Assessing the acceptance of single-arm trials in health technology appraisals: A review of NICE, CADTH, HAS, and NCPE appraisals in 2024

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SUMMARY

OBJECTIVES

- SATs are increasingly used in situations where RCTs are unfeasible, however, their acceptance varies between countries. Furthermore, companies may choose to use ITCs or RWE to improve the quality of their evidence.
- This literature review aimed to assess the frequency and acceptance of SATs in 2024 HTA submissions to NICE, CADTH, HAS, and NCPE, and to assess the use of ITCs and other evidence generation activities, and whether this impacts reimbursement outcomes.

METHODS

- 229 drug appraisal reports from 2024 were reviewed, including submissions to NICE (n=82), CADTH (n=87), HAS (n=32), and NCPE (n=28).
- Submissions were included if they featured a pivotal SAT and a reimbursement decision was issued in 2024.
- Extracted outcomes included: therapeutic area, orphan designation, use and ITCs, use of RWE, and reimbursement outcomes.

FINDINGS

- 35 submissions featuring a pivotal SAT were identified (15.3%).
- There was an even orphan versus non-orphan distribution (48.6% vs 51.4%).
- RWE use was slightly favoured versus not using RWE (54.3% vs 45.7%).
- 88.6% of included submissions utilised an ITC. 60.0% of these used MAICs, 14.3% naïve comparison, 8.6 MAIC combination (with either synthetic control, STC or naïve comparison, each 2.9%) and 5.7% STCs.
- Of the included SATs, 42.9% were reimbursed, 48.6% were reimbursed with conditions, and 8.6% did not receive reimbursement.

RECOMMENDATIONS

- Select and justify ITC methodology early.
- Align with EU joint scientific advice to pre-empt evidentiary concerns.
- Prepare for conditional acceptance via price negotiations or narrower indications.

BACKGROUND & AIMS

- Single-arm trials (SATs) are increasingly used where randomised controlled trials are unfeasible—common in rare diseases and high unmet need areas. However, the lack of a comparator poses challenges for HTA bodies, which require robust evidence of relative effectiveness to inform reimbursement.[1]
- While regulatory agencies may accept SATs, HTA acceptance often hinges on the use of indirect treatment comparisons (ITCs), or real-world evidence (RWE), to address uncertainty. Even then, decisions are frequently conditional—requiring price concessions or narrower indications.[2]
- The primary objective of the review was to assess the frequency and acceptance of SATs in 2024 health technology assessment (HTA) submissions to the National Institute for Health and Care Excellence (NICE, UK),[3] the Canadian Agency for Drugs and Technologies in Health (CADTH, Canada),[4] the Haute Autorité de Santé (HAS, France),[5] and the National Centre for Pharmacoeconomics (NCPE, Ireland).[6]
- The secondary objectives of the review were to assess the use of ITCs and other evidence generation activities, such as RWE, in relation to reimbursement outcomes and to perform a subgroup analysis for orphan products, assessing ITC use and type, RWE use, and reimbursement outcomes.

METHODS

- A review was conducted using publicly available HTA reports from four key agencies with decisions issued in 2024. A total of 229 appraisals were included: NICE (n=82), CADTH (n=87), HAS (n=32), and NCPE (n=28) (Figure 1).
- For each appraisal reviewers:
  - Identified whether the pivotal evidence was based on a SAT
  - Categorised therapies by orphan designation and therapeutic area.
  - Recorded whether an ITC was submitted and documented the method used (e.g. MAIC, STC, naïve comparison, synthetic control).
  - Analysed HTA outcomes, including full reimbursement, conditional reimbursement, or rejection.

RESULTS

- Out of the 229 appraisals reviewed, 35 (15.3%) featured an SAT.
- The most frequently represented therapeutic areas were oncology (51.4%), haematology (20.0%), metabolic disorders (8.6%), and neurology.
- Overall, 15 (42.9%) of SAT-based appraisals resulted in full reimbursement, 17 (48.6%) were conditionally reimbursed and 8.6% were not reimbursed (Figure 2).
- NICE accounted for the majority of positive reimbursement recommendations, with 13 appraisals representing 86.6% of those granted a full reimbursement recommendation.. All conditionally reimbursed SAT appraisals by NICE required further evidence generation as part of a managed access agreement.
- For CADTH, 13 (100%) SAT-based appraisals were conditionally reimbursed, with requirements typically related to adjustments to the indicated population, treatment initiation criteria, or pricing (Figure 2).
- The use of ITCs was widespread, with 31 (88.6%) SAT-based appraisals incorporating an ITC (Figure 3).
- The most frequently employed ITC method was the unanchored MAIC, used in 21 appraisals (60%), substantially more than naïve treatment comparisons, which accounted for only 5 appraisals (14.3%).

Figure 1. PRISMA diagram

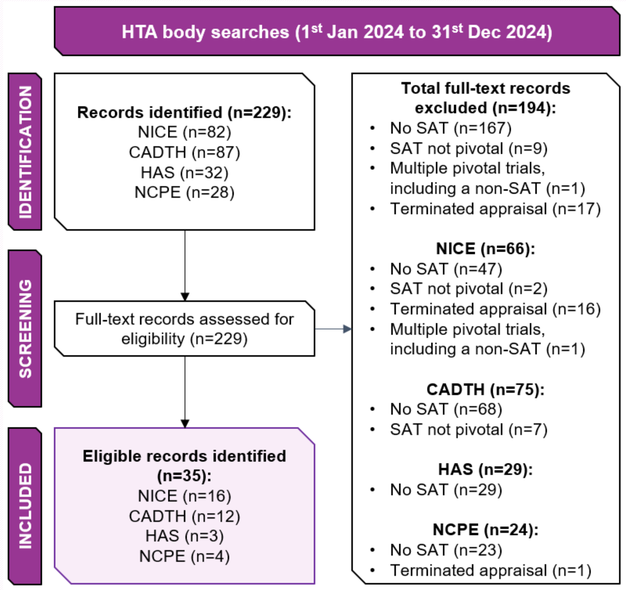


Figure 2. Reimbursement outcomes stratified by HTA body

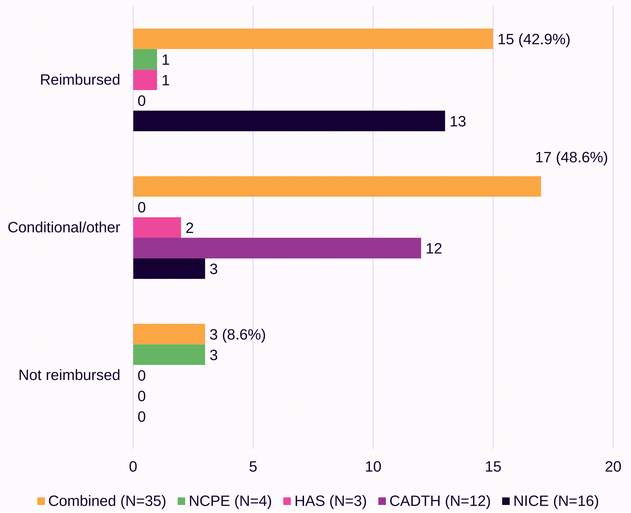
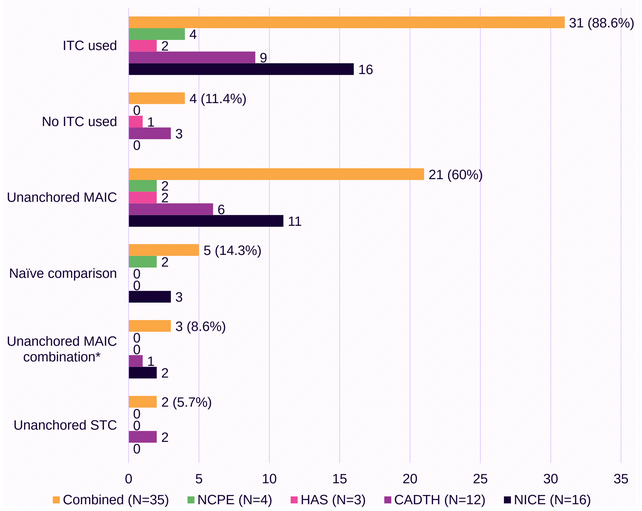


Table 1. Analysis of the reimbursement status and evidence generation activities of included orphan products

HTA body	Orphan product	ITC used	RWE used	Fully reimbursed	Conditionally reimbursed
Combined, n (%)	17 (48.6)	14 (82.3)	11 (64.7)	7 (41.1)	10 (58.8)
NICE, n (%)	7 (43.8)	7 (100.0)	6 (85.7)	5 (71.4)	2 (28.6)
CADTH, n (%)	8 (66.7)	6 (75.0)	4 (50.0)	0 (0.0)	8 (100.0)
HAS, n (%)	1 (33.3)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
NCPE, n (%)	1 (25.0)	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)

Figure 3. ITC use and type stratified by HTA body



- The choice of ITC method appeared consistent across HTA bodies, with no organisation showing a marked preference for any method compared to the overall combined HTA group (Figure 3).
- RWE also played a role in reimbursement decisions; however, it was utilised less frequently than ITCs, with 19 (54.2%) SAT-related appraisals incorporating RWE compared to 31 (88.6%) using an ITC.
- In the orphan subgroup analysis, nearly half of the SAT-based appraisals were for orphan products (n=17, 48.6%) (Table 1).
- Reimbursement outcomes for orphan products were comparable to those for non-orphan products: n=7, 41.1% versus n=8, 44.4% full reimbursed, and n=10, 58.8% versus n=7, 38.9% conditional/other reimbursement (Table 1).
- There was a modest difference in non-reimbursement rates for orphan versus non-orphan products, n=0, 0.0% vs n=3, 16.7%

CONCLUSIONS

- SATs are accepted by major HTA agencies when supported by robust indirect comparisons, particularly MAICs and STCs. However, acceptance is often conditional and highly context-dependent. In orphan and ultra-orphan indications, generating comparative evidence remains especially challenging.
- Standard of care is frequently heterogeneous, comprising off-label or symptomatic treatments, which complicates the construction of reliable comparators and limits the feasibility of robust ITCs. Manufacturers planning to rely on SATs should engage early with HTA bodies, carefully select and justify ITC methodologies, and build in mitigation strategies for uncertainty—such as flexible pricing, conditional reimbursement models, or narrower target populations.
- To maximise success, SAT-based evidence generation should be aligned with the methodological expectations of the EU JCA. Strategic, early investment in appropriate ITC methods can be a decisive factor in securing a favourable HTA outcome.

References

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