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

Ashley Jaksa, MPH
Thursday December 10, 2020
Crosstalks Online Workshop

Ashley Jaksa MPH
VP, Science at Aetion

- 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.

Data science

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

Study design	Fit-for-purpose design	Protocol development	Protocol evaluation
Data source	Fit-for-purpose data	Data quality	
Analytic methods	Fit-for-purpose methods		
Transparency & Reproducibility	Report development		

Final report evaluation

COMPREHENSIVE GUIDANCE

Regulatory

HTA

Payers

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

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 WP5; 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; FOCR - Framework for RW Endpoints

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

Study design

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

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

Protocol evaluation

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 CanREValue-Provincial Data Assets; EMA - registry data

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

Transparency & Reproducibility
Wang et. al. ISPOR-ICPE taskforce; Schneeweiss et. al. Graphical Depiction of Study Design; RWE Transparency Initiative;

Report development
STROBE, RECORD, RECORD-PE

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

COMPREHENSIVE GUIDANCE

Regulatory
FDA RWE Guidance (expected 2021)

HTA
IQWiG

Payers

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.

Regulators have weighed in, but HTA recommendations have been limited.

DATA SOURCE

Fit-for-purpose data

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

Elements of FFP	Duke Margolis	FDA Med Devices	EMA Observational Data publication	CADTH/HC
Data relevancy				
Availability of key data elements: exposure, outcome, covariates, patient-level linking	✔	✔	Missing covariate availability	✔
Representativeness	✔	✔	✔	✔
Sufficient subjects	✔		in context of size of data source	
Longitudinality	✔		✔	
Data quality				
Accuracy: validity, conformance, plausibility, completeness	✔	Missing validity of key elements, plausibility	Missing conformance and plausibility Validity was for dataset not elements	Missing conformance and plausibility
Provenance	✔	✔	✔	✔
Transparency in data processing	✔	✔	✔	✔

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

ECA CRITIQUE CATEGORY	U.S. Reg: FDA	EU Reg: EMA	UK HTA: NICE	Germany HTA: G-BA	France HTA: HAS	Canada Reg: HC	Canada HTA: pCODR	Australia HTA: PBAC
SoC inconsistent over time				✓		✓	✓	✓
ECA non-generalizable to clinical practice	•							
Unmeasured confounding	•		•		✓		✓	
Unadjusted confounders								✓
Naive comparison								
Selection bias						✓	✓	
Incorrect adjusting methods				✓				✓
Inconsistent outcomes definitions					✓	✓		
Data loss / Insufficiency								
Agency decision ▶	Accelerated approval	Accelerated approval	Recommended with restrictions (only if discount provided)	Non-quant. additional benefit	Recommended for 2L: ASMR III, SMR Substantial	Accelerated approval	Recommended with restrictions for # of cycles	Recommended with # cycle restrictions (after resubmissions)
ECA influence ▶	HIGH	MED-HIGH	LOW	LOW	HIGH	LOW	LOW	HIGH

Large percentages of patients in ECA had comparable efficacy endpoints

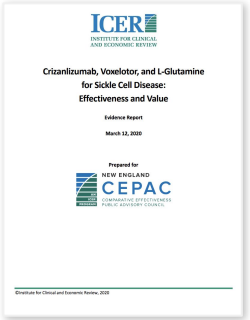
FDA noted that key differences (e.g., age, LoT) were accounted for; HAS and pCODR had criticisms

NICE mentioned that arms are balanced

✓ Critique was mentioned by the regulatory or HTA body.

AETION Daiichi-Sankyo

RWE to support ICER assessment in Sickle Cell Disease


ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value

Evidence Report

March 12, 2020

Prepared for

NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

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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

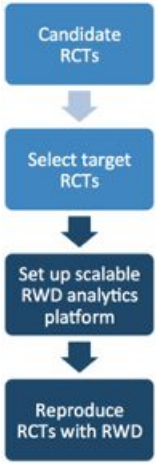
PROCESS

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.

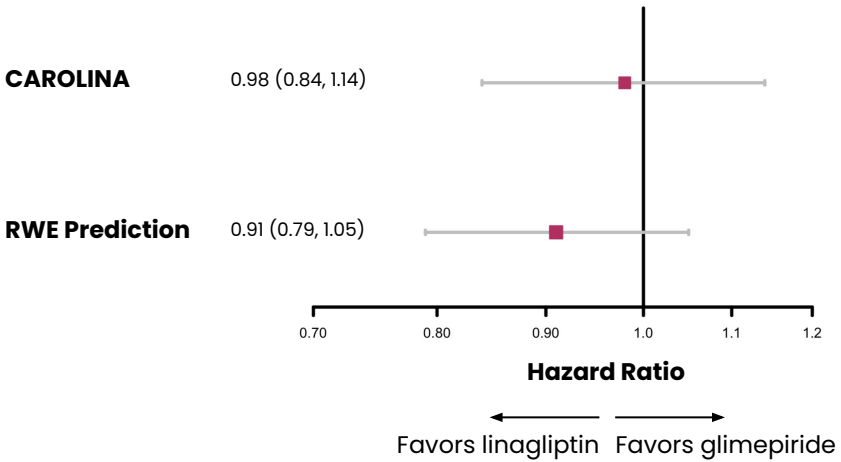
Following the DUPLICATE framework, Harvard investigators aimed to predict the CAROLINA trial results using RWE.

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

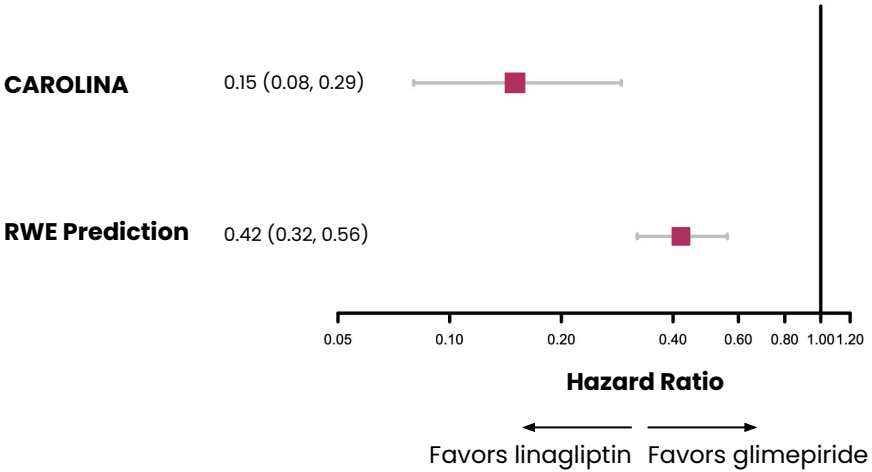
CAROLINA trial	RWE analysis
Parallel group RCT	Multi-database RWD study
6K patients	48K patients
8 years	16 weeks
3P-MACE and hypoglycemia endpoints	3P-MACE and hypoglycemia endpoints
Read out June 10, 2018 at ADA	Read out June 7, 2018 at ADA

RWE prediction presented with RCT results at ADA

3P-MACE*



Severe hypoglycemia



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

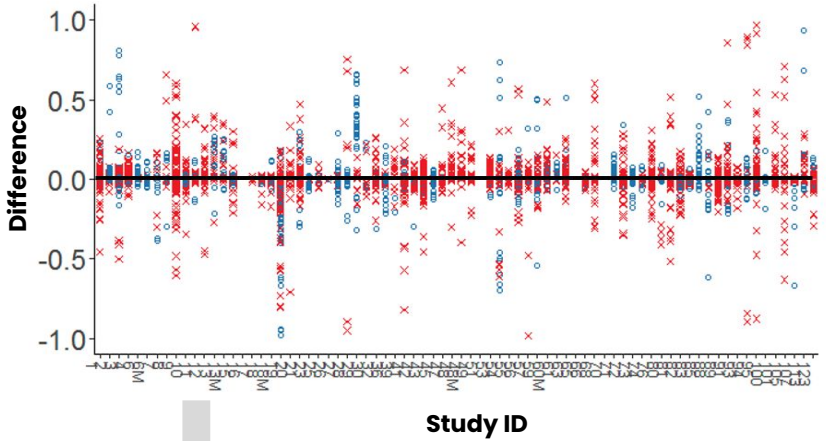
Source: As presented at ADA on June 10, 2019 in a session called "The CAROLINA Trial--First Results of the Cardiovascular Outcomes Trial Comparing Linagliptin vs. Glimepiride", moderated by Drs. Julio Rosenstock and Nikolaus Marx

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA

HARVARD MEDICAL SCHOOL

ljaf

pmda

repeatinitiative.org

The RWE field in 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

Therapeutic area	Infectious Disease	Oncology	Neuro-science	Endocrinology & Metabolism	Radiology	Hematologic	Cosmetic	Gynecology	Respiratory
Total approvals	8	11	11	6	2	4	1	1	1
Approvals with RWE study	6	6	4	3	2	1	1	1	1
RWE study substantial and and/or supportive evidence	5	2	4	2	2	1	0	1	1
RWE referenced in package insert	4	0	4	0	2	0	0	1	0

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.

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.

Drug	Indication	U.S. **Reg: FDA**	EU **Reg: EMA**	Japan **Reg: PMDA**	Canada **Reg: HC**	Canada **HTA: pCODR**	UK **HTA: NICE**	Australia **HTA: PBAC**	Germany **HTA: G-BA**	France **HTA: HAS**
blinatumomab (Blincyto)	(Ph-) R/R BCP ALL	2014	2015	2018	2015	2016	2017	2015	2016	2016
avelumab (Bavencio)	mMCC	2017	2017	2017	2017	2018	2018	2018	2018	2018
blinatumomab (Blincyto)	(MRD+) R/R BCP ALL	2018	2019	2018	2019		2019	2018	2019	
erdafitinib (Balversa)	FGFR2/3+ mUC	2019			2020					

= available

= not available at time of analysis

= only available in Japanese