Where Do We Stand With Real-World Evidence: FDA Requirements, and Emerging Implications for Managed Care

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Limitations…Trial Sample May Not be Representative

“A clinical trial is the best way to assess whether an intervention works, but arguably the worst way to assess...who will benefit”

Evidence-Based Medicine, Heterogeneity of Treatment Effects, and the Trouble with Averages
From Kravitz et al. Milbank Quarterly. 2004;82:661-687
So, What is Real World Evidence?

**Real world data** = data used for decision-making that are not collected in conventional randomized controlled trials (RCTs), includes clinical and economic data reported by patient registries, claims databases, electronic health records, patient-reported outcomes, and literature review.

**Real-world evidence** = organized information informing a conclusion or judgment based on real-world data.

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So, How Can Real World Evidence Be Used?

**Global RWE Uses**
- Comparative effectiveness between treatment options
- Post-marketing surveillance to confirm RCT outcomes
- Education about treatment benefits & long term safety
- Establishing economic value of treatments
- Informing clinical trial design

<table>
<thead>
<tr>
<th>Likely RWE Users</th>
<th>Common Uses</th>
</tr>
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<tbody>
<tr>
<td>Physicians</td>
<td>Tailoring treatment selection to patients</td>
</tr>
<tr>
<td>Guideline Org’s</td>
<td>Evaluating/updating recommendations</td>
</tr>
<tr>
<td>Hospitals</td>
<td>Tailoring resource allocation and access</td>
</tr>
<tr>
<td>Regulators</td>
<td>Approval and monitoring treatments</td>
</tr>
<tr>
<td>IRB / Researchers</td>
<td>Evaluating and protecting patients in clinical trials</td>
</tr>
<tr>
<td>Managed Care</td>
<td>Approving and monitoring reimbursement decisions</td>
</tr>
<tr>
<td>Manufacturers</td>
<td>Evaluating drug development decisions</td>
</tr>
</tbody>
</table>

Source: See notes section
But, Why Should We Care?

**NUMEROUS USE CASES IMPACTING COST + QUALITY**

- Drive quality improvement programs
- Identify individual care gaps
- Stratify the population by level of risk
- Measure long-term outcomes
- Assess population health needs

**SAVINGS FROM EFFECTIVE HEALTHCARE DATA USE**

- Research suggests that through increased and improved use of data analytics payors and providers can reduce cost by $300B

20% Possible decrease in patient mortality through streaming analytics

Source: Gartner Research, McKinsey & Co., SHYFT analysis

RWE Availability Has Hit A Tipping Point in US

**Observational Clinical Studies (by data source)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Claims</th>
<th>EMR</th>
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<tbody>
<tr>
<td>1998</td>
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<tr>
<td>2014</td>
<td>380</td>
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</tr>
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- **CAGR 32%**
- **21%**

**Insights:**

- Publications on observational and real-world evidence studies have been increasing at an annual rate 3 – 5 times faster than RCT and other clinical trials
- These studies make up nearly 20% of all clinical trial publications in 2014

Source: PubMed, SHYFT analysis
Manufacturers May Be Required to Assess And Integrate RWE Prior to Launch

21st Century Cures Act creates mandate for RWE, PRO, and other non-RCT “clinical experience”. FDA must create and issue guidance for RWE use in support of new indication submissions and post-approval monitoring.

We expect real-world evidence will become a standard part of drug submissions to the FDA.

Dr. Califf, FDA @ OHDSI 2015

Managed Care Dilemmas Associated with RWE

- How can we best ensure the right product is targeted to the right patients?
- Which technologies & procedures are better than others? What are the differentiating characteristics among them?
- Is the coding system in the US sufficiently granular to track & alter management strategies?
- What are the right incentives & levers to support innovation and appropriate access, while limiting marginal or ineffective technologies?
- How do we manage the array of technologies that end up being “additive” in terms of budget impact when things don’t “fall off the conveyor belt”?
- Do regulations or policies prevent us from doing the “prudent thing”?

Source: FDA, Congress.gov, DOE.gov, SHYFT analysis
US Managed Care and RWE Use

- **Q29** Please indicate the areas that you currently use RWE in product evaluations.

![Bar chart showing usage of RWE in various areas](chart1.png)

Source: NAMCP-GBEMTI Survey, SHYFT analysis

US Managed Care and Future RWE Requirements

- **Q33** Which one of the following types of RWE will you require in the next 3-5 years from technology manufacturers?

![Bar chart showing future RWE requirements](chart2.png)

Source: NAMCP-GBEMTI Survey, SHYFT analysis
Managed Care RWE Case Studies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Situation</th>
<th>Role of RWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xalkori</td>
<td>Accelerated approval based on strong ORR in phase 2 data with requirement for phase 3</td>
<td>Reevaluation of access / confirmation of outcomes</td>
</tr>
<tr>
<td>Immuno-oncologics</td>
<td>Breakthrough designation, with potential for very long term durable response follow-up</td>
<td>Long-term follow-up that is not feasible or cost-effective in RCT</td>
</tr>
</tbody>
</table>

Source: SHYFT analysis, IMS Consulting Analysis 2013

Key Challenges on the Path Forward for RWE

- Improving Data Capture Quality
- Analysis Capability and Data Access Bottlenecks
- Standardization (Data Architecture and Clinical Definitions)
- RWE Misapplication (When is RWE the right tool)
Challenge: Data Capture

- **RWE Wild West**: What good looks like is not standardized yet
- **Need to be Data Source Agnostic**: (“no single version of the truth”)
- **New Data Capture Technologies** (and approaches) rapidly emerging

### Orthopedics Case Study

- Orthopedics represent a significant & growing cost driver in patient care...while addressing key patient needs
- **Challenge**: Given lack of unique identifiers for individual devices which makes it practically impossible to understand how & to what extent some implants offer better value, durability, and safety records.
- Multiple orthopedic registries, both domestic & international (e.g., GLORY) have been established to characterize a variety of efficacy & safety metrics for implanted knees & hips – to address uncertainties
- **Registries provide a RWE solution...BUT** remains uncertain how & to what extent expectations for (a) new implant evidence will evolve and (b) how this information may influence clinical development & management going forward
- **Medical Device Unique Identifiers could overcome challenges...BUT** implementation will be a starting point and require long-term tracking to gather additional necessary information.
Challenge: Capability & Data Access Bottlenecks

**Situation**
- Top 10 Pharma had made a significant global investment in RWE
- Access to 10+ claims and EMR data sources
- Cross-functional use between Epidemiology, HEOR, Market Access, R&D, and Marketing

**Complication**
- RWE data sources were being underutilized due to a lack of staff with necessary programming and statistical capabilities

**Solution**
- Development of analytics platforms that can guide end-users without programming knowledge
  - Navigating data sources and coding vocabularies
  - Defining patient cohorts and outcomes
  - Assist with selection of appropriate analyses

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Challenge: Standardization

**Vocabularies**
- ICD-9, ICD-10
- CPT, HCPCS
- LOINC, SNOMED CT
- MedDRA
- FDA

**Data Models**
- FDA
- Mini-Sentinel
- OHDSI
- pcornet
- ISPOR
- PubMed

**Clinical Definitions**
- PheKB

**Takeaways:**
The push-pull of being able to define every potential medical scenario is giving rise to counterbalancing efforts to develop common models and repositories to drive standardization across technology platforms and research (especially publications)
Challenge: Standardization Risk

![How Standards Proliferate](source: XKCD.com)

Challenge: When/What Type of RWE is Right?

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Consideration</th>
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</table>
| Retrospective Database Studies (EMRs, insurance claims) | • Able to assess extremely large populations  
• Quick and relatively inexpensive  
• Good for assessing rare outcomes and long latencies.  
• Strong availability of US Claims data. Increasing availability of US electronic health data |
| Hybrid Studies                            | • Augment routine data with new data solicited from healthcare providers and patients                                                    |
| Registries and Prospective Observational Cohort Studies | • Able to assess extremely large populations  
• More expensive than database studies although less expensive than RCT  
• May form a backbone for country specific sub studies                           |
Challenge: When/What Type of RWE is Right?

- RCTs remain the gold standard where intervention is necessary
- Real world data offers many supplementary benefits
  - Effectiveness vs. efficacy
  - Comparative effectiveness for multiple interventions
  - Long term benefits and safety tracking
  - Demographic and geographic diversity
  - Broader range of interventions such as different doses and regimens
  - Ability to track adherence/compliance and resulting resource use implications
- Despite statistical adjustment techniques, inherent selection biases remain in RWE that don’t meet the same level of stringency and rigor as RCTs

Source: ISPOR RWE Working Group

Summary From Today

- Early days for longitudinal big patient data
- Push/pull of need to know vs. feasibility (gaps in data, standardization problems)
- Push/pull in ask of data vs. actual use
  - Limitations on what can be collected and how it can be used
  - Disconnect between regulatory approaches requiring liaising with experts across stakeholders and across regional/national levels
- System infrastructures and incentives have not changed enough yet in response (embracing evidence as continuum)
- There is tremendous value contained in RWE and companies that can rapidly and accurately process RWE will rise to the top
Where Do We Go From Here?

• Need for modernization of statutes
  – Ease of access between data sets
  – Interchangeability and aggregation of data sets
  – CED updates and mandates … again
  – Healthcare exchanges
• Improve data capture “infrastructure”
  – Continue advancing data capture approaches (e.g., wearables / digestables, genomics, PROs, etc.)
  – Need to streamline ease of coding
• Partnerships between multiple stakeholders