ISPOR Europe 2023 Educational Symposium

How can we shape HTA with real-world evidence to encourage rare disease innovation?

Monday, 13 November | 15:15 - 16:15

How can RWE support innovative treatments in rare diseases?

Páll Jónsson, Programme Director Data and RWE

ISPOR Europe, 13 November 2023

NICE National Institute for Health and Care Excellence

RWE in rare diseases

- Potentially includes a **larger number** of patients than clinical studies
- Can provide insights into the **natural history** of the disease and **treatment patterns**
- Reflecting **real-world treatment** settings and broader patient populations
- Provide **longitudinal data**, allowing for the assessment of long-term outcomes, treatment effectiveness, and safety over an extended period
- Patient **engagement and empowerment**: Registries often involve patients and patient organisations

- The **quality and completeness** of RWE varies
- RWE may suffer from **selection bias**. Patients participating may not be representative of the overall patient population
- Results from regional RWE may limit **transportability** in the context of decision making in other regions
- Developing and maintaining RWE can be **resource-intensive**, requiring financial investments, technical infrastructure, and dedicated personnel

NICE

RWE at NICE: a range of use cases

Table 1. Influential uses of real-world evidence discussed in appraisals since the publication of NICE's RWE framework in June 2022 (non-exhaustive).

RWE use discussed by NICE committee	Appraisal	Ref.
To demonstrate the generalisability of trail evidence to the UK population for patient characteristics	TA904, TA883	[18,19]
To estimate cost-per-use for diagnostic technology	DG48	[20]
To estimate baseline event rates, in modelling, to which relative effects from trial data are applied	TA897	[21]
To demonstrate an early signal of value for conditional recommendation of a digital therapy	HTE9	[22]
To scrutinize or support extrapolated outcomes in economic modelling	TA883, TA870, TA864, TA801	[19,23–25]
To enable effectiveness, or cost-effectiveness estimation for an important subpopulation	TA880, HST23	[26,27]
To provide reassurance that outcomes observed in key trial data are reflected in routine practice	TA872	[28]
As the main source of comparative effectiveness evidence	HST22, TA855, TA850	[29–31]
To estimate dose in clinical practice, and therefore, costs	TA866, TA808	[32,33]
To estimate rates of complications beyond the duration of available trial data and health state transition probabilities in economic modelling	TA860, TA804	[34,35]
To provide supportive evidence for an uncertain indirect treatment comparison	TA816	[36]

Duffield & Jónsson, JCER, November 2023

My key messages

RWE and clinical studies are not mutually exclusive – they are complementary.

Rare diseases frequently have challenges with data due to sparse patient populations.

Evidence gaps are inevitable, but our committees appreciate efforts to generate good and relevant data that addresses their decision problem.

NICE's RWE Framework encourages best practices for planning, conducting, and reporting RWE studies. The goal is to improve trust in good-quality RWE.

NICE's RWE Framework

RARE DISEASE PROSPECTIVE STUDIES: "*IF YOU'RE GONNA DO IT, DO IT RIGHT*"

1. **Why conduct a study?**
2. **A range of challenges…**
3. **…but a range of opportunities**
4. **Let's talk about governance**
5. **Patient-centricity**

Real world data; not a panacea

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Delta Hat

Real world data (RWD); the good bits

- Can establish exactly what long term outcomes are
  - Example: Multiple Sclerosis – we have a well defined natural history
- Can provide ‘untreated’ cohorts for comparing uncontrolled studies to (or even controlled studies)
  - Example: So many!
- Can be used to give contextual evidence that might not be captured in clinical trials
  - Example: Duchenne Muscular Dystrophy & Project HERCULES
- Can provide information that a clinical trial program would never find
  - Example: Rotavirus vaccine & intussusception

Notes:

- I s world data, a few examples from the past 18 m

: A case study in MET exon 14 (METex14) skipping non-small cell lung cancer'.

l control in relapsed/refractory follic

th Multiple Potential Entry Points: A S 060. Available at:

- I'm talking here *mostly* about real world data for use s for regulatory / health technology assessment

So, high-5s all round, and 'go team RWD'?

Well… Real world data really shouldn't be used beyond contextually for large indications

- Areas with strong evidence bases, and efficacious treatments? RWD (used for comparative effectiveness) for a *new* drug isn't adding to the body of knowledge

- (Large) Randomised studies remain central to developing knowledge

- Examples:
  - First line breast cancer, cardiovascular indications
- Rare disease examples:
  - Gaucher's disease, aHUS

- NB: Where can RWD add here? Finding the comparative effectiveness of treatments in use

And… Real world data sometimes just can’t inform

- As basic science advances ‘we’ discover new targets for treatment, when these molecules reach the market, the target might be prognostic, but probably doesn’t feature in historical datasets
  - How do we interpret any comparison to a ‘wildtype’ / unknown population?

- Examples:
  - Dabrafenib (BRAF inhibitor) in melanoma
  - Voretigene neparvovec in RPE65 mediated blindness

May as well keep going… Other times RWD does not / can not exist

- Similar treatment landscapes evolve; once a new therapy has been introduced there is a ‘lag’ before patients have time to:
  1. Receive the new treatment
  2. Fail the therapy
  3. Receive any more treatment(s)
  4. Have their outcomes observed, and recorded
  5. Do this in sufficient numbers to be informative
  6. After which there is then a ‘wait’ for the dataset to be collected, and processed

- If you are a new treatment at the end of recently changed pathway, there simply won’t be (suitable) RWD

- Examples: Where to start?
  - Conceptually simple - post CAR-T
  - Conceptually complex – post ivacaftor in cystic fibrosis

- Similarly, RWD can be hard/prohibitive to get, and if there aren’t existing registries, it’s a long and expensive process
  - If there are no existing datasets, you need to hope someone in clinical development or global HEOR did some good planning!

And one more thing!… Sometimes populations are just too specific

- RWD, generally, has a broad mix of patients
  - Probably not entirely typical, as the recording is an inherently research/academic centre type activity, but even so, fairly broad
  - Trials… are not the same
  - Often with patient level data you can find a similar group
  - Some trial inclusion criteria however, are so hyper-specific that finding data on a similar cohort is questionable – either pathways, or unobservable characteristics will be different

- Example: I went to NEJM, and looked for the most recent Multiple Myeloma study I could find; 'mezigdomide', and pulled in the inclusion criteria:
  - Received at least three previous lines of therapy, including lenalidomide, pomalidomide, a proteasome inhibitor, a glucocorticoid, and an anti-CD38 antibody
  - … "Patients in phase 2… were additionally required to have disease refractory to an immunomodulatory agent (lenalidomide or pomalidomide, or both), a glucocorticoid, a proteasome inhibitor, and an anti-CD38 antibody"
  - ECOG 0 to 2
  - Adequate bone marrow, renal, and cardiac function
  - At the time of enrollment, patients must also have had progression of disease during the 60 days after the final dose of their last antimyeloma therapy

Link to paper: https://www.nejm.org/doi/full/10.1056/NEJMoa2303194

Maybe I should stop there. Sorry for being such a killjoy

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Is **real-world evidence** the solution to **address uncertainty for rare diseases?**

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Past co-lead for WP10 IMPACT-HTA (appraisal framework for rare disease treatments)
DOLON

It's the combination of uncertainty and economics that makes rare diseases so challenging …

Greater **evidence uncertainty**

Limited ability to show added benefit

-50% Less **patients enrolled** in clinical trials[1]

+30% More likely for trials to be **single-armed, open-label,** and/or **non-randomized**[1]
vs. non-rare disease trials

Unknows of the unknows

Complex & limited knowledge

Poor economics & **higher prices**

Recoup of investment from smaller populations

20x 1,000x Smaller **patient numbers**[2]
vs. more prevalent conditions

Risk of failure

2x More likely to fail **clinical development**[3]
vs. more prevalent conditions

-6% Lower **availability/reimbursement rate**[4]
vs. all products in Europe

RWE is part of the solution ... within more flexible value assessment processes

Considered **RWE generation plans**

Addressing the uncertainty that matters

e.g., **"Value-based negotiation framework"** for innovative therapies[5]

Balancing the economics

More flexibility for rare

Flexible evidence interpretation

e.g., **evidence feasibility and reasonableness**[6,7]

Broader value framework

e.g., considers all evidence across all domains in value framework[7]

Thank You

Q&A