Clinical Trials and the Use of Real-World Data in Medical Product Development

Kara Kilpatrick, Senior Manager, Center for Observational Research, Amgen Inc.
David B. Martin, Associate Director for Real World Evidence Analytics, CDER
Eric Solowey, Vice President and Assistant General Counsel, Parexel International

Moderated by John R. Manthei, Partner, Latham & Watkins LLP
RWE: Challenges and Opportunities

“The more widespread use of [real-world evidence] can make our medical product development process more efficient, and help lower the cost of development. More importantly, it can help make sure doctors and patients are better informed about the clinical use of new products, enabling them to make more effective, efficient medical choices.” – former FDA Commissioner Scott Gottlieb

• Real-world evidence (RWE) and real-world data (RWD) have the potential to transform product development and improve patient outcomes
  – RWD relate to patient health status and/or the delivery of health care from a variety of sources
  – RWE is data regarding the usage, or the potential benefits or risks, of a medical product derived from analysis of RWD

• Harnessing RWE presents opportunities and challenges to FDA and industry:
  – Developing a regulatory framework
  – Regulating consumer-reported data
  – Ensuring patient safety and engagement
  – Patient privacy and anonymization of data
  – Interoperability between proprietary systems
Initial Steps

• Conversation has moved from whether RWE should be used in FDA regulatory decision-making to how and in what circumstances
  – Historically used in the context of healthcare delivery, coverage and reimbursement
  – Approvals using RWE to support efficacy claims have occurred when using a parallel control arm is unethical or not feasible
  – Use of prospective observational cohort study to contextualize single-arm efficacy trials expected to increase

• FDA and industry have taken key initial steps, including:
  – Guidance, Use of Electronic Health Record Data in Clinical Investigations (Jul. 2018)
  – Framework for FDA’s Real-World-Evidence Program (Dec. 2018)
  – Expansion of RWE Demonstration Project: from RCT replication to prediction
Promise of Further Development

• New Leadership at FDA: backgrounds in and proponents of use of big data
  – Ned Sharpless, Acting FDA Commissioner
    • Previously served as Director of the National Cancer Institute, where he advocated for more extensive use (particularly sharing, integration, and analysis) of big data in the context of cancer research and care
    • Highlighted the use of IBM Watson to support oncology treatment decisions in his time as an academic
  – Amy Abernethy, Principal Deputy Commissioner
    • Joined FDA from Flatiron Health, where she focused on converting EMR data into information that could be submitted to FDA

• FDA and industry are poised to continue to advance the use of RWE
  – Leveraging RWE to support approvals
  – Further guidance contemplated by the Agency’s RWE framework
Regulatory Approach to the Use of Real-World Data and Evidence

Eric Solowey
Vice President and Assistant General Counsel
Parexel International
May 2, 2019
Agenda

• 21st Century Cures Act
• Real World Data vs. Real World Evidence
• Framework for FDA’s Real World Evidence Program
• Guidance on Use of Electronic Health Record Data in Clinical Investigations
21st Century Cures Act (2016) §3022

<table>
<thead>
<tr>
<th>PROGRAM</th>
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<tbody>
<tr>
<td>• Establish program to evaluate use of RWE</td>
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<tr>
<td>– Support approval of a new indication for approved drug</td>
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<td>– Help satisfy post-approval requirements</td>
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<thead>
<tr>
<th>FRAMEWORK</th>
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<tr>
<td>• Draft framework for implementation of the program. Framework to include information describing:</td>
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<tr>
<td>– Sources of RWE</td>
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<tr>
<td>– Gaps in data collection activities</td>
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<tr>
<td>– Standards/methods for collection and analysis</td>
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<td>• Draft due Dec. 2021</td>
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<tr>
<th>GUIDANCE</th>
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<tbody>
<tr>
<td>• Use program to inform guidance for industry:</td>
</tr>
<tr>
<td>– Circumstances under which RWE would be used within scope of program</td>
</tr>
<tr>
<td>– Standards and methodologies for collection and analysis of RWE</td>
</tr>
<tr>
<td>• Consult with interested parties.</td>
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</table>

• Draft framework for implementation of the program. Framework to include information describing:
  – Sources of RWE
  – Gaps in data collection activities
  – Standards/methods for collection and analysis
  – Priorities, challenges, pilot opportunities

• Consult with interested parties.
# Real World Data vs. Real World Evidence

<table>
<thead>
<tr>
<th>REAL WORLD DATA (RWD)</th>
<th>REAL WORLD EVIDENCE (RWE)</th>
</tr>
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<tbody>
<tr>
<td>“Data relating to patient health status and/or delivery of health care routinely collected from a variety of sources”</td>
<td>“Data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials.” [21 U.S.C. § 355g(b)]</td>
</tr>
<tr>
<td>• Electronic health records</td>
<td>• “Clinical evidence about the usage and potential benefits or risks of a medical product derived from the analysis of RWD.” [Framework page 4]</td>
</tr>
<tr>
<td>• Medical billing and claims</td>
<td></td>
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<tr>
<td>• Product and disease registries</td>
<td></td>
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<tr>
<td>• Data from other sources (e.g. from mobile devices)</td>
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1 Framework for FDA’s Real World Evidence Program (2018)
Objectives of Framework

Evaluate potential use of RWE to support changes to labeling about drug product effectiveness, including

– Adding or modifying indication
– Change in dose, dose regimen, or route of administration
– Adding new population
– Adding comparative effectiveness or safety information
Framework Considerations

1. Whether RWD are fit for use
2. Whether study design provides adequate evidence to answer the regulatory question
3. Whether study conduct meets FDA regulatory requirements
4. How to develop data standards
1. Whether RWD is Fit for Use

**RELIABILITY AND RELEVANCE**

- FDA to issue guidance on how to assess reliability and relevance of RWD
  - Medical claims
  - EHR
  - Data from outside US
  - Registries
- Reliability: does data adequately represent underlying medical concepts?
- Relevance: are data fit for the intended purpose?

**ADDRESSING GAPS**

- FDA to issue guidance on potential gaps in RWD and ways to address
  - RWD may be incomplete or stored in different formats
  - Explore use of mobile technologies, electronic patient reported outcome tools, wearables, and biosensors
  - Explore ways to link data about patient across multiple data sources while protecting patient privacy.
2. Whether Study Design Provides Adequate Evidence for Regulatory Question

<table>
<thead>
<tr>
<th>PRAGMATIC DESIGN ELEMENTS</th>
<th>EXTERNAL CONTROL ARMS</th>
<th>OBSERVATIONAL STUDIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FDA to develop guidance on trials that include pragmatic design elements for each stage of trial:</td>
<td>• FDA to develop guidance on using RWD to generate external control arms</td>
<td>• FDA to develop guidance about observational study designs</td>
</tr>
<tr>
<td>- recruitment and enrollment; facilitating interventions; assessing outcomes</td>
<td></td>
<td>• Build upon Pharmacoepidemiologic Guidance (used in safety context) to develop guidance in efficacy context.</td>
</tr>
<tr>
<td>• Pragmatic design = more closely resembles routine clinical practice</td>
<td></td>
<td>• Observational Study is a non-interventional clinical study design.</td>
</tr>
</tbody>
</table>
3. Whether Study Conduct meets FDA Regulatory Requirements

**ELECTRONIC SOURCE DATA**

- FDA to consider whether additional requirements are needed on use of electronic source data
- Some standards already exist
  - 21 CFR Part 11
    - Quality, authenticity and reliability of electronic records
  - FDA Guidance (e.g. Electronic Source Data in Clinical Investigations)

**STUDIES GENERATING RWE**

- FDA to consider new guidance on regulatory considerations raised by different study designs
  - Randomized clinical trials integrated into health care system
  - Observational studies intended to generate RWE for regulatory decision-making
- HIPAA will not be addressed in the Framework
4. Data Standards for RWD and RWE

**DATA STANDARDS**

FDA to identify data standards that apply to proposed uses of RWD/RWE at FDA

**IMPLEMENTATION CONSIDERATIONS**

FDA to develop implementation strategies, e.g.

- Integration with existing FDA systems
- Impact on reviewer workload
- Tools and training for FDA reviewers
Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

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)
Center for Devices and Radiological Health (CDRH)

July 2018
Procedural
FDA Guidance: Using Electronic Health Records in clinical investigations

• FDA expectations when EHR used as a data source in clinical investigations
• Focus on FDA’s ability to verify the quality and integrity of the data
• Issued July, 2018
• Guidance issued pursuant to 21st Century Cures Act
## FDA Guidance: Using Electronic Health Records in clinical investigations

<table>
<thead>
<tr>
<th>COVERED</th>
<th>NOT COVERED</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prospective clinical investigations of drugs, biologics and medical</td>
<td>• Post-marketing safety studies</td>
</tr>
<tr>
<td>devices</td>
<td>• Using EHR to evaluate feasibility or for recruitment</td>
</tr>
<tr>
<td>• Foreign clinical studies not conducted under an investigational new</td>
<td>• Data collected for registries and natural history studies</td>
</tr>
<tr>
<td>drug application (IND) or investigational device exception (IDE)</td>
<td></td>
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</tbody>
</table>
## FDA Guidance: Using Electronic Health Records in clinical investigations (Best Practices)

### SECURITY OF EHR SYSTEM

- Policies for use of EHR at site in place
- Appropriate security measures employed to protect study data
- Access limited to authorized users
- Authors of records are identifiable
- Audit trails available to track changes to data
- Records retained for FDA
- FDA encourages use of systems certified in ONC Health IT Program

### DATA

- EHR is data originator
- After data entered into eCRF, only investigator or delegated study personnel can modify
- Audit trail of changes
- eCRF signed

### INFORMED CONSENT

- Identify parties who can access patient’s data

### RETENTION/INSPECTION

- Retain EHR records
- Drugs: 2 years after application approved or after investigation discontinued; 21 CFR 312
- Devices: 2 years after investigation end or records not otherwise needed; 21 CFR 812
- Make available to FDA in EHR or certified copies

### UNBLINDING

- Consider whether interoperable EHR and EDC has potential to unblind treatment allocation
Thank You
Evaluating Real World Evidence

David Martin, MD, MPH
Associate Director for Real World Evidence Analytics
Office of Medical Policy
FDA Center for Drug Evaluation and Research

FDLI
May 2, 2019
Disclosure and Disclaimer

- David Martin received funding from the Patient Centered Outcomes Research Trust Fund to develop the FDA My Studies Mobile App.
- No conflicts of interest to disclose.
- The views expressed are those of the author and should not be construed as FDA’s views or policies.
- The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.
Scope of RWE Program Under 21st Century Cures Act

Under the Cures Act, FDA’s RWE Program must evaluate the potential use of RWD to generate RWE of product effectiveness to help support approval of new indications for drugs approved under FD&C Act Section 505(c) or to help to support or satisfy postapproval study requirements. FDA’s RWE Program will also apply to biological products licensed under section 351 of the Public Health Service Act.
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff


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

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-9507 or CDRH at cdrhhelp@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-888-475-4700 or 240-845-6016.

• FDA guidance document which describes the potential use of Real World Evidence throughout the total product lifecycle for devices
  • Draft issued prior to 21st Century Cures Act

• Definitions of Real World Data and Real World Evidence are harmonized with the FDA Framework

• CDRH, CBER, and CDER are coordinating as the 21st CC RWE program proceeds
Definitions

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.

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.
Outlines FDA’s plan to implement the RWE program

Focus on adding or modifying an indication, comparative effectiveness, and comparative safety

Multifaceted program
  – Internal processes
  – Guidance development
  – Stakeholder engagement
  – Demonstration projects

Comment period closed April 16, 2019
RWE Use is Not New to FDA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Status</th>
<th>Data</th>
</tr>
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</table>
| **Lutathera** *(lutetium 177 dotate)* | GEP-NET Gastropanc. Neuroendo tumors             | Approved 2017 | - Open label clinical trial  
- Analysis of 360 patients in an investigator sponsored, open-label, single-arm, single institution study 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 group weighted analysis of patient level data on chart review of 694 patients at EU and US study sites* |
| **Carbaglu** *(carbagluconic acid)* | Treatment of NAGS deficiency                     | Approved 2010 | - Retrospective, non-random, un-blinded case series of 23 patients compared to historical control group |
| **Myzyrne** *(sphingomyelinase)* | 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 |

*https://www.nature.com/bcj/journal/v6/n9/full/bcj201684a.html*
310.8 million cumulative patient identifiers between 2000 and 2018

Of members with medical and drug coverage, there are:
- 70.1 million members are currently accruing new data
- 11.7 billion pharmacy dispensings
- 15.0 billion unique medical encounters
- 48.5 million members with at least one laboratory test result
- 668 million person-years of data
Benchmark

• Substantial evidence standard unchanged
  – Goal is to distinguish the effect of the drug from other influences such as spontaneous change in disease course, placebo effect, or bias
  – Common practices:
    • Probabilistic control of confounding through randomization
    • Blinding
    • Controlled/Standardized outcome assessment
    • Adjudication criteria
    • Audits
Framework for Evaluating RWD/RWE for Use in Regulatory Decisions

Considerations

• Whether the RWD are fit for use

• Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question

• Whether the study conduct meets FDA regulatory requirements
Three Opportunities with Demonstration Projects

• **Expand the quantity, quality, and diversity of RWD**
  – Broaden the range of RCT endpoints that can be captured
  – Increase statistical power
  – Reduce the number of unmeasured confounders
  – Engage with patients through mobile technology

• **Gain practical experience with “Real World” randomized designs and registries**
  – Inform regulatory considerations

• **Assess the performance of non-interventional designs**
  – “Pressure test” widely accepted designs
  – Consider new paradigms
## Endpoints in FDA Registrational trials
### 2007-2015

<table>
<thead>
<tr>
<th>Type of Endpoint</th>
<th>% of NDA</th>
<th>Examples of Endpoints Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry data</td>
<td>11</td>
<td>HBA1c, pregnancy test, GFR</td>
</tr>
<tr>
<td>Hematology</td>
<td>6</td>
<td>Severe neutropenia, Apheresis yield &gt; 5 million CD34+ cells/kg</td>
</tr>
<tr>
<td>Pathology</td>
<td>2</td>
<td>Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells</td>
</tr>
<tr>
<td>Microbiology</td>
<td>6</td>
<td>Sustained virological response, plasma viral load, conversion to negative sputum</td>
</tr>
<tr>
<td>Imaging +/- (survival, clinical signs)</td>
<td>17</td>
<td>Bone mineral density; vertebral fractures, spleen volume, progression free survival</td>
</tr>
<tr>
<td>Physiological/functional measurement</td>
<td>9</td>
<td>6 minute walk, normal sinus rhythm, FEV1, sleep studies</td>
</tr>
<tr>
<td>Clinical event /clinical sign</td>
<td>19</td>
<td>Death, hospitalization, MACE, MS relapse, Lice free head</td>
</tr>
<tr>
<td>CRO/PRO</td>
<td>30</td>
<td>Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score</td>
</tr>
</tbody>
</table>
EHRs: Potential and Challenge

Potential for a more complete and granular clinical picture

Challenges include:

– Data in pathology/radiology and clinical notes are often unstructured (80%) and images might be necessary

– Structured data ≠ Standardized data

– Typing ≠ consistency/complete documentation

– Clinical outcome measures for drug approvals may not be used or consistently recorded in practice
FDA My Studies

- **Mobile App**
  - Standard frameworks - ResearchKit (iOS), ResearchStack (Android)
  - Gateway capability

- **Web-based configuration portal**

- **Secure Storage Environment**
  - 21 CFR Part 11 and FISMA complaint
  - Partitioned for distributed research

- One private sector research organization has successfully re-purposed the app in a test environment.

- App integral to two new demonstration projects

- FDA SBIA webinar scheduled for May 9
FDA MyStudies: now open source

- https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625228.htm
- https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm
Assessment of Non-Interventional Designs

• High throughput replication of phase 3 & 4 RCTs over three years to provide empirical evidence base to inform the potential level of confidence in high quality non-interventional designs

• FDA reviewers and researchers from the BWH/HMS Division of Pharmacoepidemiology jointly
  – Selected 40 trials in which claims data are sufficiently fit for purpose in a research environment
    • Oral hypoglycemic, novel oral anticoagulant, antiplatelet, antihypertensive, anti-osteoporosis, asthma, COPD, heart failure, anti-arrhythmic, and lipid lowering medications
  – Concurred with pre-specified measures of agreement
  – Reviewed an implementation process

• Goal: 30 attempted replications completed by March 2020
Implementation Process

1. Prospective engagement with FDA during protocol development and initial feasibility and power calculations
2. FDA review of final definitions of cohort identification, exposure, outcome, and covariates
3. While blind to differential outcome, final power analyses and covariate balance checks are completed – joint go/no go decision
4. Study protocol registered on ClinicalTrials.gov
5. Analyze outcome data and calculate effect measures
6. Document findings
7. Apply prespecified measures of agreement
8. Audit trail visible to FDA throughout the process – FDA sub-team may at its option engage in additional post-hoc sensitivity analyses for training purposes
RELIANCE trial

- **RofLumilast or Azithromycin to prevent COPD Exacerbations**
  - Randomized “real world” trial; 1,600 adults in each arm
  - **Azithromycin** - macrolide with anti-inflammatory properties
  - **Roflumilast** - noncorticosteroid anti-inflammatory; phosphodiesterase type 4 inhibitor
  - Both guideline recommended but Roflumilast is FDA approved for this indication

- **Primary outcomes**
  - All cause hospitalization
  - All cause mortality

- **Follow-up**
  - 6-36 months, no visits, call center, Patient Portal, Site EMR
  - CMS linkage through FDA-Catalyst for outcomes and exposures
    - Enrollment files: all cause mortality
    - Inpatient claims files: all cause hospitalization for fee for service
    - Part C (Medicare Managed Care): new data source – will request if feasible
    - Part D: medication dispensing

- **FDA-Catalyst privacy-sparing distributed regression validation activity**
Foundation for use of Electronic Data

Guidance for Industry
Electronic Source Data in Clinical Investigations

Use of Electronic Informed Consent
Questions and Answers
Guidance for Institutional Review Boards, Investigators, and Sponsors

Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)

September 2013
Prepared

U.S. Department of Health and Human Services
Office for Human Research Protection (OHRP)

Draft Guidance

July 2013
Prepared

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)

June 2017
Prepared
Themes from stakeholder comments

- Translating regulatory endpoints in real world data sources
- Real World Data submission
- Data Quality Assessment
- Real World study designs
Conclusion

- Framework serves as a roadmap for more fully incorporating RWD and RWE into the regulatory paradigm
- RWE remains a top FDA priority and it is relevant to other agencies
- FDA is committed to understanding its full potential
- Multi-stakeholder effort and collaborations will benefit everyone
Use of Real-world Evidence (RWE) for Regulatory Decision-making: An Industry Perspective

Kara Kilpatrick, MPH
Center for Observational Research, Amgen, Inc.
Why should RWE constitute an integral part of the drug development and regulatory cycle?

“As advances are being made in the electronic capture of clinical and patient-reported data, the methods for linking such data to administrative claims and other data types, and the study designs and analytic techniques used to generate evidence, new insights from patient experiences are supporting an array of health care decisions that enable improvement in the quality, safety, and value of care.”

Duke Margolis Center for Health Policy

https://healthpolicy.duke.edu/sites/default/files/atoms/files/dg_1_15_16_0.pdf

Ideal incorporation of RWE could facilitate faster, more relevant, and more targeted benefit-risk decision-making.
The evolving regulatory and broader external environment

FDA Expands Real-World Evidence Partnership with Brigham and Women's Hospital and Aetion

RCT DUPLICATE adds new studies to inform FDA - the first to use real-world evidence to predict treatment safety and efficacy

AETION.

TriNetX raises $40M Series D for real-world evidence research platform

The funding will fuel the company's international expansion as well as development of its analytics platform.

By Dave Muoio (content/dave-muoio) | March 14, 2019

Worldwide Outlook on the Real World Evidence (RWE) Solutions Market 2019-2024 - Emerging Roles of Wearable Devices & AI in RWE Presents Ample Opportunities

NEWS PROVIDED BY Research and Markets → Apr 03, 2019, 11:45 ET

Flatiron, Foundation Medicine study points to real-world data’s utility in oncology

Data published in JAMA on lung cancer patients treated with immunotherapy drugs, gleaned from EHRs and genomic sequencing, backs up clinical trial data and validates clinico-genomic database, the companies said.

By ALARIC DIEMENT | Post a comment / Apr 9, 2019 at 3:00 PM

2019 FDLI Annual Conference | Access materials at fdli.org/annual2019
Where is the opportunity?

Patients

- Unmet need / Disease burden
- Safety
- Effectiveness
- Clinical trial optimization
- Personalized medicine

“As the breadth and reliability of RWE increases, so do the opportunities for FDA to make use of this information.”

Leveraging RWE to obtain new product approval for blinatumomab

Complete remission (and median overall survival) in the historical comparator group was confirmed by the blinatumomab phase 3 clinical trial standard of care (SOC) arm

Success of a RWE use case will depend upon scientific credibility of the study design and if data are fit for regulatory purposes.

Regulatory Context
What specific decision is being considered?
- New indication
- Labeling revision
- Safety revision
- Benefit-risk profile

Clinical Context
Can the clinical question be reliably addressed with RWE?
- Prevalence of the disease
- Clinical equipoise
- Expected treatment effect size

Data Considerations
Are the RWD sources of sufficient quality?
- Minimal missing data
- Sufficient data reliability and validity
- Established data quality assurance procedures

Methods Considerations
Are the methodological approaches of sufficient rigor?
- Interventional or observational
- Prospective, retrospective, or hybrid
- Appropriate analytic approach
- Established credibility (protocol developed and replication of results achieved and planned)

Although importance of RWE is appreciated by industry, barriers to its use to inform regulatory decisions remain

- **Knowledge, awareness and certainty**
  - Lack of understanding of observational research methodology
  - Mistrust of data captured outside of RCTs
  - Regulatory guidance for use of RWE evolving

- **Talent and capabilities**
  - Product development organizations have been optimized to deliver RCTs
  - Lack of experience across organizations on impactful use of RWE

- **Systems and processes**
  - Lack of ‘fit for purpose’ processes for observational research
  - Organizational structures must facilitate effective interaction between individuals with RWE expertise and team leaders (decision makers)

The visible support of senior leaders across the health care ecosystem will facilitate and de-risk appropriate use of RWE
To advance these efforts, collaboration and transparency are critical.

Academic, industry, and regulatory scientists