RWE for regulatory and HTA decision-making: learning by doing

Ashley Jaksa, MPH
Thursday December 10, 2020
Crosstalks Online Workshop
At Aetion, I lead engagements with HTA and Regulatory bodies to assist in setting standards around RWE generation and use in decision-making.

I work with biopharma customers to develop RWE that meets the needs of regulators and HTAs.

Previously, lead Analytical Services at Context Matters, where I consulted with biopharma on designing and executing HTA focused analysis.

Previously worked for CVS Health, a leading U.S. PBM and Specialty Pharmacy.

MPH from Yale University and BA from University of Michigan.
Aetion Evidence Platform is scientifically validated software for generating real-world evidence at scale.
OUR NORTH STAR
A world in which we know what health treatments work, for whom, and what we should pay for them.

OUR MISSION
To power critical decisions in health care with data science-driven technology.
Today’s objectives

1. Status of RWE guidance and standards
   - Current status of regulator and HTA RWE standards and recommendations
   - Where further work is needed

2. ‘Learn by doing’ approach
   - What can we learn from historical RWE use and demonstration projects
Sync on definitions

Real-world data (RWD)
Data relating to patient health status and/or the delivery of health care routinely collected from electronic health records (EHRs), claims, registries, PROs and devices, etc.

Real-world evidence (RWE)
Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Source: FDA.gov
What’s so compelling about real-world evidence?

→ RWE provides us the opportunity to ask more questions, understand broader populations, and generate more evidence than we could feasibly do with clinical trials.
Status of RWE guidance and standards
Framework: The landscape of RWE recommendations and guidance

**COMMITMENT TO USE RWE**
- Regulatory
- HTA
- Payers

**BUILDING BLOCKS OF RWE: FRAGMENTED POSITION PIECES & RECOMMENDATIONS**
- When can RWE be used?
- Role of stakeholders
- Role of Patients and Caregivers
- Demonstration projects

**ANALYTIC METHODS**
- Study design: Fit-for-purpose design
- Data source: Fit-for-purpose data
- Protocol development
- Protocol evaluation

**REPORT DEVELOPMENT**
- Transparency & Reproducibility: Report development

**COMPREHENSIVE GUIDANCE**
- Final report evaluation

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Moving from fragmented recommendations to comprehensive guidance

**COMMITMENT TO USE RWE**

- **Regulatory**
  - FDA-RWE Framework;
  - Health Canada-Optimizing RWE in Regulatory Decisions;
  - EU Big Data Task Force

- **HTA**
  - ICER 2020–2023 Value Framework; NICE Statement of Intent; INESSS

- **Payers**
  - NHC- Patient Perspectives on RWE
  - FOCR - Framework for RW Endpoints

**BUILDING BLOCKS OF RWE: FRAGMENTED POSITION PIECES & RECOMMENDATIONS**

**When can RWE be used?**
- NICE DSU Report; CADTH-Elements of RWE Quality; ICER-RWE Coverage Decisions; EUnetHTA JA3 WPS; RWE4Decision; ISPOR - Using RWD for coverage & payment decisions; GetReal WP3; Duke – A Framework for Regulatory Use of RWE

**Role of stakeholders**
- ICER-RWE Coverage Decisions; HTAi, RWE4Decision;

**Role of Patients and Caregivers**
- RWE4Decision; NHC- Patient Perspectives on RWE; FOCA - Framework for RW Endpoints

**Demonstration projects**
- RCT DUPLICATE; REPEAT; ICER 24-month pilots; ICER SCD;
- TLV Pilots; FDA INFORMED Collaborations; Evidence Accelerator

**Analytic methods**
- Fit-for-purpose methods
  - Schneeweiss et. al. HDPS; Schneeweiss et. al. Sensitivity Analysis; NICE TSD17, ISPOR good practices; Franklin et al. Assessment of Confounders; EMA/HMA - Data Analytics

**Data source**
- Fit-for-purpose data
  - EMA/HMA-Observational Data; FDA - Medical Devices; CADTH-Elements of RWE Quality; Duke-Fitness for Use;

**Data quality**
- EMA; FDA - EHR data; MHRA -Data integrity and compliance; CADTH; EUnetHTA Request CanIValue- Provincial Data Assets; EMA - registry data

**Protocol development**
- FDA; EMA PASS; AIFA Study Requirements; CADTH; ISPOR-ICPE Task Force; AHRQ; PCORI; ISPE GPP; ENCePP; Franklin et. al;

**Protocol evaluation**
- FDA-ECA;
- EMA-ECA;
- GetReal PCTs;
- ISPOR good practices; FOCR - ECAS;
- Gatto et. al. SPACE; MHRA RWD based Trials

**Study design**
- Fit-for-purpose design
  - FDA-ECAs; EMA-ECAs; GetReal PCTs; ISPOR good practices; FOCR - ECAS;
  - Hernan et. al. Target trial;
  - Gatto et. al. SPACE; MHRA RWD based Trials

**COMPREHENSIVE GUIDANCE**

- **Final report evaluation**
  - NICE QUEENS checklist;
  - GRACE;
  - ISPOR checklist;
  - ISPOR-NPC-AMCP;
  - Cochrane ROBINS-I;

- **Regulatory**
  - FDA RWE Guidance (expected 2021)

- **HTA**
  - IQWIG

- **Payers**
  - RWE Transparency Initiative;
**STUDY DESIGN**

**Use of External Control Arms**

**FDA and EMA** have published guidelines on choosing control groups and what conditions are necessary for persuasive ECAs:

- Well defined natural history
- Objective endpoint
- Patient comparability
- Good covariate measurement
- Large effect size

**Friends of Cancer Research** (FOCR) published white paper on potential bias with ECA’s and analytical methods to mitigate bias.

Despite increased use of single-arm trials and ECAs in HTA submissions, HTAs recommendations on use of ECAs has been limited.
High level of agreement from all stakeholders on the importance of matching the data to the research question, however only small handful of groups have defined “fit-for-purpose” and differences emerge.

### Comparison of fit–for–purpose criteria

<table>
<thead>
<tr>
<th>Elements of FFP</th>
<th>Duke Margolis</th>
<th>FDA Med Devices</th>
<th>EMA Observational Data publication</th>
<th>CADTH/HC</th>
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</thead>
<tbody>
<tr>
<td><strong>Data relevancy</strong></td>
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<tr>
<td>Availability of key data elements: exposure, outcome, covariates, patient-level linking</td>
<td>✔</td>
<td>✔</td>
<td>Missing covariate availability</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Representativeness</strong></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Sufficient subjects</strong></td>
<td>✔</td>
<td>✔</td>
<td>in context of size of data source</td>
<td>✔</td>
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<tr>
<td><strong>Longitudinality</strong></td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
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<tr>
<td><strong>Data quality</strong></td>
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<tr>
<td>Accuracy: validity, conformance, plausibility, completeness</td>
<td>✔</td>
<td>✔</td>
<td>Missing validity of key elements, plausibility</td>
<td>✔</td>
</tr>
<tr>
<td>Missing conformance and plausibility</td>
<td>✔</td>
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<td>✔</td>
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<tr>
<td>Validity was for dataset not elements</td>
<td>✔</td>
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<td><strong>Provenance</strong></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td><strong>Transparency in data processing</strong></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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</table>
Make progress toward comprehensive guidance – learn by doing

Lessons from historical use of RWE
Lessons from demonstration projects
External Control Arms: strategy to understand the counterfactual experience in single-arm studies

IN FDA APPROVALS SINCE 1995

13% ▲
Increase in the proportion of indications supported by only single-arm trials (Zhang 2020)

Study presented at ISPOR EU 2020

Objective
Compared regulatory and HTA agencies’ evaluations of oncology ECAs to determine influential factors.

Methods
FDA multi-disciplinary reviews for oncology submissions from 2014–2019 were screened. We selected four drug approvals that included an ECA to support efficacy claims. Regulatory (FDA, EMA, PMDA, HC) and HTA (pCODR, NICE, G-BA, HAS, and PBAC) submissions for these four drugs were evaluated.

Qualitative assessment of:
- Common critiques of the ECA across decision-makers
- Influence of the ECA on decision
### Blinatumomab Ph- ALL: Summary of ECA critiques

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<tr>
<td>SoC inconsistent over time</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>ECA non-generalizable to clinical practice</td>
<td>Large percentages of patients in ECA had comparable efficacy endpoints</td>
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<tr>
<td>Unmeasured confounding</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Unadjusted confounders</td>
<td>FDA noted that key differences (e.g., age, LoT) were accounted for; HAS and pCODR had criticisms</td>
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<tr>
<td>Naive comparison</td>
<td>NICE mentioned that arms are balanced</td>
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<tr>
<td>Selection bias</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Incorrect adjusting methods</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Inconsistent outcomes definitions</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Data loss / Insufficiency</td>
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<tr>
<td><strong>Agency decision</strong></td>
<td>Accelerated approval</td>
<td>Accelerated approval</td>
<td>Recommended with restrictions (only if discount provided)</td>
<td>Non-quant. additional benefit</td>
<td>Recommended for 2L: ASMR III, SMR Substantial</td>
<td>Accelerated approval</td>
<td>Recommended with restrictions for # of cycles</td>
<td>Recommended with # cycle restrictions (after resubmissions)</td>
</tr>
<tr>
<td><strong>ECA influence</strong></td>
<td>HIGH</td>
<td>MED-HIGH</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>HIGH</td>
<td>LOW</td>
<td>LOW</td>
</tr>
</tbody>
</table>

✓ Critique was mentioned by the regulatory or HTA body.
RWE to support ICER assessment in Sickle Cell Disease

The role of real-world evidence in value assessment

Improving granularity and timeliness of inputs
- Incidence of known comorbidities (acute and chronic) for SCD stratified by age groups
- Real-world costs

Testing assumptions
- Understanding if optimal usual care observed in RCTs reflects real-world experience

Sanity checking other inputs
- Patient survey on societal effects of SCD was considered representative because patient characteristics matched RWE

Changing structure of cost-effectiveness model
- Facilitated more complex model
- Incidence of chronic conditions by all age strata used to understand how chronic conditions accumulate over patients’ lifetime
RCT DUPLICATE, an FDA demonstration project

OBJECTIVES

**Identify indications and outcomes** where RWE can support regulatory decision-making

**Confirm the design and analytic choices** that make RWE studies interpretable for decision-making (causal conclusions)

**Develop a process** that ensures transparency and reproducibility of data and findings

PROCESS

Illustrative; based on 30 completed studies

**Stage 1:** Searched 1000+ RCTs to identify 30 completed phase III/IV RCTs used for FDA approval

**Stage 2:** Use 3 RWD sources (2 commercial + fee-for-service Medicare) to replicate RCT results, using Aetion Evidence Platform

**Stage 3:** Collect results, compare with reported RCT results, assess reasons for concordance or divergence, work with FDA to produce empirically-based regulatory guidance

https://www.rctduplicate.org/
Pilot RWD prediction: CAROLINA Trial

The CAROLINA trial evaluated the safety of Tradjenta (linagliptin) compared with sulfonylurea glimepiride in patients with type 2 diabetes and increased CV risk or established CV disease.

Following the DUPLICATE framework, Harvard investigators aimed to predict the CAROLINA trial results using RWE.

The RWE study yielded equivalent results as the multi-year RCT.

<table>
<thead>
<tr>
<th>CAROLINA trial</th>
<th>RWE analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel group RCT</td>
<td>Multi-database RWD study</td>
</tr>
<tr>
<td>6K patients</td>
<td>48K patients</td>
</tr>
<tr>
<td>8 years</td>
<td>16 weeks</td>
</tr>
<tr>
<td>3P-MACE and hypoglycemia endpoints</td>
<td>3P-MACE and hypoglycemia endpoints</td>
</tr>
<tr>
<td>Read out June 10, 2018 at ADA</td>
<td>Read out June 7, 2018 at ADA</td>
</tr>
</tbody>
</table>
RWE prediction presented with RCT results at ADA

### 3P-MACE*

<table>
<thead>
<tr>
<th>Source: CAROLINA</th>
<th>RWE Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hazard Ratio</strong></td>
<td>Favors linagliptin</td>
</tr>
<tr>
<td><strong>Favors</strong></td>
<td><strong>64</strong> (%)</td>
</tr>
<tr>
<td><strong>Favors</strong> glimepiride</td>
<td><strong>84 (1.05)</strong></td>
</tr>
</tbody>
</table>

### Severe hypoglycemia

<table>
<thead>
<tr>
<th>Source: CAROLINA</th>
<th>RWE Prediction</th>
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<tbody>
<tr>
<td><strong>Hazard Ratio</strong></td>
<td>Favors linagliptin</td>
</tr>
<tr>
<td><strong>Favors</strong></td>
<td><strong>19</strong> (%)</td>
</tr>
<tr>
<td><strong>Favors</strong> glimepiride</td>
<td><strong>91 (1.05)</strong></td>
</tr>
</tbody>
</table>

*3P-MACE = three-point major adverse cardiovascular event

**Source:** As presented at ADA on June 10, 2019 in a session called “The CAROLINA Trial—First Results of the Cardiovascular Outcomes Trial Comparing Linagliptin vs. Glimepiride”, moderated by Drs. Julio Rosenstock and Nikolaus Marx
REPEAT Initiative to develop RWE reporting standards

Powered by Aetion Evidence Platform, conducted by Harvard/BWH, with regulators and HTAs advising

Replicating 150 previously published RWD studies to:

- Measure current state of reproducibility and robustness of RWE studies
- Highlight areas that need improvement
- Propose specific, empirically-based recommendations to improve the conduct and quality of RWE studies

FDA-EMA-PMDA-Industry consortium: Structured Reporting Template + Study Registration

repeatinitiative.org
The RWE field is on a path to comprehensive guidance for when and where RWE can be used in decision-making. However, further progress is needed.

We are learning from:

**Historical uses of RWE**
- What RWE study quality components are critical for success and how agencies differ in their critiques of the evidence
- How can RWE be used in HTA decision-making

**Demonstration projects**
- Duplicating RCTs with RWE is informing where RWE can “get it right”
- What TAs are most relevant for RWE
- What level of transparency is needed to replicate studies and further increase trust in RWE
Thank you

ashley.jaksa@aetion.com
FDA approvals relied on RWE across TAs, especially with infectious disease, oncology, and neuroscience

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Infectious Disease</th>
<th>Oncology</th>
<th>Neuro-science</th>
<th>Endocrinology &amp; Metabolism</th>
<th>Radiology</th>
<th>Hematologic</th>
<th>Cosmetic</th>
<th>Gynecology</th>
<th>Respiratory</th>
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<tbody>
<tr>
<td>Total approvals</td>
<td>8</td>
<td>11</td>
<td>11</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Approvals with RWE study</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>RWE study substantial and/or supportive evidence</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RWE referenced in package insert</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
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Note: Bubble size reflects 2019 FDA approvals. Neurology includes both CNS and Neurodegenerative approvals. Following TAs (each with 1 in-scope approval and 0 RWE submissions in the approval) are excluded from this visual: Dermatology, Gastrointestinal, Inflammation & Immunology, Ophthalmology. Excludes assays, solutions, and blood grouping reagents. Source: Aetion analysis; FDA approval documents.
How do Regulatory and HTA bodies evaluate external control arms?

Objective
Compared regulatory and HTA agencies’ evaluations of oncology ECAs to determine influential factors.

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FDA multi-disciplinary reviews for oncology submissions from 2014-2019 were screened. We selected four drug approvals that included an ECA to support efficacy claims. Regulatory (FDA, EMA, PMDA, HC) and HTA (pCODR, NICE, G-BA, HAS, and PBAC) submissions for these four drugs were evaluated.

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<tbody>
<tr>
<td>avelumab (Bavencio)</td>
<td>mMCC</td>
<td>2017</td>
<td>2017</td>
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<td>2018</td>
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<td>2018</td>
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<tr>
<td>erdafitinib (Balversa)</td>
<td>FGFR2/3+ mUC</td>
<td>2019</td>
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<td>2020</td>
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