HTA284

Acceptability of Indirect Treatment Comparisons in Orphan Versus Non-Orphan NICE Technology Appraisals

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Background

+ Indirect treatment comparisons (ITCs) are used in NICE technology appraisals (TAs) to compare treatments when direct evidence is limited.
+ This study examined whether NICE's assessment of ITC acceptability differs between orphan and non-orphan appraisals.

Objectives

+ Assess how NICE evaluates the acceptability of ITCs in TAs.
+ Compare ITC acceptability between orphan disease and non-orphan appraisals.
+ Examine differences in acceptance outcomes and key committee concerns across disease contexts.

Methods

+ Reviewed NICE technology appraisals published between April 2023 and May 2026; data were extracted and assessed by two independent reviewers.
+ NICE technology appraisals were the unit of analysis. Eligible appraisals used at least one ITC and were classified by disease context, principal ITC method and committee assessment of ITC acceptability.
+ ITCs were classified as accepted where NICE committee documentation indicated that the analysis was considered credible or usable for decision-making. Accepted ITCs were further categorised as having no, standard or major caveats. ITCs considered not credible or insufficiently robust for decision-making were classified as not accepted. ITC acceptability was assessed separately from the final NICE recommendation.
+ Evaluated ITC acceptability, use of different ITC methods, level of caveats/uncertainty, and key committee concerns.
+ We tested for differences between orphan and non-orphan appraisals the proportions of appraisals whose ITCs that were accepted, and the proportions of appraisals with accepted ITCs that had major caveats or high uncertainty.

Two independent reviewers

272 NICE TAs reviewed

138 ITC appraisals (used at least one ITC method)

Disease context | **ITC method** | **Acceptance outcome**

+ **Orphan vs non-orphan**
+ **Four acceptance categories**
+ **Committee concerns compared**

Results

ITCs were used in more than half of reviewed appraisals (Figure 1)

+ Of 272 NICE technology appraisals reviewed, 138 (50.7%) used at least one ITC. Overall ITC acceptance was higher in non-orphan than orphan appraisals (88.2% vs 80.0%).
+ However, among accepted ITCs, major caveats and/or high uncertainty were more common in orphan appraisals (63.9% vs 28.0%).

Figure 1. Selection of NICE technology appraisals for the ITC analysis

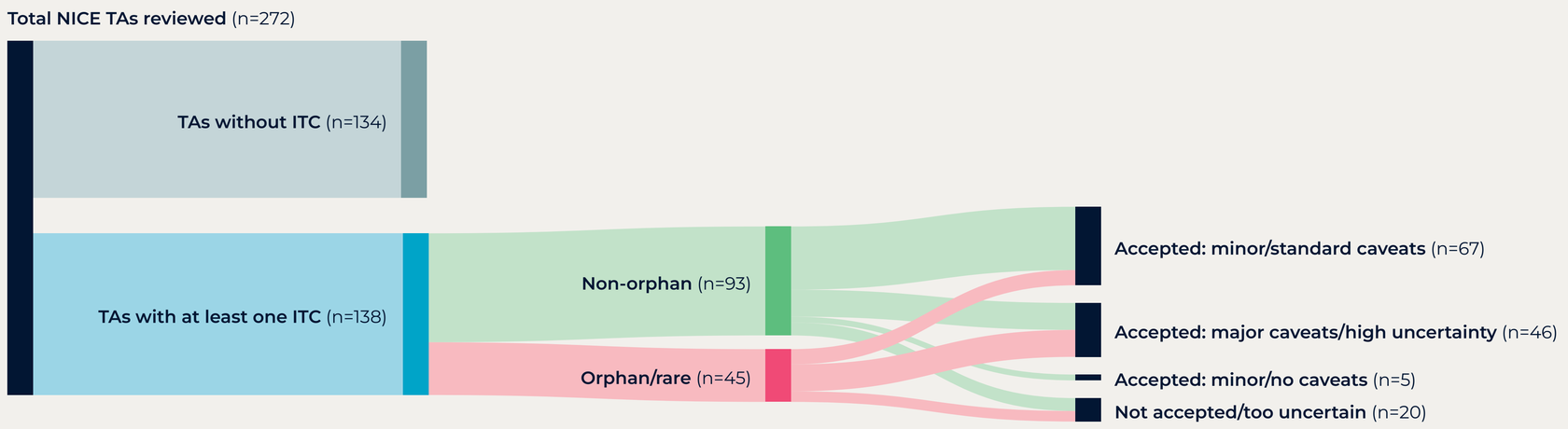
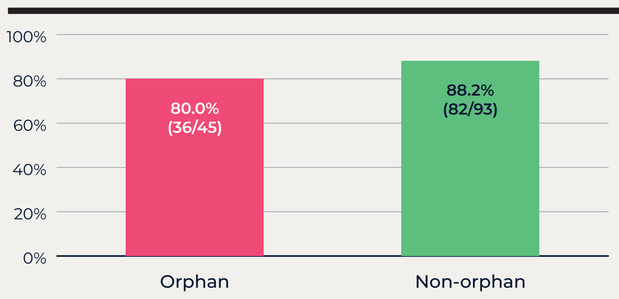


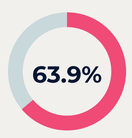
Figure 2. ITC acceptance by disease context (%)*



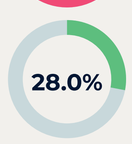
Overall acceptance was higher in non-orphan appraisals

+ The ITC evidence was accepted in 36 of 45 orphan appraisals (80.0%) and 82 of 93 non-orphan appraisals (88.2%) (Figure 2).
+ The observed acceptance rate was 8.2 percentage points higher in non-orphan appraisals.

*ITC acceptance was assessed from NICE committee documentation and reflects the committee's assessment of the ITC evidence, not the final NICE recommendation.



Orphan accepted ITCs with major caveats or high uncertainty

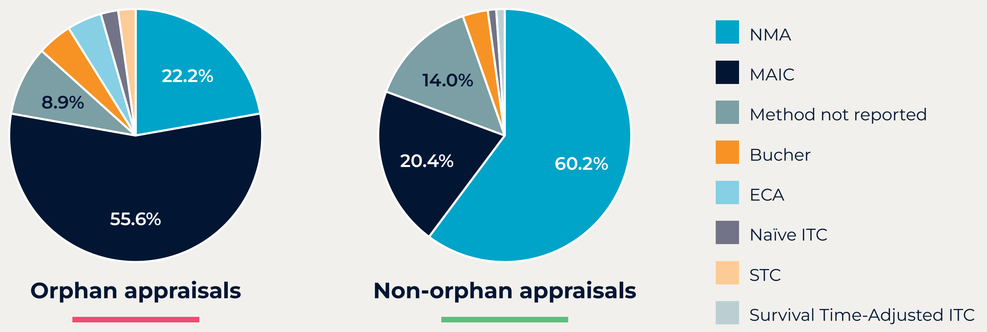


Non-orphan accepted ITCs with major caveats or high uncertainty

Limited rare-disease evidence may prompt greater scrutiny from NICE committees

+ Among accepted ITCs, 63.9% (23 of 36) in orphan appraisals carried major caveats or high uncertainty, compared with 28.0% (23 of 82) in non-orphan appraisals.
+ Common concerns were single-arm evidence, limited adjustment for prognostic factors, small samples, residual confounding and immature survival data.

Figure 3. ITC method distribution (%) in orphan and non-orphan appraisals†



MAIC and NMA were the leading ITC methods in both groups (Figure 3)

+ MAIC was the most frequently used ITC method in orphan appraisals (55.6%), followed by NMA (22.2%).
+ In non-orphan appraisals, NMA was most frequently used (60.2%), followed by MAIC (20.4%).

†Where more than one ITC method was reported, the principal method informing the appraisal was classified.

Table 1. Key differences in ITC acceptability and uncertainty

Measure	Overall (orphan and non-orphan combined)	Orphan	Non-orphan	Difference (orphan – non-orphan)	Interpretation	Evidence base
Overall ITC acceptance	85.5%	80.0%	88.2%	**−8.2 pp**	Higher acceptance rate in non-orphan appraisals	Appraisals using at least one ITC
Major caveats / high uncertainty among accepted	39.0%	63.9%	28.0%	**+35.9 pp**	Major caveats and/or high uncertainty were more frequently observed in orphan appraisals	All accepted ITCs
Leading ITC methods	NMA: 47.8% MAIC: 31.9%	NMA: 22.2% MAIC: 55.6%	NMA: 60.2% MAIC: 20.4%	—	Greater use of complex ITC methods (MAIC) in orphan appraisals	All ITC TAs

Conclusions

+ ITCs were accepted in 85.5% of appraisals where they were submitted. Acceptances were more common in orphan appraisals, but this was not statistically significant (88.2% vs 80.0%, P=0.20; see **Figure 2**).
+ Acceptance did not imply equivalent confidence in the evidence. Among accepted ITCs, major caveats and/or high uncertainty were far more common in orphan than non-orphan appraisals – and this was statistically significant (63.9% vs 28.0%, P<0.005; see **Table 1**).
+ Limited evidence in rare diseases may prompt greater scrutiny from NICE committees, without necessarily reducing the likelihood that an ITC is accepted.

References:

1. **NICE. Technology appraisal data: appraisal recommendations.** 2026. [Accessed June 2026].

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3. **Hale G, Morris J, Barker-Yip J**. Flexibility in assessment of rare disease technologies via NICE's single technology appraisal route: a thematic analysis. Journal of Comparative Effectiveness Research. 2023;12(11):e230093.

Disclosures:
This research was conducted by LCP Health, Lane Clark & Peacock LLP.
The authors declare no conflicts of interest related to this work.

Limitations:
This was a descriptive review of publicly available NICE documentation. Classification of ITC acceptability and caveats required reviewer judgement, and differences between groups may also reflect therapeutic area, appraisal pathway, study design and the availability of comparative evidence.

Abbreviations

ECA, external control arm; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; STC, simulated treatment comparison; TA, technology appraisal.

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