# Real-world data as external controls for single-arm trials:

## Role in regulatory and health technology assessments

Jörg Tomeczkowski[1], Giulio Partemio[2], Tom Nijhuis[3], Nicole Kubitz[1], Shane Kavanagh[4]

[1]Janssen-Cilag GmbH, Neuss, Germany; [2]IQVIA Ltd, London, UK; [3]IQVIA BV, Amsterdam, The Netherlands; [4]Janssen Pharmaceutica NV, Beerse, Belgium

## INTRODUCTION

### BACKGROUND:

- For single-arm trials (SATs), external controls (ECs) can be used to generate comparative evidence.[1]
- The use of real-world data (RWD) and real-world evidence by regulatory agencies as ECs has become more common over the past two decades.[2]
- Currently, there is limited understanding on the impact of RWD as ECs for SATs on Health Technology Assessment (HTA) decision making.

### OBJECTIVES:

To evaluate:

i) impact of RWD as ECs for SAT-based HTA decision-making, and
ii) reasons for positive or negative HTA decisions.

## METHODS

Reports on SATs published by 8 HTA agencies between 2015-2020 (G-BA, Germany; HAS, France; NICE, England; AIFA, Italy; AEMPS, Spain; ZIN, Netherlands; CADTH, Canada; PBAC, Australia) were screened.

- Inclusion criteria: Indirect treatment comparisons (ITC) using SAT data and RWD as an EC, were reported for a product/indication by at least one HTA agency.
- Exclusion criteria: Products/ indications were excluded if SATs were only used to generate pharmacokinetic data, or if both SAT and additional RCT evidence was reported by regulatory or HTA agencies.

For the included products/ indications, published reports by regulatory and HTA agencies were evaluated to capture information on the regulatory pathway, therapeutic area, indication (adult and/or pediatric), effect size, and ITC method.

Explorative analysis of the data was performed, and descriptive statistics were used to present the findings.

## RESULTS

Of 50 products with SAT-based approval, 18 products for 21 indications were identified for analysis.

A total of 105 HTA reports were included in this analysis: G-BA (19), HAS (17), NICE (17), AEMPS (11), AIFA (10), ZIN (6), PBAC (9), and CADTH (16). Of these, 85 assessments included RWD.

**Table 1.** Effect of RWD reporting by regulatory agencies on reporting of RWD by HTA agencies

| RWD in EMA or FDA report | reported (12/21 indications) | not-reported (9/21 indications) | reported vs. not reported |
|---|---|---|---|
| | n/N* (%) | n/N (%) | OR (95% CI) p-value |
| RWD reported by HTA agencies | 61/64 (95%) | 24/49 (59%) | 14.4 [3.87, 53.65] 0.0001 |

*Where N= number of total reports and n = number of reports with RWD

When RWD were reported by the EMA and/or the FDA, RWD were **significantly more likely** to also be reported by HTA agencies (Table 1).

The overall rate of RWD use for HTA decision-making was 43% (39/85).

**Table 2.** Real-world data used for HTA decision-making by subpopulation

| RWD in EMA or FDA report | reported | not-reported | Reported vs not-reported |
|---|---|---|---|
| | n/N* (%) | n/N (%) | OR (95% CI) p-value |
| RWD used for HTA decision | | | |
| Overall population | | | |
| Overall | 32/61 (52%) | 7/24 (29%) | 4.99 [1.83,13.58] 0.017 |
| Subpopulation: pediatric indication, Interaction p=0,0273 | | | |
| With pediatric | 22/34 (65%) | 1/5 (20%) | 7.33 [0.73,73.25] 0.089 |
| Without pediatric | 6/27 (22%) | 6/19 (32%) | 0.62 [0.16, 2.33] 0.4785 |
| Subpopulation: genetic disease, interaction p=0.0001 | | | |
| Genetic disease | 20/22 (91%) | 0/0 (0%) | n.a. [n.a.; n.a.] n.a |
| Non-genetic disease | 19/63 (30 %) | 0/0 (0%) | n.a. [n.a.; n.a.] n.a |

*Where N= number of total reports and n = number of reports with RWD. N.a. = not applicable

**Table 3.** Real-world data used for HTA decision-making by effect size

| Effect size Outcome | Strong | not-strong | strong vs. not strong |
|---|---|---|---|
| | n/N (%) | n/N (%) | OR (95% CI) p-value |
| RWD used by G-BA, HAS, CADTH for HTA decision-making | 9/15 (56%) | 6/31 (19%) | 6.25 [1.60, 24.45] 0.0085 |

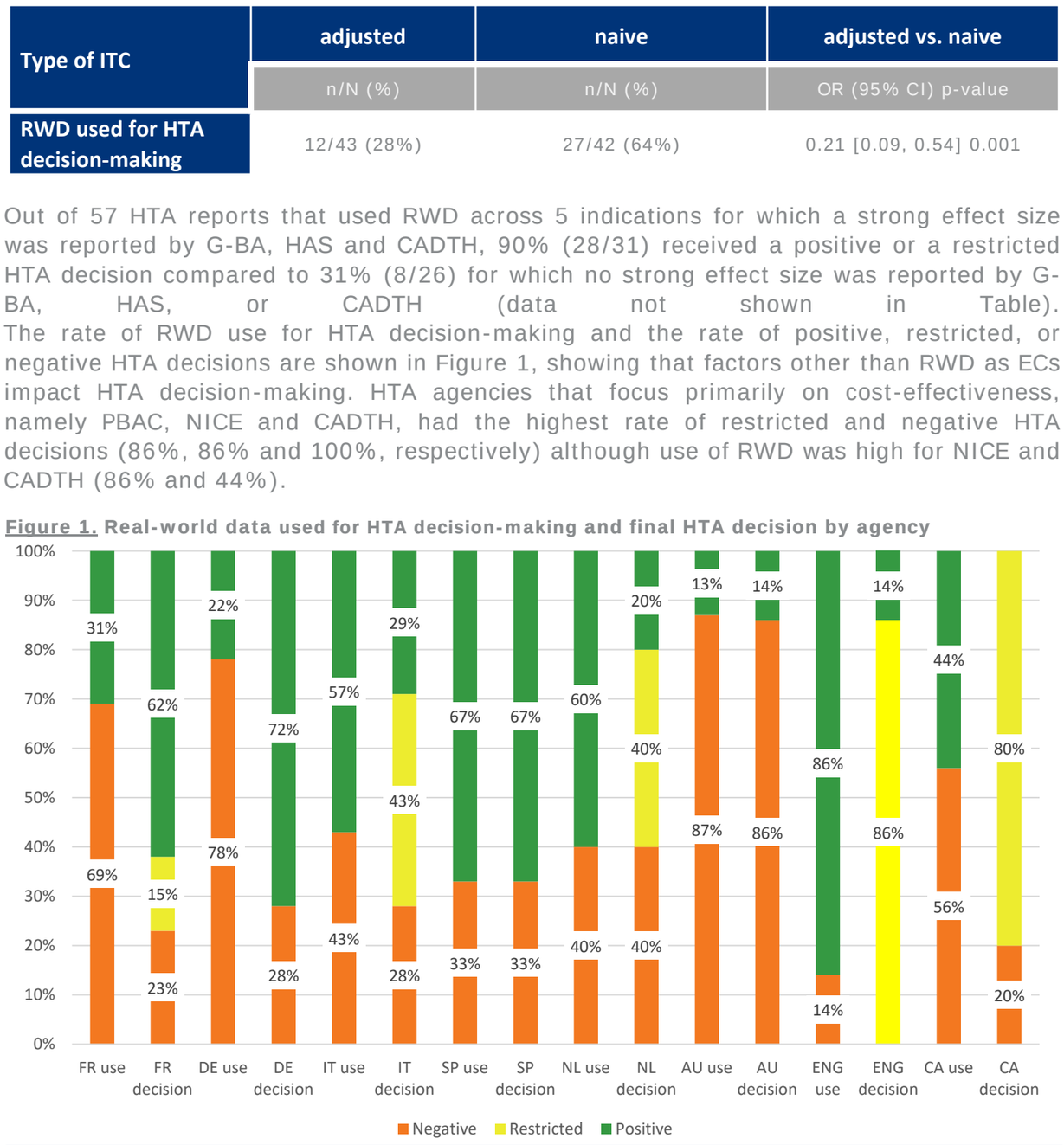
Among various factors, **strong effect size and/or genetic disease** were most influential for consideration of RWD for HTA decision-making (Table 2+3).

**Table 4.** Real-world data used for HTA decision-making by Type of ITC

| Type of ITC | adjusted | naive | adjusted vs. naive |
|---|---|---|---|
| | n/N (%) | n/N (%) | OR (95% CI) p-value |
| RWD used for HTA decision-making | 12/43 (28%) | 27/42 (64%) | 0.21 [0.09, 0.54] 0.001 |

Out of 57 HTA reports that used RWD across 5 indications for which a strong effect size was reported by G-BA, HAS and CADTH, 90% (28/31) received a positive or a restricted HTA decision compared to 31% (8/26) for which no strong effect size was reported by G-BA, HAS, or CADTH (data not shown in Table). The rate of RWD use for HTA decision-making and the rate of positive, restricted, or negative HTA decisions are shown in Figure 1, showing that factors other than RWD as ECs impact HTA decision-making. HTA agencies that focus primarily on cost-effectiveness, namely PBAC, NICE and CADTH, had the highest rate of restricted and negative HTA decisions (86%, 86% and 100%, respectively) although use of RWD was high for NICE and CADTH (86% and 44%).

**Figure 1.** Real-world data used for HTA decision-making and final HTA decision by agency




HTA agencies that **focus primarily on cost-effectiveness**, namely PBAC, NICE and CADTH, had the **highest rate of restricted and negative HTA decisions** (86%, 86%, and 100%, respectively) although **the use of RWD was high for NICE and CADTH** (86% and 44%)

## DISCUSSION

- Although RWD was used by G-BA and HAS for HTA decision-making in 22% and 31% respectively, a positive HTA decision was demonstrated by G-BA in 72% and by HAS 62% of the HTAs. NICE used in 86% of HTA RWD but HTA decision was positive in 14% only. Die differences may be attributed to other decision-making factors such as high unmet needs/ orphan indications (G-BA and HAS) or cost-effectiveness considerations (NICE).
- A strong effect size was required by G-BA, HAS, and CADTH.[3-5] In fact, HAS and G-BA issued a positive or restricted decision for all assessments where a strong effect size was demonstrated consistent with their methods guidance.
- The high consideration rate of naïve ITCs when compared to other ITCs could potentially be attributed to strong methodological requirements for adjusted ITCs and the least favorable/conservative estimates in naïve ITCs informing the base case. This contrasts with recently published guidelines from G-BA, HAS, and NICE. Given this contrast, no definitive causal relationship can be drawn between ITC methodology and positive HTA decisions.

### LIMITATIONS:

- Some of HTA agencies did not explicitly comment on the reasoning behind their decision; in these cases, we took a conservative approach and assumed RWD was not used for HTA decision-making even if the HTA decision was positive.
- The submissions of the assessments analyzed might have included several ITCs, often without a clear explanation for the chosen methodology in the report issued.

## CONCLUSIONS

- RWD were most often used by HTA agencies for decision-making if the evidence was previously submitted to a regulatory agency and if it the effect size was strong, which correlated with pediatric and/or genetic disease indications.
- Although adjustments for ITCs are required according to G-BA, HAS and NICE methods, strong effect sizes in naïve ITC seemed to have a more positive influence on HTA decision-making compared to less-strong effects in adjusted ITCs although statistically significant.
- Factors contributing to positive HTA decisions were RWD as ECs but also unmet needs, orphan drug designation, or ongoing randomized controlled trials in clinical-effectiveness markets. In cost-effectiveness markets restricted or negative HTA decisions were mainly driven by absence of cost-effectiveness despite RWD being frequently used to inform decisions in cost-effectiveness markets.

## REFERENCES

1. US Food and Drug Administration. Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions. Updated May 2022. Available at: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
2. US Food and Drug Administration. FDA Issues Draft Guidances on Real-World Evidence, Prepares to Publish More in Future. Updated January 2022. Available at: https://www.fda.gov/drugs/news-events-human-drugs/fda-issues-draft-guidances-real-world-evidence-prepares-publish-more-future
3.IQWiG. Development of scientific concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to 35a Social Code Book V- rapid report. Updated May 2020. Available at: https://www.iqwig.de/en/projects/a19-43.html
4. McCormick, J. I., Berescu, L. D., & Tadros, N. (2018). Common drug review recommendations for orphan drugs in Canada: basis of recommendations and comparison with similar reviews in Quebec, Australia, Scotland and New Zealand. *Orphanet journal of rare diseases*, *13*(1), 27. https://doi.org/10.1186/s13023-018-0759-9
5. Impact HTA. Country vignette of appraisal processes for rare disease medicines in France. Updated April 2019. Available at: Country vignette of appraisal/reimbursement processes for rare disease medicines in France (impact-hta.eu)

**Disclosures:** Authors Tomeczkowski, Kavanagh, and Kubitz are employees of Janssen, which is currently marketing products considered in this research. Authors Partemio and Nijhuis are employees of IQVIA Real World Insights; IQVIA is purchasing different RWD databases and was paid for the data analyses. Medical writing support was provided by Deloitte and funded by Janssen.

Janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson