Real World Evidence
A Path Forward

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FDA
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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

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/
“...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
Post-Market Safety Assessment

Signal Identification:
Potential safety concern identified

Signal Refinement:
Initial evaluation of safety concerns

Signal Evaluation:
Detailed assessment

Case Reports
Registries
Observational Studies
Clinical Trials

Data Mining (e.g. TreeScan)
Modular Programs
>Level 2 Modular Programs/Protocol-based Assessments
Epidemiology – Final Guidance

• Pertains to pharmacoepidemiology safety studies using electronic healthcare data
• Final guidance was issued May 14, 2013
• Real-world evidence can inform therapeutic development, outcomes research, patient care, research on health systems, quality improvement, safety surveillance and well-controlled effectiveness trials.

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

• Discussions of real world evidence must be informed by a clear understanding of the methods used, so that the best methods that have been developed and validated can be combined with the most appropriate research settings.
Turning RWD into RWE

RWE Study Design

RWD – Assessing Fitness for Use

Data Standards and Implementation

Regulatory Considerations

Engage with FDA early on this journey
Laying the Foundation

Stakeholder Engagement

FDA’S THERAPEUTIC AREA STANDARDS PROJECT

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

Data Standards

Guidances

Demonstration Projects

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

Use of Electronic Health Record Data in Clinical Investigations (Draft)

Use of 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
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. 1

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**

- **Sentinel**
  - CDM
  - 19 Data Partners*

- **PCORNET CDM**
  - CDM
  - 13 CDRN + 21 PPRN*

- **FDA, PCOR, and other Researchers**
  - Portal
  - Tools
  - Mechanism to crosswalk the models

- **OHDSI/OMOP**
  - CDM
  - 14 Data Partners*

- **i2b2**
  - CDM
  - > 60*

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* 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.

~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

Randomized
- Traditional RCT
- RWD for Site Selection
- Recruitment/enrollment
- Mobile technology captures outcome
- Outcome identification through EHR/claims
- Intervention embedded into practice - Pragmatic

Non-randomized
- Registry trials/study
- External Control Only
- Prospective Cohort Study
- Case – Control

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

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• Dianne Paraoan
• Robert Ball
• Michael Blum
• Laura Esserman
• Leslie Curtis
• Sean Khozin
• Mitra Rocca
• Mary Ann Slack
• Vaishali Popot
Questions/ Comments

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RealWorldEvidence@fda.hhs.gov
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 trials 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 the applicability of RWE for different regulatory use cases.
We need to close the gaps in data necessary to close the gaps in evidence and ultimately the gaps in care.

Kevin Haynes, HealthCore
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
Real World Evidence Project

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

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- 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)
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 …

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

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.
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](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](http://www.HealthStudyAssessment.org)
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*
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

Matching Real World Data and Evidence to Regulatory Use Cases

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William J. Koopman Professor of Medicine
Division of Clinical Immunology & Rheumatology
University of Alabama at Birmingham
Co-Director, UAB Pharmacoepidemiology and Pharmacoeconomics Unit
Acknowledgements & Disclosures

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- PCORI Patient Powered Research Network (PPRN)

Research grants or consulting

<table>
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<th>Amgen, Abbvie, BMS, CORRONA, Lilly, Janssen, Myriad, Pfizer, Sanofi/Regeneron</th>
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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**

** 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
Watch and learn important information about the study.

You must watch the video to continue.
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
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
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

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](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
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. © 2013 Amgen Inc. Pharmacoepidemiology and Drug Safety published by John Wiley & Sons, Ltd.
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
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
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
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