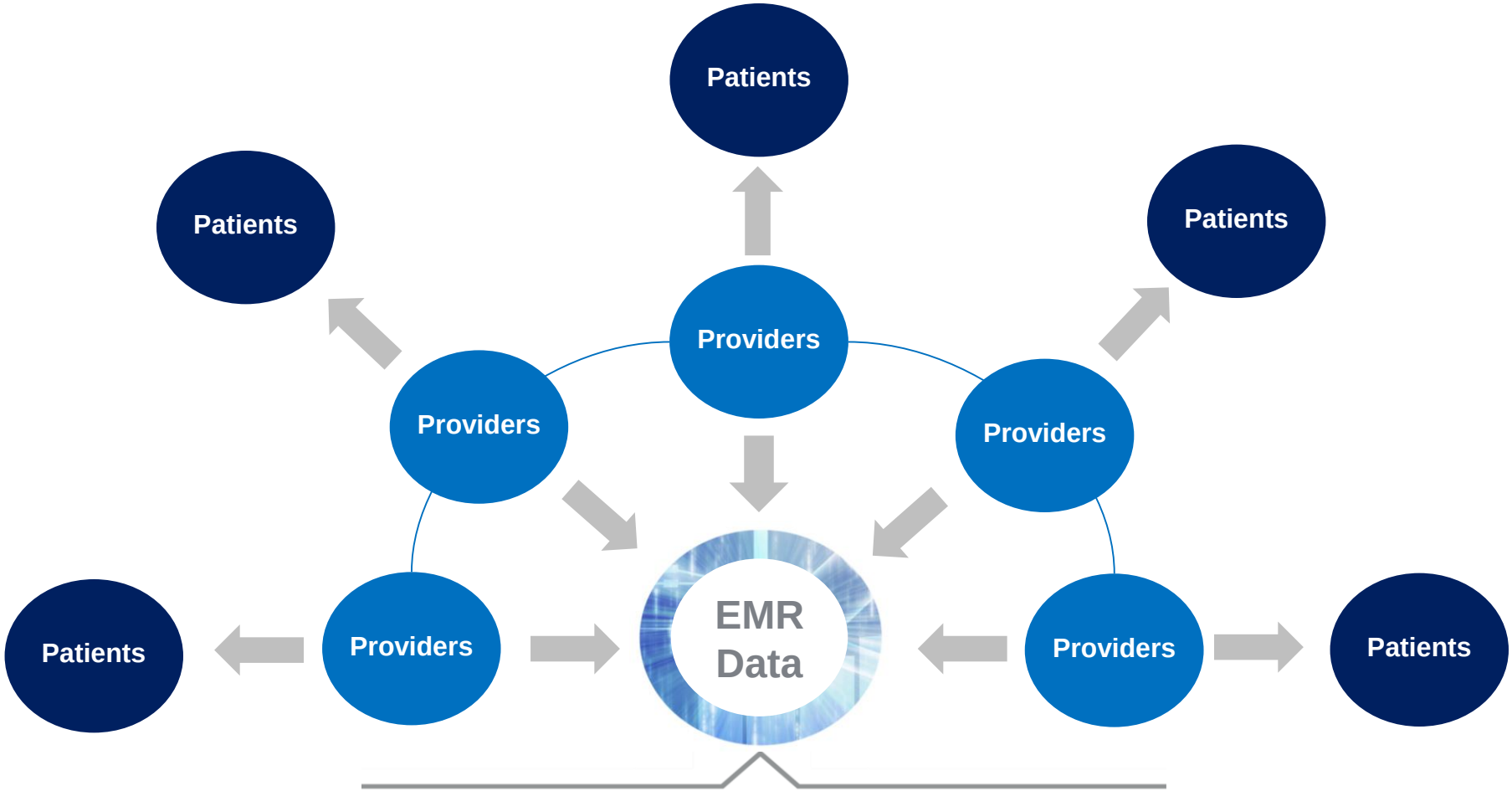
Use-Cases for RWD in Early Development

- To date, focus on use of the data …
  - Hypothesis-generating comparative effectiveness research in off-label indications ➔ How do products perform in real-world practice?
  - Protocol feasibility ➔ How stringent are a study's inclusion/exclusion criteria in terms of patient eligibility?

Use-Cases for RWD in Early Development

- New focus on use of the IT systems that house the data to transform the clinical trial process …
  - Identification of patients who might be candidates for inclusion in study ➔ Look for patients first, sites second
  - Leverage electronic communication channels for recruitment ➔ Notify providers of patients of interest, enlist their help in outreach
  - Establish data flows between EMRs & eCRFs ➔Automate data capture, reduce redundancies in data entry

EMR Systems Create Provider/Patient Networks



But Use of EMRs in Trials Faces Compatibility Issues …

Characteristic	EMR Data	Trial Data
Data collected for …	Individual patient health tracking & physician orders support	Assessment of drug safety & efficacy
Patients included	All in practice	Selected based on protocol
Provider-induced variability in data collection	Lots	Minimal
Practice-based customization of data collection	Yes	No
Data formats	Structured & unstructured	Structured & controlled vocabularies
Timing of data collection	Tied to patient encounters	Tied to protocol
Data quality assurance	Limited	Research specific validation rules
Data standards	HL7	CDISC

CTTI

THANK YOU.

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

david.thompson@inventivhealth.com

www.ctti-clinicaltrials.org

Collaborating to Improve the Acceptability of Real World Evidence by Healthcare Decision-Makers

Marc Berger, MD
Richard Willke, PhD

Duke-Margolis Center for Health Policy:
A Framework for Regulatory Use of Real World Evidence - September 13, 2017

- Founded in 1995

- **Mission:** *To promote health economics and outcomes research excellence to improve decision making for health globally.*

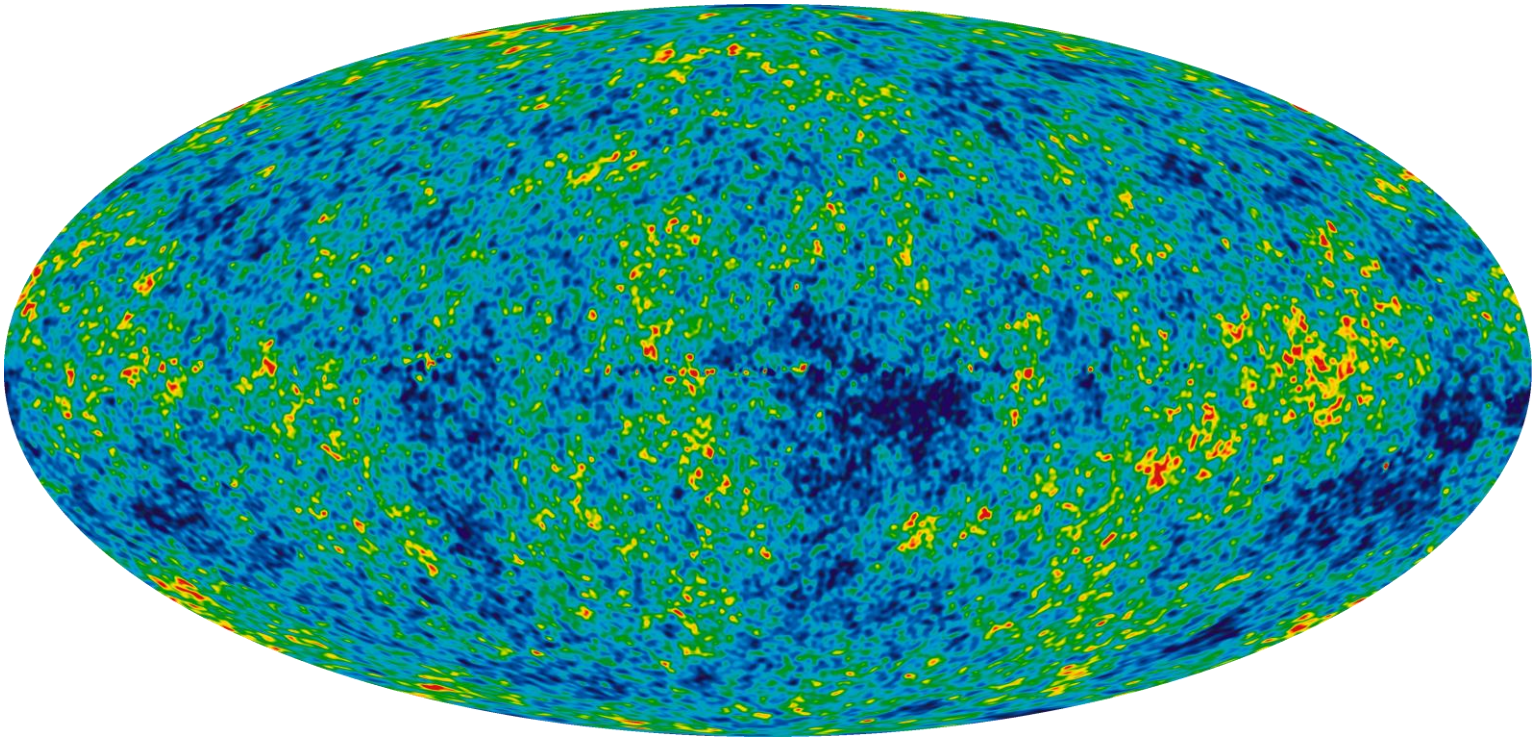
- **Vision:** *ISPOR is the leading global scientific and educational organization for health economics and outcomes research and their use in decision making to improve health.*

ISPOR's Global Stakeholders

The Challenge of Real World Evidence

So much data, so much potential information

– but is it reliable and trustworthy?



Making RWE useful requires:

- Quality production
  - Careful data collection[1]
  - Good analytic methods[1]
  - Transparent study procedures to enable replication[1,2]
  - Good procedural practices - “study hygiene”[1,2]

- Responsible consumption
  - Informed interpretation[3]
  - Fit-for-purpose application

1. Good practices in these areas are all addressed in ISPOR Task Force Reports
https://www.ispor.org/workpaper/practices_index.asp
2. Joint ISPOR – ISPE Task Force Reports – September 2017
3. ISPOR – AMCP – NPC CER Collaborative
www.HealthStudyAssessment.org

Received: 21 July 2017 | Revised: 26 July 2017 | Accepted: 28 July 2017
DOI: 10.1002/pds.4297

WILEY

ORIGINAL REPORT

Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making

Marc L. Berger[1] | Harold Sox[2] | Richard J. Willke[3] | Diana L. Brixner[4] | Hans-Georg Eichler[5] | Wim Goettsch[6] | David Madigan[7] | Amr Makady[6] | Sebastian Schneeweiss[8] | Rosanna Tarricone[9] | Shirley V. Wang[8] | John Watkins[10] | C. Daniel Mullins[11]

WILEY

ORIGINAL REPORT

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

Shirley V. Wang[1,2] | Sebastian Schneeweiss[1,2] | Marc L. Berger[3] | Jeffrey Brown[4] | Frank de Vries[5] | Ian Douglas[6] | Joshua J. Gagne[1,2] | Rosa Gini[7] | Olaf Klungel[8] | C. Daniel Mullins[9] | Michael D. Nguyen[10] | Jeremy A. Rassen[11] | Liam Smeeth[6] | Miriam Sturkenboom[12] |
on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making

Online simultaneous publication in September 2017

- *Value in Health*
- *Pharmacoepidemiology and Drug Safety*

Good Procedural Practices for Clinical Studies ("Study Hygiene")

- **Pre-Approval RCTs**
  - Pre-registration on public website (ClinicalTrials.Gov)
  - Completion of an *a priori* protocol and data analysis plan
  - Transparent documentation for any changes in study procedures
  - Expectation that all RCT results will be made public

- **Real World Data Studies**
  - ***No well-accepted recommendations for good procedural practices***
    - A few groups have begun to weigh in here; needs reinforcement
    - Must address data dredging, publication bias issues
    - Other concerns include internal validity, inaccurate recording of health events, opaque reporting

Following/adapting RCT-like practices is a logical starting point

Transparency (ISPOR-led) Manuscript

Key Definition/Distinction: Categories of RWD Treatment Effectiveness Studies

- **Exploratory Study**
  - Typically does not hypothesize the presence of a specific treatment effect and/or its magnitude
  - Primarily serves as first step to learn about possible treatment effects
  - Less pre-planned and allows for process-adjustments as investigators gain knowledge of the data
- **Hypothesis-Evaluating Treatment Effectiveness (HETE) Study**
  - Evaluates the presence or absence of a pre-specified treatment effect and/or its magnitude
  - Tests a specific hypothesis in a specific data set
  - In conjunction with other evidence, may lead to treatment recommendations

Recommendations for HETE Studies

- Pre-registration: post study protocol and analysis plan on public registration site prior to conducting the study analysis
  - e.g., clinicaltrials.gov, ENCEPP, HSRProj
- Publish study results with attestation to conformance and/or deviation from original analysis plan
  - Medical Journal, Web-site, Study Registry
- Provide opportunities to replicate findings
- Perform studies on a different data set than the one used to generate the hypotheses to be tested unless it is not feasible
- Authors should work with individuals to address methodologic criticisms of their study; publishing or posting on public websites the criticisms and responses would be useful
- Include key stakeholders (patients, caregivers, clinicians, clinical administrators, HTA/payers, manufacturers) in designing, conducting, and disseminating the research

Reproducibility (ISPE-led) report

- This report focuses on enhancing existing reporting guidelines (RECORD) by identifying a minimum set of items necessary to report in detail in order achieve fully reproducible evidence from large healthcare database cohort studies.

- Data and code sharing should be encouraged when data use agreements and IP permit, however **clear, natural language description** of key operational and design details should be the **basis of sharing the scientific thought process**

Specific issues addressed

- The guidance document and checklist enhancement to RECORD guidelines developed by this work group addresses issues related to:
  - Specific operational decisions behind analytic data extraction from raw longitudinal data, with a focus on temporal anchors
  - The minimum reporting necessary for independent investigators to be able to reproduce a database cohort study, starting from analytic data extraction from a raw longitudinal data source
  - The minimum reporting on characteristics of the analytic cohort (before and after adjustment) necessary to assess whether a study has been reproduced

Closing thoughts

- To enhance the trustworthiness of real world evidence, the recommendations of the Joint ISPOR-ISPE Taskforce need to be widely adopted.
- This will require actions to be taken by a variety of stakeholders including journal editors, regulatory authorities, providers, payers, and HTA authorities.
- An upcoming meeting will begin this conversation.

ISPOR/ISPE "Summit on Real-World Evidence in Health Care Decision Making"
October 20, 2017
Grand Hyatt Hotel, Washington, DC

https://www.ispor.org/EventReg/DisplayEvent.aspx?EventId=67

Matching Real World Data and Evidence to Regulatory Use Cases

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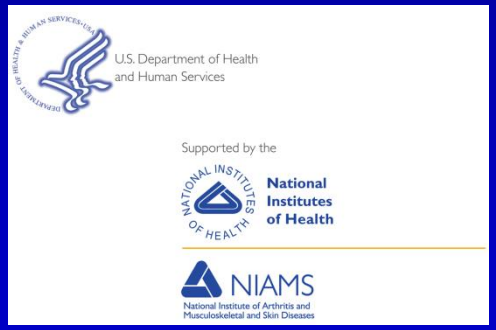
Acknowledgements & Disclosures

Funding

- NIAMS UM1 AR065705
- PCORI Patient Powered Research Network (PPRN)



Research grants or consulting	Amgen, Abbvie, BMS, CORRONA, Lilly, Janssen, Myriad, Pfizer, Sanofi/Regeneron

Outline

- Pre-licensure evidence generation
- Pragmatic Clinical Trials
  - Site Selection
  - eConsent
- Data linkages, HIPAA authorization
- Post-approval safety commitments

Pre-Licensure Evidence Generation for Regulatory Agencies

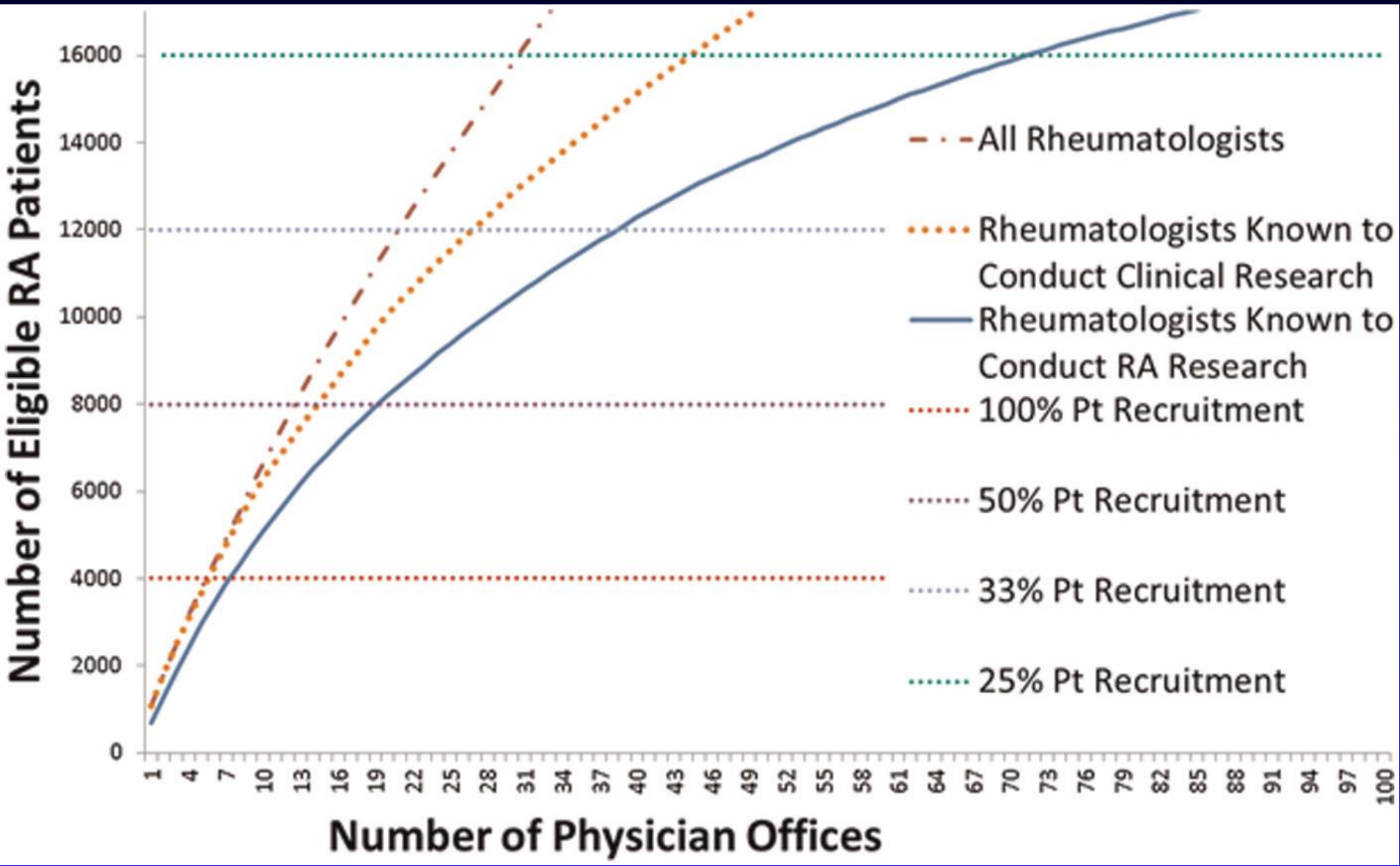
- **Background rates of rare adverse events sometimes not available for patients with uncommon diseases (e.g. psoriatic arthritis, rheumatoid arthritis)**
- **Real-world data (including from health plan claims) may be useful to provide background rates to inform post-marketing safety evaluation*, provide evidence to FDA on safety contextualization****

* Curtis JR, Semin Arthritis Rheum. 2015 Feb;44(4):381-8.
** https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm570453.htm

Pragmatic Clinical Trial Example: the VERVE Zoster Vaccine trial

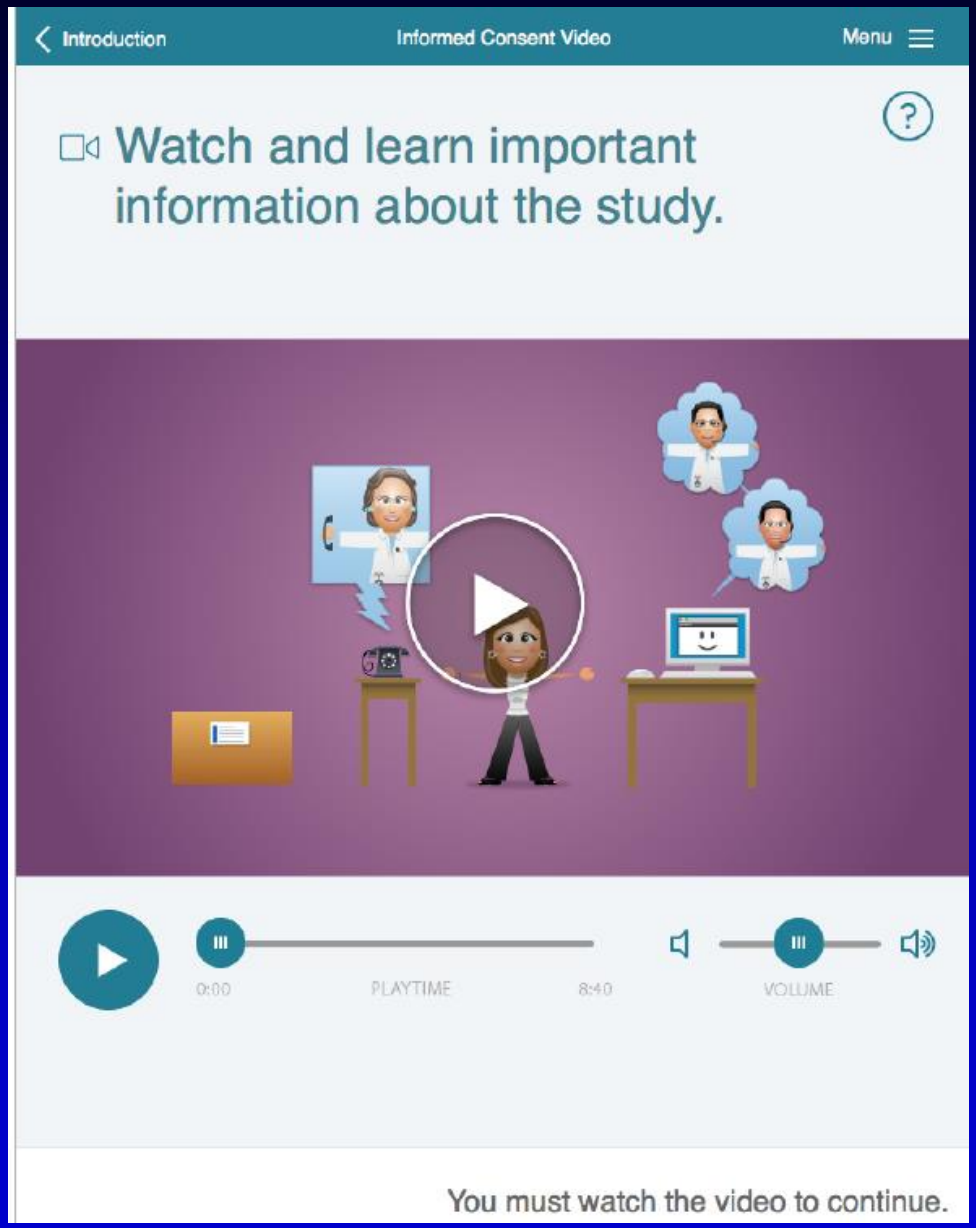
- Randomized, blinded, large pragmatic trial of 1,000 patients age 50+ on anti-TNF therapy randomized 1:1 to vaccine vs. placebo
- 42 days active follow-up for safety outcome
- Follow-up for longer-term effectiveness outcome with claims/EHR data linkage on majority of patients
- Capacity for biospecimen, clinical data collection annually
- Internet-based iPad assisted screening, randomization via eConsent system
- Consent includes authorization to obtain medical records centrally, & link to external data sources (e.g. health plan claims, EHR data in PCORnet)

VERVE: Identifying Sites, Pre-screening Patients



Curtis JR et. al., Clin Trials. 2014 Feb;11(1):96-101

Direct to to Patient Electronic Consent



Knowledge Review Menu

Question 1 of 6

The main reason this study is being conducted is to...

- determine the safety and effectiveness of the zoster vaccine in patients treated with biologic medications who are at least 50 years old
- find a vaccine with no side effects
- help pay for shingles treatments
- compare different kinds of shingles medications

Knowledge Review

Menu

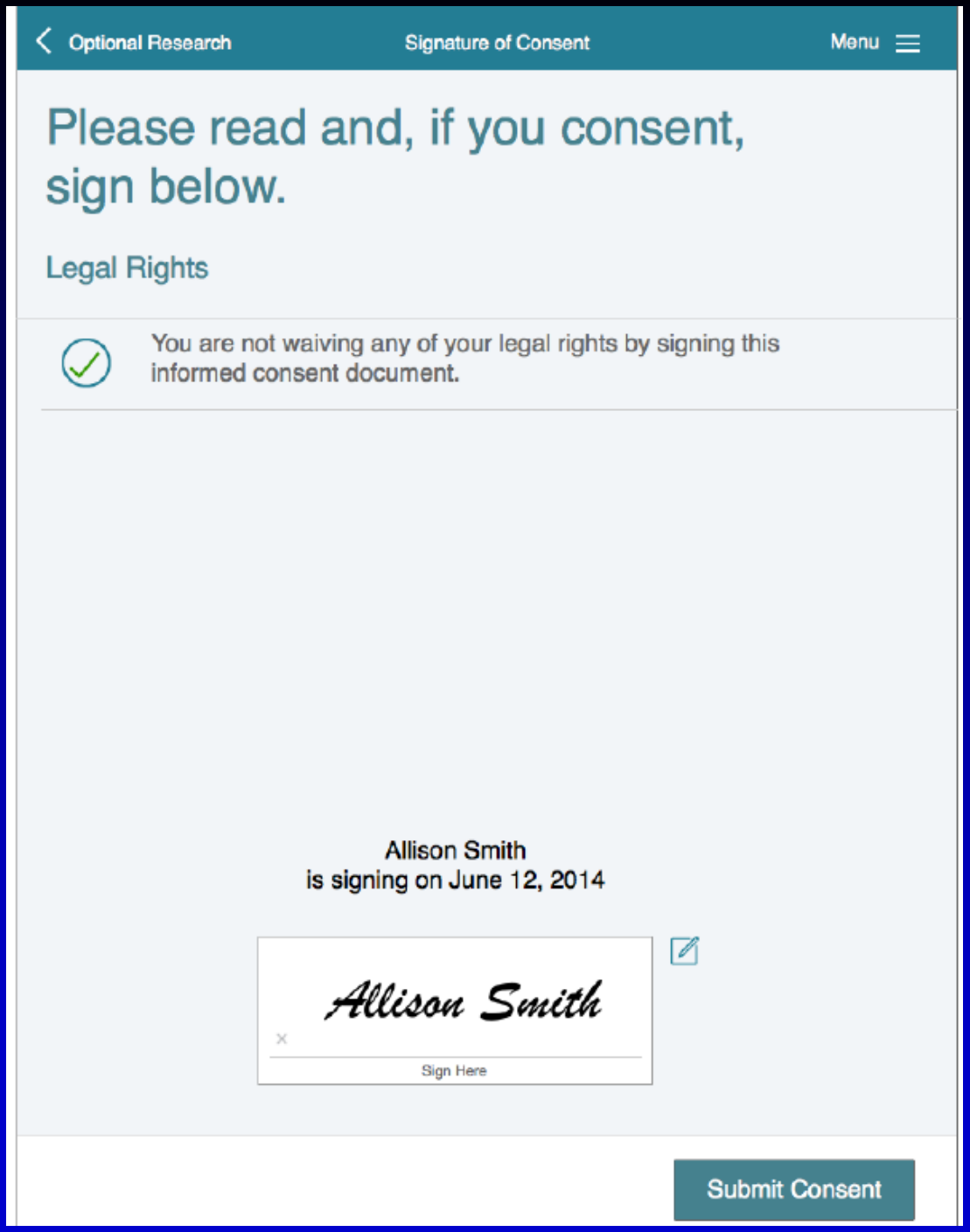
Question 1 of 6

The main reason this study is being conducted is to...

View the part of the Informed Consent that this question references and answer again.

HINT

- ○ determine the safety and effectiveness of the zoster vaccine in patients treated with biologic medicaitons who are at least 50 years old
- ✕ find a vaccine with no side effects.
- ○ help pay for shingles treatments
- ○ compare different kinds of shingles medications


Optional Research
Signature of Consent
Menu
Please read and, if you consent, sign below.
Legal Rights
You are not waiving any of your legal rights by signing this informed consent document.
Allison Smith
is signing on June 12, 2014
Allison Smith
Sign Here
Submit Consent

HIPAA Authorization for Medical Record Release for Safety Event Adjudication

- Other examples available from safety studies*
- Example: “I consent to give access to my private (confidential) personal information to…”
  - Staff from (sponsor), and anyone acting on their behalf for quality assurance and quality control
  - Staff from (clinical research organization) who review and process study data

* https://clinicaltrials.gov/ct2/show/NCT01331837; Giles JT et. al., ACR 2016, abstract 3L

Outcomes Able to Be Ascertained with High Validity* in Real World Data

- Adverse Medical Events such as
  - Myocardial Infarction and CHD events
  - Stroke
  - Serious Infection requiring hospitalization
  - Herpes Zoster
  - GI: Peptic Ulcer Disease, Bleed, Perforation
  - Fracture (non-vertebral and vertebral)
  - Malignancy (e.g. lymphoma, solid tumors)
- Most procedures (e.g. surgery, device implants)
- Costs
- Death

** based upon the availability of high-quality validation studies comparing claims-based algorithms to medical records*

Linkages to Real-World Data to Identify Safety Outcomes

- Claims data used alone to identify outcome (maximize specificity)
- Claims data used only to find cases
  - Step 1: use claims data to find potential cases (maximize sensitivity)
  - Step 2: confirm suspected cases through medical record review (improve specificity)
  - Facilitated by medical record release form at baseline visit
- Patients don’t have to come back for safety visits
- Minimal loss to follow-up if RWD source available

Will the IRB Permit Linkage with RWD?

- Yes; better to plan for this capacity in advance
- Example language: “Data from this study may be linked with data supplied by…
  Your social security number may be used to match your data in the administrative database.
  Your data will be kept confidential according to the Privacy Act of 1974, and will be used only for research purposes”
- Can involve an honest broker
- Personal Identifying Information (PII) can be hashed if needed

Post-Marketing Safety Commitment

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; 22: 1107–1114
Published online 15 July 2013 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.3477

ORIGINAL REPORT

Design and methods of a postmarketing pharmacoepidemiology study assessing long-term safety of Prolia® (denosumab) for the treatment of postmenopausal osteoporosis‡

ABSTRACT

Purpose To describe the rationale and methods for a prospective, open-cohort study assessing the long-term safety of Prolia® for treatment of postmenopausal osteoporosis (PMO) in postmarketing settings.

Methods Data will be derived from United States Medicare, United Healthcare, and Nordic (Denmark, Sweden, Norway) national registries. Observation will begin on the date of first Prolia® regulatory approval (May 26, 2010) and continue for 10 years. Women with PMO will be identified by postmenopausal age, osteoporosis diagnosis, osteoporotic fracture, or osteoporosis treatment. Exposure to Prolia® and bisphosphonates will be updated during follow-up; exposure cohorts will be defined based on patient-years during which patients are on- or post-treatment. Nine adverse events (AEs) will be assessed based on diagnosis codes: osteonecrosis of the jaw (ONJ), atypical femoral fracture (AFF), fracture healing complications, hypocalcemia, infection, dermatologic AEs, acute pancreatitis, hypersensitivity, and new primary malignancy. Medical review will confirm selected potential cases of ONJ and AFF. Incidence rates (IRs) of AEs will be described overall and for exposure cohorts; multivariate Cox proportional hazard regression models will compare IRs of AEs across exposure cohorts. Utilization patterns of Prolia® for approved, and unapproved indications will be described.

Conclusion This study is based on comprehensive preliminary research and considers methodological challenges specific to the study population. The integrated data systems used in this regulatory committed program can serve as a powerful data resource to assess diverse and rare AEs over time.

Discussion

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Pursing RWE Development Programs that Support Regulatory Use

Amy E. Rudolph

Vice President and Head, US HE&OR and Early Development
Novartis Pharmaceuticals, East Hanover, NJ, USA

NOVARTIS

Key Tenets to Consider for RWE guidance

- Wide agreement on need for RWE:
  - Current and future environment complexity demands evidence that spans the data continuum
  - New technology & new indication submissions must evolve toward data compendiums
- Proposed tenets for RWE guidance may include the following
  - Bias management
    - Recognition that bias mitigation cannot be absolute
  - Defining boundaries of acceptable evidence
    - What is “good enough”?
    - Primary vs. secondary evidence
  - Direction on database suitability
  - Parameters of acceptability of patient-centric data
    - Sensor data
    - Adherence/persistence

NOVARTIS

Pursuing RWE Development Programs that Support Regulatory Use

Jacqueline Law, Ph.D., Vice President, Global Head, Real World Data Science

Genentech, A Member of Roche Group

Duke Margolis, Sept 13, 2017

Pursuing RWE Development Programs that Support Regulatory Use

Opportunities and interests to leverage RWD to support broader healthcare decision-making

- Advances in medicines, diagnostics and technology, improvement in RWD, increasing drug development costs, pricing pressure

How to confidently move from concept to practice? Some ideas –

- Standards on ‘Data’ e.g. data collection, quality, endpoint definitions
- Requirements on patient & data privacy e.g. informed consent, HIPPA
- Submission requirements e.g. data package, audit, source data verification
- Early input from FDA on development programs utilizing RWD
- Precompetitive sharing of use cases

Doing now what patients need next

Public Meeting: A Framework for Regulatory Use of Real-World Evidence

September 13, 2017

Margolis.RWE@Duke.edu

@DukeMargolis #RWE