HTA90

Quality of Clinical Evidence submitted to a National HTA Agency in Ireland

10 years of Drugs for Oncology

Heather Eames[1], Joy Leahy[1], Lea Trela-Larsen[1], Laura McCullagh[1,2]

1. National Centre for Pharmacoeconomics, Dublin, Ireland,
2. Trinity College Dublin, Ireland.

NCPE National Centre for Pharmacoeconomics, Ireland

INTRODUCTION

- The National Centre for Pharmacoeconomics (NCPE) is responsible for the Health Technology Assessment (HTA) of drugs for the state payer in Ireland.
- The quality of evidence included in full HTA submissions remains variable, despite specification of evidence requirements at earlier stages of the NCPE appraisal process.
- Randomised Controlled Trials (RCTs) are generally considered to provide the highest quality clinical evidence, surpassed only by meta-analyses [1]. However, the study quality can be threatened by several factors [2], including;
  - **Study design** – The potential for bias in subjective outcomes is higher in open-label studies than in blinded studies.
  - **Relevance of comparator arm –** The comparator arm treatment acts as a reference point for new interventions, and should be reflective of standard of care (SoC), where possible.
  - **Duration of follow-up –** The study duration should be long enough to detect a relevant difference between the trial arms.
- Non-randomised studies (single-arm trials and basket trials) are of much lower quality evidence than RCTs. They are limited by the high potential for confounding due to the lack of randomisation and comparison with SoC [3].
- Indirect treatment comparisons (ITCs) are required in the absence of an RCT comparing the intervention with SoC. ITCs are subject to several modelling assumptions which are difficult to completely satisfy, often resulting in bias [4].
- The incidence of cancer is increasing, accompanied by increasing costs for cancer drugs. Several of which have been approved by the European Medicines Agency, despite outstanding uncertainties in the clinical evidence [5].

This research aims to:

- Identify at which stage was uncertainty introduced to the assessment of the clinical evidence.
- Determine whether presence of clinical evidence characteristics are associated with recommendations made by the HTA agency.

METHODS

- A retrospective analysis was conducted on the NCPE HTA database, which collects information on all HTA submissions. Additional data extraction of key clinical evidence characteristics (as informed by EUNetHTA guidance) of the "main study" supporting the health-economic model, and ITC (if applicable), was conducted.
- The NCPE HTA recommendations were re-categorised as being 'Positive/Conditional Positive' and 'Conditional Negative/Negative', as described in Table 1.
- The evidence for each HTA was assessed under the hierarchy described in Figure 1. Pearson's Chi squared test was used to determine whether there was a statistically significant difference in the proportion of HTAs within each stage of evidence. All analyses were conducted in R (4.3.0).
- A secondary logistic multivariate regression analysis was conducted in order to validate findings.

NCPE Formal Reimbursement Recommendation	Infers that the NCPE believe that (versus SoC) the drug is expected to [a]:	Classification used in this Research
The NCPE recommends that the drug be considered for reimbursement	• work as well or better • be value for money	Positive
The NCPE recommends that the drug may be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments	• work as well or better • be too expensive • not represent value for money	Conditional-positive
The NCPE recommends that the drug not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments	• work as well or better **OR** be unclear whether the medicine works as well or better **AND** • be too expensive • be very poor value for money	Conditional-negative
The NCPE recommends that the medicine is not considered for reimbursement	• Have differing reasons for why reimbursement is not recommended	Negative

Table 1: NCPE full HTA assessment outcomes

NCPE: National Centre for Pharmacoeconomics; SoC: Standard of care

[a] Plain language wording based on the full HTA assessment.

References;
[1]. Concato J, Shah N, Horwitz RI. Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs. New England Journal of Medicine. 2000;342(25):1887-92.
[2] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013; Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781.
[3] European Medicines Agency "Reflection paper on establishing efficacy based on single arm trials submitted as pivotal evidence in a marketing authorisation" 2022; Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-establishing-efficacy-based-single-arm-trials-submitted-pivotal-evidence-marketing_en.pdf.
[4] Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, et al. Conducting Indirect-Treatment-Comparison and Network-Meta-Analysis Studies: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 2. Value in Health. 2011;14(4):429-37.
[5] Bloem LT, Schelhaas J, López-Anglada L, Herberts C, van Hennik PB, Tenhunen O. European Conditional Marketing Authorization in a Rapidly Evolving Treatment Landscape: A Comprehensive Study of Anticancer Medicinal Products in 2006–2020. Clinical Pharmacology & Therapeutics. 2023;114(1):148-60
[6] Stéphane Roze, Nicolas Bertrand, Lauriane Eberst, and Isabelle Borget Journal of Clinical Oncology 2019; 37:15_suppl, e18350

RESULTS

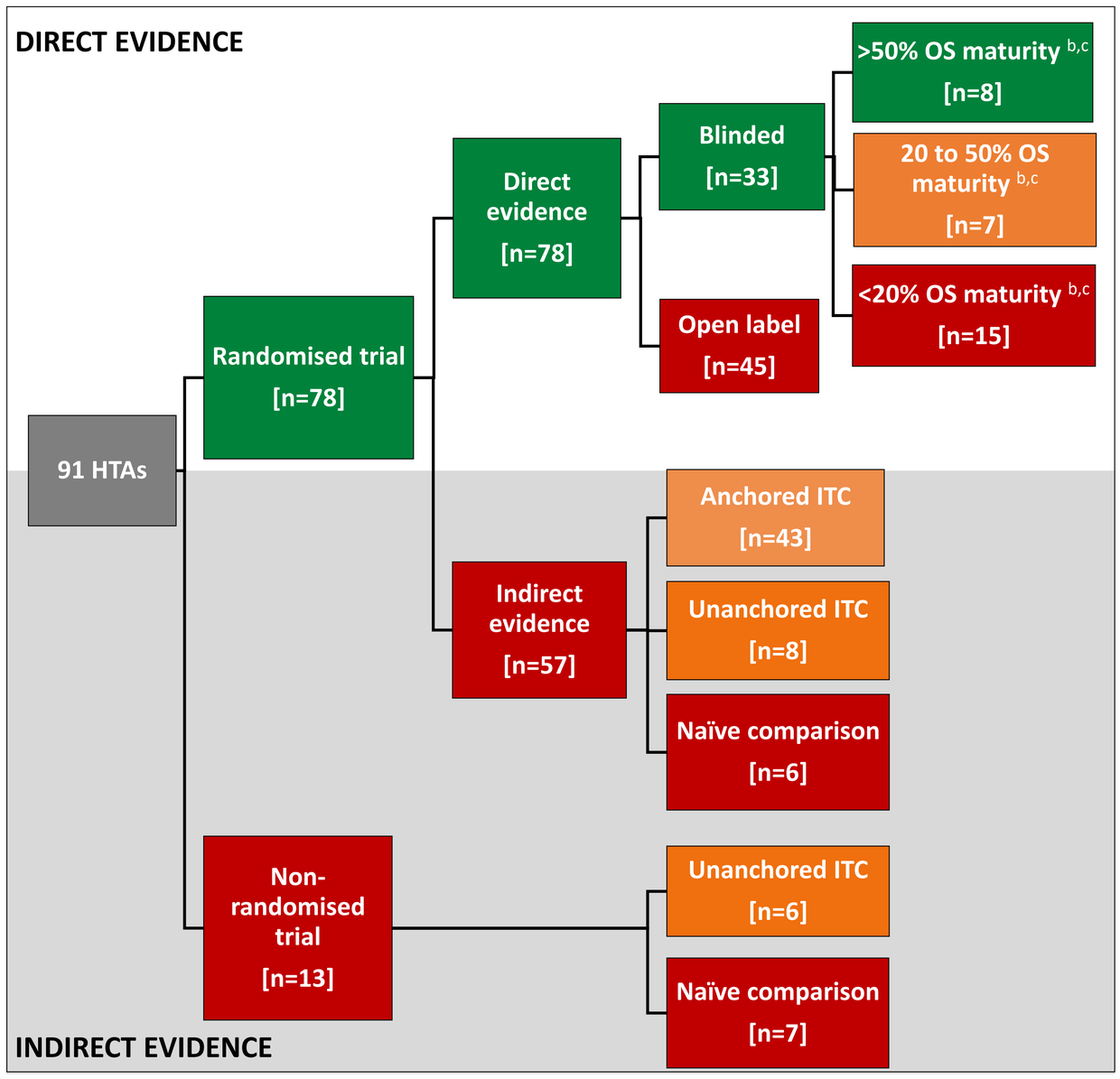

Figure 1: Flow diagram of clinical evidence included in HTAs across the clinical evidence characteristics [a]

HTA: Health Technology Assessment, ITC: Indirect Treatment Comparison, OS: Overall Survival

[a] Note: The white area represents the HTAs with direct evidence and the grey area represents those with indirect evidence.

[b] The OS maturity levels were informed by Roze et al.[6]

[c] OS data maturity was not reported for three clinical trials.

- A total of 91 HTAs for oncology drugs were completed by the NCPE from May 2012 to March 2023, inclusive.
- Majority of HTAs were supported by clinical efficacy evidence from a double-arm RCT (85.7%). HTAs supported by RCTs were numerically more likely to receive a 'Conditional Positive/Positive' recommendation (44%), compared to those without RCT evidence (23%).
- 33 of the 78 RCTs were double-blind in design. Across all HTAs which included a RCT as clinical evidence, the proportion of 'Conditional-Positive/Positive' recommendations were lower for those supported by blinded RCTs, compared with open-label RCTs (39.3% versus 48.8%).
- Overall, HTAs supported by studies with greater than 50% OS maturity were more likely to receive a 'Conditional-Positive/Positive' recommendation (57.1%), than those with 20 to 50% OS maturity (42.8%), and those with less than 20% OS maturity (31.3%).
- An ITC was conducted for 57 HTAs that possessed direct comparative evidence but lacked comparative evidence with SoC. HTAs supported by anchored and unanchored ITCs resulted in similar reimbursement recommendations.
- The vast majority of HTAs supported by non-randomised trials, received a 'Conditional Negative/ Negative' recommendation (76.93%), compared to those supported by RCT evidence (56.41%).
- In the main, these outcomes were supported by the outputs of the multivariate regression analysis

CONCLUSION

- This study suggests that HTAs supported by RCTs are more likely to receive a 'Conditional-positive/Positive' recommendation. Overall, only eight HTAs were supported by direct clinical evidence from a double-blind RCT with OS data exceeding 50% maturity.
- A key limitation of this study is that the quality of evidence submitted is only one domain of the HTA evaluation process. No tests were statistically significant; partly explained by small sample sizes.