Roundtable Report - 18 September 2025

Real-World Evidence for HTA Decision-Making in Oncology

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1. Introduction

On the 18th of September 2025, the RWE4Decisions multi-stakeholder Learning Network hosted a Roundtable on **the role that Real-World Evidence (RWE) can play in oncology health technology assessment (HTA) decision-making** to bridge evidence gaps and support patient access to innovative therapies. The Roundtable featured one keynote presentation and three case studies, followed by lively multi-stakeholder disucssions with over 60 participants representing HTA/Payers, national health ministries and regulators, EU institutions, patients, data analysts, registry holders, academics, and the pharmaceutical industry.

2. Keynote presentation: Dr Beate Wiesseler (Head of the Drug Assessment Department, IQWIG; Chair of the HTA Coordination Group Subgroup for the Development of Methodological and Procedural Guidance): HTA Coordination Group Guidance on the Validity of Clinical Studies and Evidence Synthesis

To commence the discussions, the keynote speaker set the stage by presenting the HTA Coordination Group's guidance relevant for consideration of RWE in assessments.

The EU HTA Regulation establishes the framework for Joint Clinical Assessments (JCAs), EU-level evaluations of new technologies. As defined in Article 9(1) of the Regulation, JCAs should describe **the relative effects of new health technologies**, compared to standards of care defined by all Member States in the assessment scope, and their degree of certainty. The assessment scope is built from nationally defined Patient, Intervention, Comparison, Outcome (PICO) models, and should cover the needs of all Member States, who may define their individual research questions and comparators in line with the national standard of care.

The exact meaning of real-world data (RWD) and RWE in the context of JCAs is uncertain. In general, RWD is understood as data generated from routine clinical practice, but these may not always be relevant across healthcare systems. The key issue lies in the **study designs and the certainty of the results they produce**. Questions often arise regarding the availability of comparative data to describe relative effects, or regarding methodological issues (e.g. interventional or observational studies as the source, randomisation of data). The discussion around RWD is further complicated by inconsistent definitions of the term and differing views on eligible study designs – for example, the European Medicines Agencies (EMA) restricts their DARWIN-EU project to observational data sources and non-interventional studies.

Under the HTA Regulation, two guidances have been created by the Methodological and Procedural Guidance Subgroup and endorsed by the HTA Coordination Group: the Guidance on Validity of Clinical Studies for JCAs, and the Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons.

The Guidance on Validity of Clinical Studies includes three key recommendations: firstly, it offers three dimensions for evaluating the **certainty of results** (internal validity, external validity, and precision). Secondly, it defines the **study types** and **appropriate methods for assessing the risk of bias** in these. Thirdly, it covers different **design aspects and particularities**, including

RWD, RWE, and registries. Nevertheless, the Guidance clarifies that RWD is not a study design, and that all requirements for real study designs should apply to this type of data and for the study design used in a specific dataset.

The Evidence Synthesis Guidance additionally describes the **requirements to be met for the types of comparisons for different study designs**: direct comparisons from RCTs (individual or meta-analyses), indirect treatment comparisons from RCTs, and non-randomised studies and unanchored indirect tratment comparisions. There is a plurality of methods that can be used in a JCA, as long as the underlying assumptions are met and the effect estimates provided are valid for the assessment scope.

The presenter then introduced two case studies to illustrate the contrasting quality and applicability of RWD. The first case involved the assessment of a **CAR T-cell therapy,** where the comparator was an individualised treatment considering the patient characteristics, and an unanchored indirect comparison of a single-arm trial and an external RWD control were received. The RWD dataset had been built from non-interventional retrospective studies from various datasources. However, it did not meet the necessary methodological requirements due to missing data on relevant patient characteristics, confounders, adverse symptoms and quality of life, and differences in time and type of treatment.

The second example, presenting a **randomised registry-based trial**, had very high-quality data from a routine practice dataset. This was considered to qualify as RWD, having different opportunities to describe treatment effects than the first example. The trial used the national comprehensive Swedish Coronary Angiography and Angioplasy Registry (SCAAR) for the identification of patients, randomisation, collection of baseline and procedural variables, and follow-up.

To conclude, the presentation highlighted that, as terms, RWD/RWE alone are not sufficiently informative *per se* – **the relevance of a dataset for HTA depends on the study design and the suitability of the data to answer the JCA research question**. The Guidance Documents endorsed by the Coordination Group describe the **requirements for all types of study designs**, and enable the use of data from routine practice if the datasets are fit for purpose.

3. Case studies

The above presentation fed into a panel discussion which reflected on the evolving role of RWE in HTA/Payer decision-making through the presentation of practical case studies from different jurisdictions.

i. Shaun Rowark (NICE): How we're thinking of using RWE in oncology HTA at NICE

The second presentation offered an insight into the use of RWE in oncology HTA at NICE, where oncology represents the majority of HTA – since 2020, these represented approximately 53% of all appraisals (251 in total), thus making the use of RWE in oncology particularly important. The vast majority of appraisals are considered for **severity modifiers** – for NICE, this is an algorithm that weighs the health benefits of medicines for severe diseases higher, raising then the cost-effectiveness threshold. Robust data on survival and starting age are important for this process.

The economic modelling for oncology at NICE is generally predictable, as there is a lot of precedent and the issues raised are generally consistent, often relating to extrapolation, trial

evidence, looking at calculations for severity modifiers, and the generalisability of the trial data in observed clinical practice. Additionally, the English Systemic Anti-Cancer Therapy (SACT) dataset is generally well accepted in terms of a robust oncology dataset.

Two case studies were presented relating to use of RWE when making an appraisal. The first, related to medicine for metastatic colorectal cancer, specifically looked at the **overall survival** (OS) and **mean starting age** for the comparator, to which the cost-effectiveness was highly sensitive. Using data from the SACT dataset, NICE was able to observe differences in the mean starting age and the OS curve, allowing greater accuracy when making the calculations for the severity modifiers.

In the second, for medicines for metastatic urothelial cancer, RWD was used to understand the use of another medicine within the treatment pathway and the real-world estimate use of maintenance therapy. The SACT was used alongside *Blueteq*, a dataset looking at the duration of high-cost drugs use, to considerably reduce uncertainty for cohorts, thus impacting the severity of the calculations and enabling NICE to make a final decision.

NICE also uses RWE in **post-launch evidence generation** (PLEG) – a number of examples from the Cancer Drugs Fund were presented, where SACT was used in preference to trial data for OS, for conducting scenario analyses (e.g. providing reassurance of OS), for determining baseline characteristics in order to compare the patient profile to the trial, or for reweighing trial results from trials to reflect the characteristics of eligible patients.

The presentation concluded by reflecting on the use of RWD for oncology HTA. For live decision-making, it is used for **reducing uncertainty by reducing the range of cost-effective estimates**. While feedback has been supportive of RWE use for generalisability of clinical trial data or for severity criteria in borderline cases, the current limiting factor at NICE is the capacity of the analytical team. Finally, challenges remain in defining relevant cohorts and capturing them in the relevant dataset – as datasets were not originally developed for this research purpose, identifying precise cohorts can undermine validity. The ideal RWE scenario is one where you can synthesise the baseline data or the comparatore relative effectiveness to also draw onto the trial data.

ii. Dr Robert Szulkin (TLV): RWD in treatment effect evaluation of Jaypirca (pirtobrutinib) at TLV

The focus then shifted on the inclusion of RWD in the evaluation by TLV of the treatment effect of **Jaypirca**. This medicine is used for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least two lines of systemic therapy, including BTK inhibitors. The prevalence is quite low in Sweden (an estimated 20 patients), but treatment alternatives are lacking upon progression on BTK inhibitors. While some patients qualify for CAR T-cell therapy, those who do not are generally treated with immunochemotherapy, resulting in a median survival of approximately 9.7 months.

The evidence for Jaypirca is based solely on single-armed trials, including approximately 90 MCL patients. Of these, 56.7% had a complete or partial response, and the median OS was of approximately 9 months. The EMA also considered the progression-free survival (PFS) and the OS to be promising.

External comparator arms were needed to assess the treatment effect. The developers used US electronic health records from the *Concert AI* database, containing the data of 128 MCL

patients, and used data from the *SCHOLAR-2* European observational study for a sensitivity analysis. The treatment arms were matched based on important confounders and prognostic factors.

Jaypirca showed a significantly better OS than the other two databases, but no significant difference in PFS. However, some concerns remained relating to the **transportability of the US and European RWD to the Swedish context**; immature survival rates were observed, their extrapolations were considered overoptimistic, and some of the patients in the treatment arm were healthier (with many being CAR T-eligible). To complement this, TLV requested data from the Swedish Lymphoma Register, which showed that the median survival rate was of only 5.77 months, leading to the conclusion that Jaypirca had a much better treatment effect.

As a final decision, TLV approved a higher price for Jaypirca because of better treatment effect than the alternatives, based on the evidence that Jaypirca seemed to have a better OS. As cases where small, one-armed trials are becoming more and more common, this was an **important example of how RWD can be used as a complementary data source**.

iii. Dr Mattias Ekman (AstraZeneca): Using RWD to support the validation of survival extrapolation in an HTA submission – The SOLO-1 case in Sweden

The final presenter discussed a **Swedish case** on the use of RWD to support the validation of survival extrapolation in an HTA submission. It concerned a biomarker-specific population: BRCA-mutated patients with advanced ovarian cancer, treated with the first PARP inhibitor for this indication. It was based on **clinical trial evidence compared to the placebo arm**, without the need for indirect treatment comparisons. The primary endpoint was PFS, while secondary endpoints included time to second progression (PFS2), OS, time to subsequent therapy or death, and the time from randomisation to the second subsequent therapy or death.

The PFS curve showed a 70% reduction in the risk of disease progression or death. However, the OS data were immature, creating uncertainty when extrapolating lifetime treatment effects in the cost-effectiveness model. Several arguments supported the assumption of an eventual OS benefit, including the immaturity of the existing OS data, correlations observed between PFS and OS in other cancer trials, the strong relationship between PFS2 and OS, and evidence from prior studies where initially converging curves later separated again. Additionally, real-world data suggested that for patients remaining relapse-free over time, mortality risk tends to decline, further supporting the plausibility of a long-term survival benefit.

As the biomarker-specific population made it difficult to identify RWD in the Nordics, a **suitable registry was identified in Scotland**, enabling the selection of BRCA-positive patients to form a matched population comparable to the clinical trial. To strengthen the data's generalizability, literature sources were added. Comparing the PFS extrapolations and Kaplan-Meier data in the trial with the Scottish data showed that the placebo curve closely aligned with the long-term RWD outcomes. Further validation for the long-run OS modelling for the placebo was drawn from the Ontario Cancer Registry, including BRCA-mutated patients with up to ten years of follow-up.

The clinical data and approach were presented in a meeting with TLV and the Swedish healthcare regions. PFS and OS data were modelled from KM data for 24 months, after which the OS treatment effect was predicted by the PFS and supported by PFS2 data. In light of their initial skepticism towards the large extrapolated OS gain, TLV requested several more conservative

scenarios with a smallet treatment effect, but ultimately assessed the intervention as cost-effective despite the uncertainties.

The case illustrated both the **advantages and limitations of RWD**, which could be used in this context to **validate the placebo**, but **not the treatment effect**. Nevertheless, in the absence of this data, the extrapolations would have been more conservative even for the placebo arm, worsening cost-effectiveness and possibily stalling reimbursement.

iv. Q&A

The presentations section finished with a Q&A, from which the following learnings resulted:

- One of the key requirements to use RWD for assessment of comparative effectiveness is to have identified all possible confounders and collect adequate data for the corresponding adjustments. Therefore data needs are much larger than in a randomised design, and prospective planning is generally needed.
- Some non-randomised studies using RWD as data sources may reproduce RCT findings, but not all of them and no clear factors have been identified to determine whether this is the case or not. ,
- At the European level, prior evidence for the JCA must be provided by the HTD in their dossier. The JCA then describes uncertainties regarding the datasets, and the decision on whether to accept them remains at the discretion of the Member States, which may come to differing conclusions based on their national decision-making frameworks.
- The transportability and generalisability of RWD can be supported through broader evidence, such as a literature review and the combination of registry data with published real-world studies.
- Time constraints in the evaluation window, legal barriers, and RWD skepticism may limit an HTA's ability to request and analyse RWD and registry data.
- Direct access to datasets greatly improves efficiency and enables broader RWD use.

3. Breakout group discussions

Following the presentations, participants were divided into multi-stakeholder breakout rooms facilitated by Steve Williamson (NICE), Saunya Dover (CDA-AMC), and Christine Leopold (Utrecht University), with the support of scribes Katja Berg (AstraZeneca), Melinda Hanisch (MSD), and Tove Holm-Larsen (Ghent University).

Discussions highlighted several key themes and challenges of the practical use of RWD in oncology assessments, including the need for more reference cases to guide RWE generation, the persistent issues around data quality and transferability, and the strategic role of registries in capturing meaningful patient data.

- **The use of real-world data to demonstrate treatment effectiveness**
    - RWE can be used at various stages of HTA, including initial assessments, as comparator arms in single-arm trials, and at the time of reassessment. This flexibility allows RWE to support decision-making throughout the product lifecycle.
    - Post-launch RWE is expected to play a growing role in understanding treatment effects, especially in sub-populations and long-term outcomes, although systems for re-assessment are not yet fully established.

  - RWE is particularly useful in modelling and informing assumptions when RCTs are not feasible, such as in small oncology populations or for advanced therapies.
  - JCAs were identified as a promising framework for demonstrating the usefulness of RWE, especially in addressing multiple PICOs.
- **Strengthening guidance through reference cases**
  - There is a clear need for more and better reference cases to illustrate how RWE can be effectively used in HTA, which would help build trust and inform future guidance.
  - Reference cases are also seen as essential for developing frameworks and guidelines, such as those proposed by ISPOR.
  - Scientific advice initiatives, such as those involving the Canada's Drug Agency (CDA) and NICE, are helping to define acceptable datasets and methods, although uptakes and impact may take time. Joint Scientific Consultations in the frame of the HTA regulation will go in the same direction.

- **Addressing data quality and interoperability challenges**
  - Data quality and availability are persistent challenges, with concerns about bias and representation of all relevant confounders.
  - Standardising endpoints and harmonising data collection frameworks are seen as critical steps, though disease specificity remains a barrier.
  - There is often a lack of legal and regulatory frameworks, limiting access to patient-level data and slowing the integration of RWE into HTA processes.

- **Enhancing the role of registries to leverage the value of patient data in HTA**
  - Registries are essential for capturing patient-level data and supporting post-market commitments, especially in countries with heterogeneous data landscapes.
  - Early integration of biological tests into registries was recommended to improve data granularity and relevance for HTA.
  - Agreement on what data should be collected (including patient-reported outcomes and treatment context) is needed to ensure registries support planning and resource allocation.

- **Anticipating RWE needs through horizon scanning**
  - Horizon scanning can help identify evidence gaps early and guide data collection strategies before HTA evaluations.
  - It also supports understanding of system-level impacts, such as delivery costs and service disruptions, which are often overlooked in traditional assessments.

4. Conclusion

The roundtable discussions highlighted both the opportunities and ongoing challenges in integrating RWD and RWE into HTA decision-making for oncology. The case studies and presentations demonstrated how RWE can be instrumental in addressing evidence gaps, validating trial assumptions, and supporting cost-effectiveness analyses, particularly when randomised data are limited or unavailable. This included the use of RWD from other jurisdictions, with appropriate methods to assess the transferability of such data. The discussions underscored the growing acceptance of RWE as a complementary data source,

while emphasising the need for robust methodological standards, improved data quality, and stronger guidance on its appropriate use. Participants also pointed to the importance of data accessibility, interoperability, and legal clarity to enable timely analyses within HTA processes. Ultimately, the roundtable reinforced that with better infrastructure, clearer frameworks, and continued collaboration across stakeholders, RWE can play a transformative role in improving oncology decision-making and patient access to innovative therapies.

RWE4Decisions is an HTA/Payer-led multi-stakeholder Learning Network, which, in 2024, developed of a set of new Stakeholder Actions to generate better real-world evidence for HTA/payer decisions about highly innovative technologies.

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