# Beyond RCTs: The role of Real-World Evidence in NICE Submissions for Rare Diseases

HTA166

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## Introduction

- The Highly Specialised Technologies (HST) process by the National Institute for Health and Care Excellence (NICE) in the UK evaluates technologies for severe rare diseases.
- Randomised controlled trials (RCT) may be infeasible for rare diseases, thus making real-world evidence (RWE) a valuable source of information. Acceptance of RWE has been rising in Health Technology Assessment (HTA), as demonstrated by the introduction of the NICE RWE framework in June 2022.[a]

**Objective:** To determine how RWE is used within HST submissions following the introduction of the NICE RWE framework and to explore how RWE was perceived by the external assessment group (EAG) and NICE committee in these appraisals.

**Key definitions from the NICE RWE framework:**

**Real-world data (RWD):** Data collected outside the context of a highly controlled clinical trial. They can come from many different sources including patient health records, administrative records, patient registries, surveys, observational cohort studies and digital health technologies.

**Real-world evidence (RWE):** Evidence generated from the analysis of real-world data. This includes studies using real-world data to form an external control to a clinical trial.

## Methods

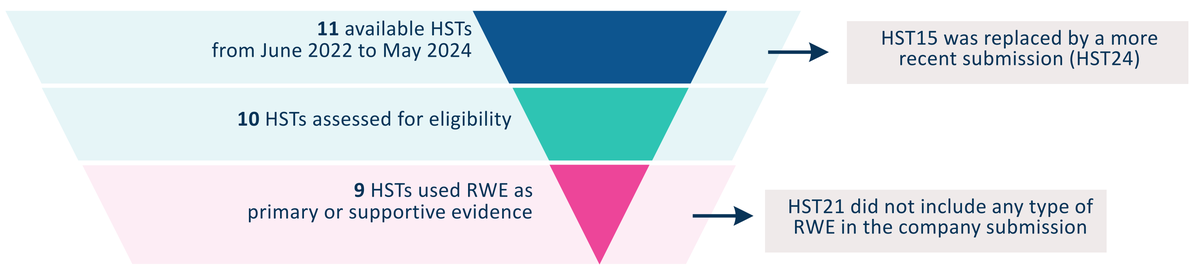
- A targeted review of all NICE HST appraisals published since introduction of the NICE RWE framework was conducted.
- Relevant information from the following documents was extracted:
  - **Company submissions**: Including use of RWE as primary evidence (i.e. comprising the main clinical effectiveness evidence) or secondary/supportive evidence; details on data sources, data collection, and study designs; quality assessment; any analyses conducted with RWE.
  - **EAG reports** and **NICE committee appraisals**: Including comments and critique of the RWE.

## Results

### Overview

- Eleven HST appraisals were identified from the search **(Figure 1).**
- Ten HST appraisals were reviewed for the use of RWE; nine included RWE as primary and/or supportive clinical evidence, eight of which received a positive recommendation from NICE.

**Figure 1. HST appraisal selection process**

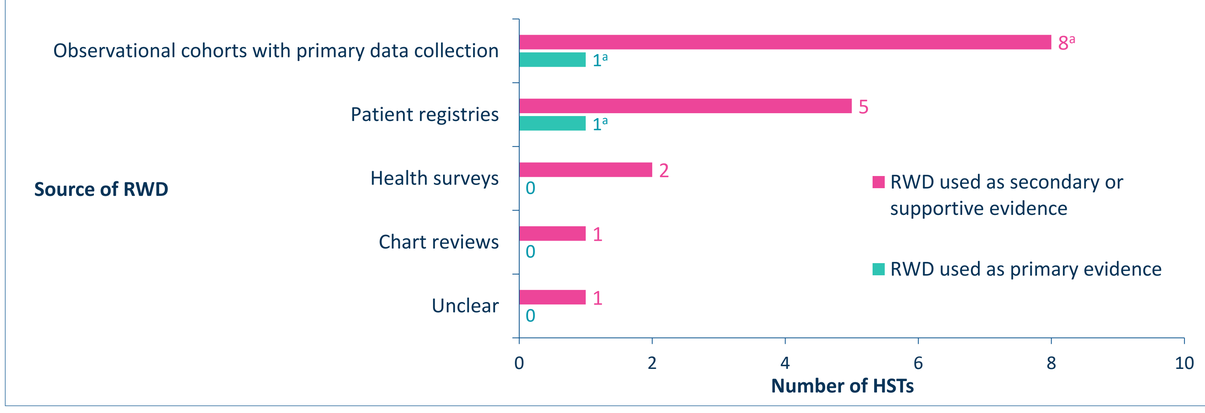



**Abbreviations:** HST, Highly Specialised Technology; RWE, Real-world evidence.

### RWD sources

- Eight HST appraisals reported the sources of RWD used in the company submissions. HST28 did not specify the design of the RWE study or name the RWD source **(Figure 2).**
- HST22 was the only appraisal that included RWD as its primary source of evidence. All others (7/8 HSTs) used randomised or non-randomised clinical trial evidence primarily.
- The most used RWD sources were observational cohorts with primary data collection, including new studies designed for the research question or existing studies with additional data collection (8/8 HSTs), followed by patient registries (6/8 HSTs) and health surveys (2/8 HST).

**Figure 2. RWD sources**

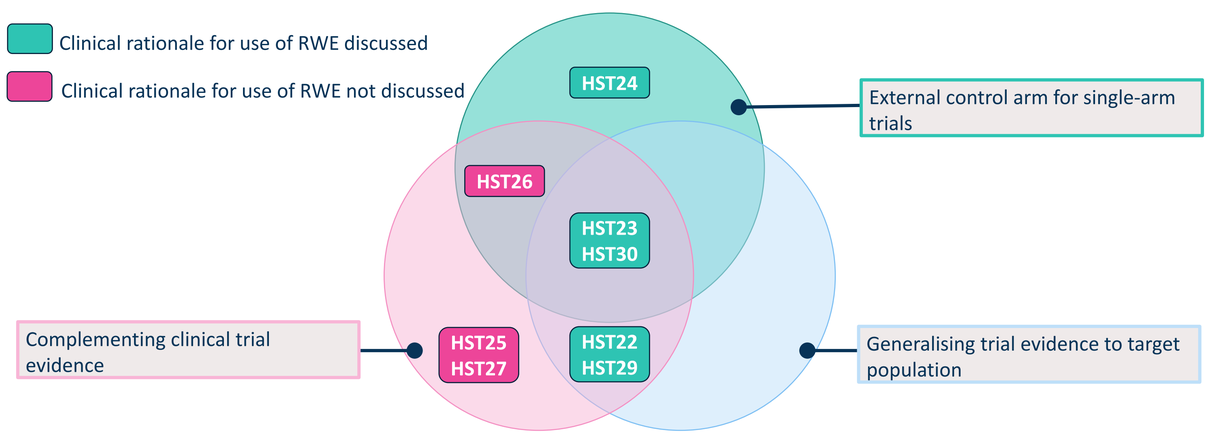



**Abbreviations:** HST, Highly Specialised Technology; RWD, Real-world data. [a]HST22 included several RWD sources: one observational cohort and one registry as primary source of evidence, and one natural history study as supportive evidence.

### RWE uses

- Five HST appraisals discussed the clinical rationale for including RWE in addition to clinical trial evidence, for example, alignment with the decision problem, provision of historical control, and insight into patient experience.
- RWE was often used for more than one purpose, including generalising randomised trials to the target population (4/8 HSTs), acting as an external control arm (4/8 HSTs) and complementing clinical trial findings (7/8 HSTs) **(Figure 3)**.
- Two HST appraisals (HST22 and HST26) reported using RWE in population-adjusted indirect treatment comparisons, both of which employed propensity score matching.
- The NICE RWE framework was not referenced by the company in any HST submission.

**Figure 3. RWE uses**




**Abbreviations:** HST, Highly Specialised Technology; RWE, Real-world evidence.

### EAG and NICE comments

- The EAG and NICE committee accepted the use of RWE in most HSTs.
- However, in all HSTs the EAG and/or committee noted concerns regarding RWE **(Figure 4).**
- To overcome uncertainties with clinical and cost-effectiveness, the EAG recommended collection of additional long-term RWD in 5/10 HSTs.
- The committee echoed the criticism by the EAG on the uncertainty in the clinical evidence for some HSTs, but overall considered the analyses appropriate and noted that RWE was informative.
- In HST27, the committee noted much uncertainty associated with the RWE and specifically recommended usage of the RWE framework to improve the robustness of the clinical evidence. Notably, HST27 did not receive a positive recommendation.

**Figure 4 . Overview of EAG and NICE committee comments**

| HSTs | Recommended by NICE? | Positive feedback on RWE | | Criticism of RWE | | | |
|---|---|---|---|---|---|---|---|
| | | Suitable RWD source | Other positive feedback | Unsuitable RWD source | Uncertainty in clinical evidence | Recommendation of further RWD collection | Other criticism |
| HST21[a] | ✓ | NC | NC | NC | NC | **EAG** | NC |
| HST22 | ✓ | NC | NC | NC | **EAG, NICE** Imbalance between groups included in the ITC | NC | **EAG** Incomplete quality assessment of RWE |
| HST23 | ✓ | NC | NC | **NICE** Historical RWD leading to bias | **EAG** Small sample size | **EAG** | NC |
| HST24 | ✓ | NC | NC | NC | **EAG, NICE** Uncertain long-term clinical effectiveness | **EAG** | NC |
| HST25 | ✓ | NC | NC | **NICE** Lack of generalisability to population | NC | NC | NC |
| HST26 | ✓ | **NICE** | NC | NC | NC | **EAG** | NC |
| HST27 | X | NC | NC | NC | **NICE** Small sample size; limited information on methodology and population characteristics | NC | NC |
| HST28[b] | ✓ | NC | NC | NC | NC | NC | NC |
| HST29 | ✓ | NC | **EAG** RWD support key assumptions in the economic model | NC | **EAG, NICE** Small sample size | NC | **EAG** Double counting of patients in the analysis |
| HST30 | ✓ | NC | NC | NC | **EAG, NICE** Uncertainty regarding the completeness of the RWD source | **EAG** | NC |

Positive comments on RWE from NICE committee or EAG | Criticism of RWE from NICE committee or EAG | Criticism of RWE from both NICE committee and EAG

**Abbreviations:** EAG, Evidence assessment group; HST, Highly Specialised Technology; NC, Not commented on by EAG or NICE; NICE, National Institute for Health and Care Excellence; RWD, Real-world data; RWE, Real-world evidence. [a] RWE was not included in the company submission of HST21.[b] HST28 did not have any comments on the use of RWE by the EAG or NICE.

### Implications for future research

- The introduction of the RWE framework is recent and HSTs are infrequently conducted. Therefore, future research investigating the impact of the framework is needed to consolidate these findings.
- To enable a comparison of how RWE was used by companies before and after the introduction of the framework, appraisals published before June 2022 could be assessed.
- This study predominately explored the use of RWE as a source of clinical effectiveness. Further exploration of the use of RWE in cost-effectiveness analyses is needed.
- There have been RWE frameworks published by other HTA agencies outside the UK; it may be informative to compare the use of RWE for rare diseases across different countries.

## Conclusions

- Most NICE HST submissions published since 2022 used RWE as supportive evidence to complement randomised and non-randomised clinical trial evidence.
- Although companies did not explicitly refer to the NICE RWE framework, the use of RWE seems to be aligned with the NICE guidance, as RWE was typically used to generalise randomised trial results to the target population, to act as external control arms and to complement clinical trial findings.
- Despite its general acceptance by the EAG and the NICE committee, companies should be aware that high uncertainty in RWE sample size, population and methodology can lead to criticism.

***References:*** *[a] National Institute for Health and Care Excellence. Real-world evidence framework: Overview. June 2022.*

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