



Rachael Piper¹, Imogen Taylor¹, Oliver Darlington¹

1. *Initiate Consultancy, London, UK.*

SUMMARY

OBJECTIVES

- To review trends in the usage of indirect treatment comparisons (ITC) to support health technology assessments (HTAs) in Ireland.
- Analyse the types of methods used when conducting ITCs and assess the impact of using direct vs. indirect evidence on reimbursement outcomes in Ireland.
- Collate a list of common limitations/critiques noted by the National Centre for Pharmacoeconomics (NCPE) review groups regarding the use of ITCs in HTAs.
- Highlight best practices when including indirect evidence in HTA submissions to improve the chances of successful reimbursement.

METHODS

- A systemic review of all the HTAs completed by the NCPE between January 2018 and June 2023 was conducted.
- Data extraction included the date of review, therapy name and class, ITC usage and methodology, and reimbursement outcome.
- Descriptive statistics were performed to define trends in the usage of ITCs.
- A qualitative synthesis of reviewer's comments was undertaken to determine limitations and best practices when using ITCs to support HTAs.

FINDINGS

- Between 2018 and 2023 a total of 129 HTAs were completed by NCPE, of which 71 (55%) included indirect evidence.
- The most common ITC methodology used was network meta-analyses (NMA) (n=36, 51%), followed by matched-adjusted ITCs (n=19, 27%), and naïve comparisons (n=12, 17%).
- Use of ITCs to establish comparative efficacy as opposed to head-to-head trial data did not negatively impact recommendations, with 33.8% and 27.6% of submissions resulting in a positive recommendation, respectively.

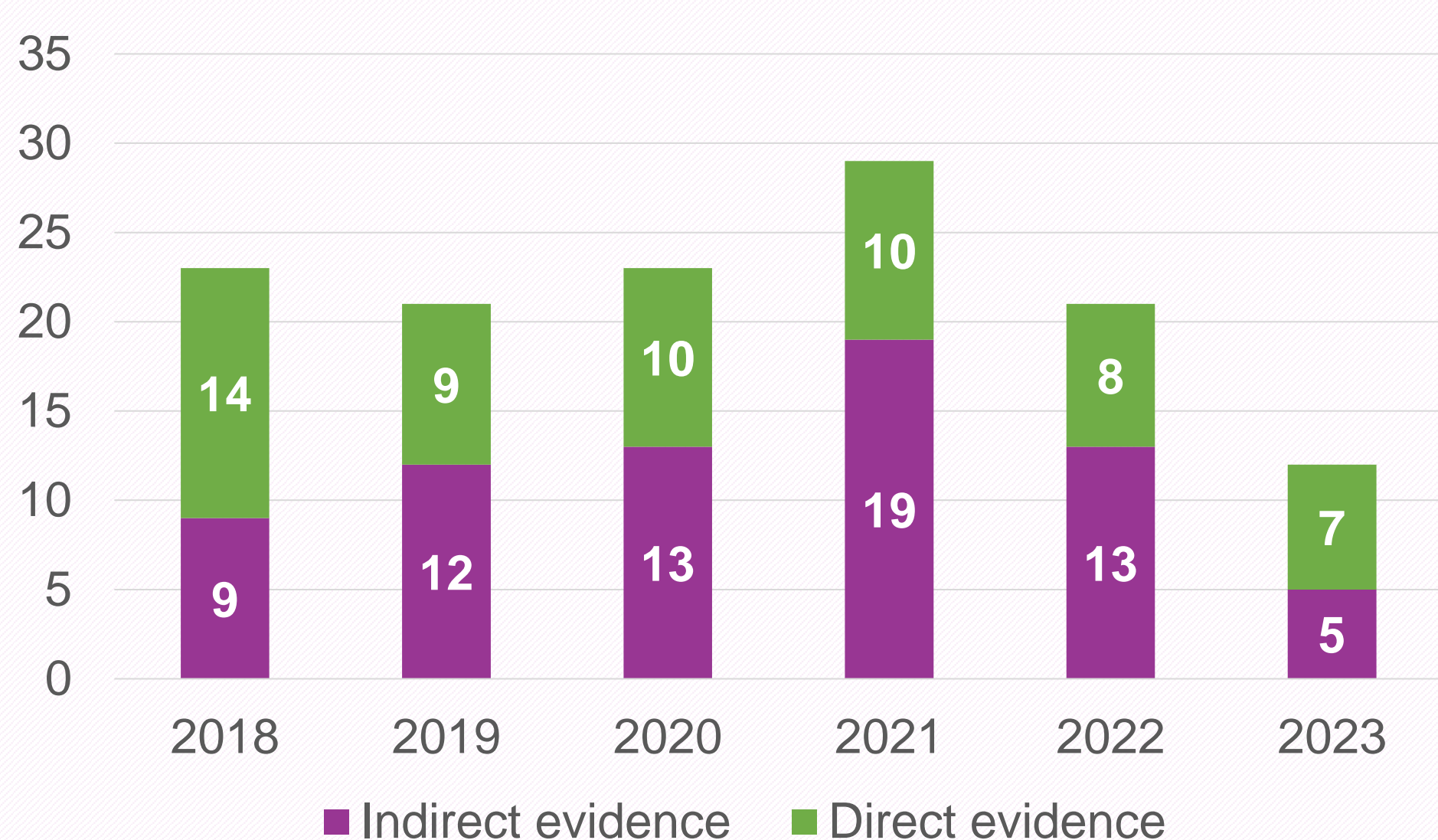
BACKGROUND & AIMS

- Following the marketing authorisation of a new treatment, national health technology assessment (HTA) bodies evaluate the additional therapeutic benefit of the product compared with existing treatments to determine if it would represent a cost-effective use of resources.
- In Ireland, the HTA body which undertakes these evaluations is the National Centre for Pharmacoeconomics (NCPE).¹
- The gold standard for assessing the relative effectiveness of two or more therapies is in a randomised control trial. However, in the absence of head-to-head trial data, ITCs can be used.
- ITCs generate estimates of the comparative efficacy of therapies by using data from separate trials.
- In this analysis, we aimed to review trends in the use of ITCs to support HTA in Ireland, investigating the types of methodologies used, and the impact of submitting indirect evidence on achieving reimbursement success.

METHODS

- A systemic review was conducted of all the HTAs completed by the NCPE between January 2018 and June 2023.¹
- Key data was extracted, including date of review, therapy name and class, and reimbursement outcomes. In addition, details on the usage of indirect evidence and methodologies were taken from "technical summary" documents.
- Descriptive statistics were performed to define trends in the usage of ITCs. A chi-squared test for proportions was used to assess the impact of the use of direct vs. indirect evidence on the chance of achieving a positive recommendation, with the NCPE recommending the new drug "be considered for reimbursement" or "be considered for reimbursement if cost effectiveness can be improved relative to existing treatments".
- A qualitative synthesis of reviewer's comments was undertaken to determine limitations and best practices when using ITCs to support HTAs.

Figure 1. The usage of direct vs. indirect evidence to support HTA in Ireland 2018-2023.



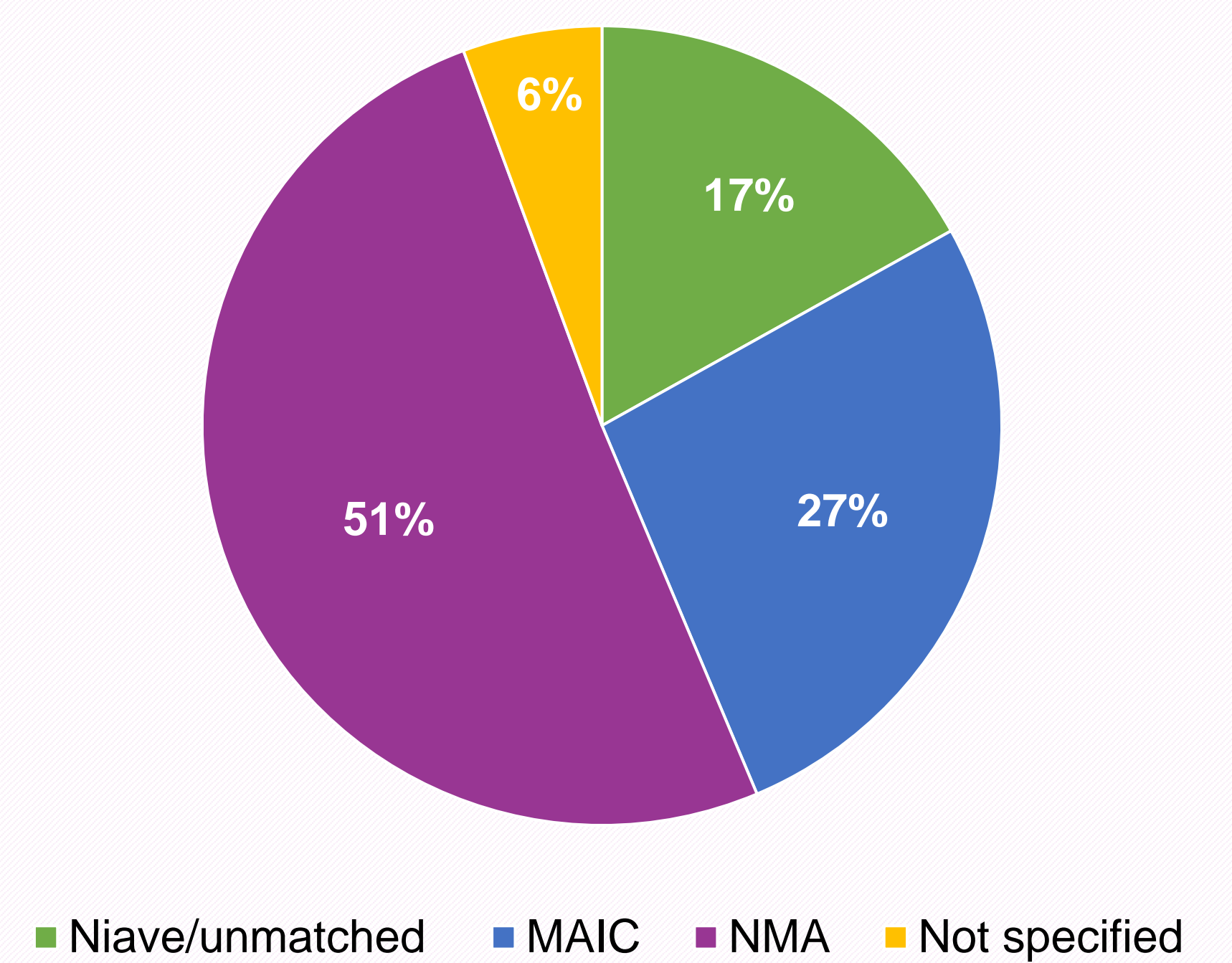
RESULTS

- Between 2018 and 2023 a total of 129 HTAs were completed by NCPE, of which approximately half (n = 71) included the use of indirect evidence to support claims of additional therapeutic benefit/non-inferiority compared to existing treatments.
- Year-on-year, the proportion of submissions containing indirect evidence has remained relatively consistent, ranging between 40-66% (Figure 1).
- There was no statistically significant differences in the probability of achieving a positive reimbursement outcome when using ITCs to establish comparative efficacy (34%) versus using head-to-head trial data (28%) (P = 0.57) (Table 1).
- The most common methodology used was network meta-analysis (NMA, n=36, 51%), followed by matching-adjusted ITCs (n=19, 27%). Naïve/unmatched comparisons were used in 17% of submissions including ITCs (n=12) (Figure 2).
- Regarding common critiques of ITCs, unresolved heterogeneity between trials was frequently noted as a concern by the NCPE review group; including differences in treatment regimens of comparators, patient baseline characteristics, and endpoint definitions across trials.

Table 1. HTA submission outcomes in Ireland 2018-2023

	Positive recommendation	Negative recommendation	Total
Indirect evidence	24	47	71
Direct evidence	16	42	58
Total	40	89	129

Figure 2. ITC methods used to support HTA in Ireland 2018-2023.



- When conducting matched comparisons, the review group often concluded that applicants failed to adequately adjust for all potential prognostic or effect modifying factors, resulting in residual bias.
- Other limitations noted by the reviewers included general data concerns, e.g., immaturity of trial data and low patient numbers of the included trials.
- Reviews deemed the use of naïve/unadjusted comparisons to be insufficient for decision making purposes, often suggesting more sophisticated analyses would provide more robust results.
- In cases where the review group considered the ITC methods to be appropriate, caution was still advised when interpreting findings, especially when superiority was being demonstrated, given the uncertainty of indirect evidence.

CONCLUSIONS & BEST PRACTICES

- The NCPE generally accept ITCs as a technique that allows demonstration of the relative efficacy of a new drug versus existing comparators in the absence of head-to-head data.
- Provided the methodology and underlying assumptions of the ITC are well justified, presenting indirect evidence as opposed to direct evidence does not appear to hinder chances of reimbursement success in Ireland.
- NCPE reviewers are likely to judge submissions with indirect evidence more favourably if an applicant conducts appropriate due diligence to ensure trials included in ITCs are sufficiently similar. This is most easily achieved via a stringent systematic literature review and subsequent feasibility assessment.
- While it is generally assumed that applicants should adopt the most parsimonious ITC methodology, the NCPE review group consistently deem naïve/unadjusted analyses to be insufficiently robust for decision making, thus, where possible more sophisticated methods which include population adjustment or incorporate information for the wider treatment network (e.g., NMA) should be explored.
- When considering population adjustment methods, all potential effect modifying variables (and prognostic factors if treatment network is unanchored) should be adjusted for.
- Working knowledge of the NCPE submission guidelines and preferences can lead to more favourable outcomes when submitting indirect evidence to support HTAs in Ireland and maximise the changes of reimbursement.

References

1. National centre for Pharmacoeconomics, Ireland, Electronic database for HTA submissions: Accessible via <https://www.ncpe.ie/category/drugs/>