Indirect Treatment Comparison Methods in NICE Immuno-Oncology Technology Appraisals: Implementation and Critique

HTA232

Pagotto A,[1] Langford B,[1] Rinciog C,[1] Sawyer L[1]

[1]Symmetron Limited, London, England • Poster inquiries: apagotto@symmetron.net • www.symmetron.net • Presented at ISPOR 2022 Vienna Annual Meeting

Introduction

- In recent years, immuno-oncology (I-O) therapies have emerged as novel treatment options for cancer; their clinical and cost effectiveness have been evaluated by Health Technology Assessment (HTA) bodies in comparison to standard of care and other targeted therapies.[1,2,3]
- Indirect Treatment Comparison (ITC) techniques have frequently been employed in HTA appraisals to assess the efficacy of I-O therapies in the absence of head-to-head trials.

Objective: To evaluate the different approaches and main critiques to the implementation of ITC methods in I-O appraisals submitted to the National Institute for Health and Care Excellence (NICE) in the UK.

Methods

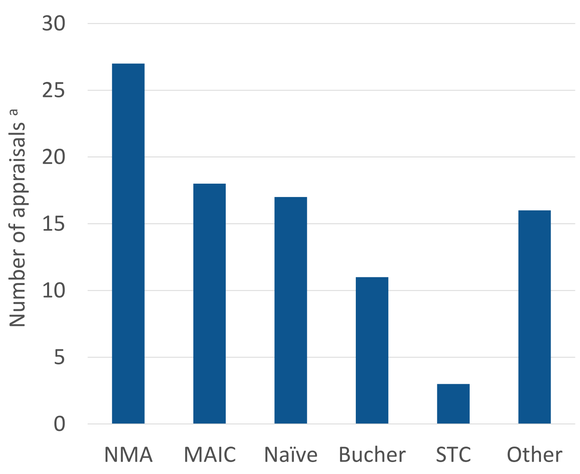
- The Cancer Research Institute classification[1] was used to identify I-O therapies with technology appraisals published between January 2011 and March 2022 from the NICE website (excluding terminated appraisals).[4]
- General information and NICE recommendations for each I-O technology were obtained from the NICE website. ITC methods and Evidence Review Groups (ERGs) and NICE committees' critiques of these methods were extracted from NICE Final Appraisal Documents (FADs) and categorised. When relevant information was not reported, the manufacturer's submission and the ERG report were examined, if available.

Results

Appraisal overview

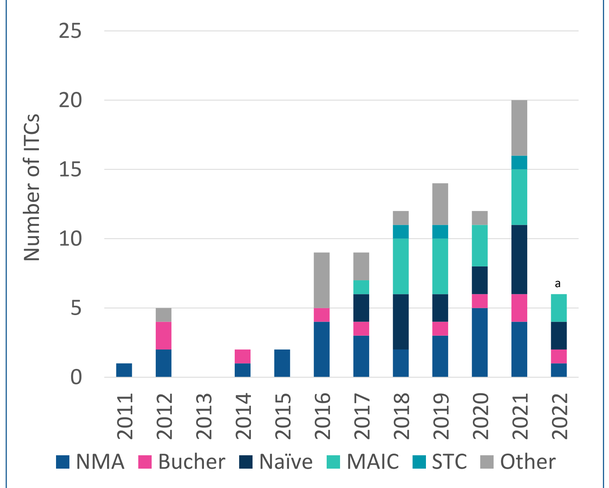
- Of the 92 I-O appraisals identified, 64.1% included at least one ITC.
- The most common methods used in appraisals were network meta-analyses (NMAs), matching-adjusted indirect comparisons (MAICs), naïve comparisons and Bucher comparisons (**Figure 1**).
- Use of ITCs has increased in recent years. MAICs, simulated treatment comparisons (STCs) and naïve comparisons were employed from 2017 onwards, after publication of the 2016 NICE Decision Support Unit guidance on population-adjusted indirect comparison methods (**Figure 2**).[5]
- Naïve comparisons were mostly conducted alongside MAICs. In 8 of these appraisals, NICE focussed their critique on the MAIC results; however, in 4 appraisals the ERG preferred the naïve comparison presented by the manufacturer due to concerns about bias.
- The key outcomes assessed in the I-O ITCs were overall survival (64.4% of appraisals) and progression-free survival (57.6% of appraisals).

Figure 1. Types of ITCs used in I-O appraisals



[a] Some I-O appraisals included more than one ITC.

Figure 2. Use of ITC methods in I-O appraisals by year



[a] I-O appraisals published between January and March 2022 were included.

NMAs included in I-O appraisals

- **Bayesian vs. frequentist**: Of the 27 NMAs included in the I-O appraisals, the majority were conducted using a Bayesian framework only; frequentist analyses were uncommon (**Figure 3**).
- **Fixed vs random effects models**: Almost two-thirds of I-O appraisals including an NMA reported the use of both a fixed effects model and a random effects model (**Figure 4**). In 25.9% of NMAs, only a fixed effects model was used due to the sparsity of the network.
- **Survival models**: The proportional hazards assumption (PH) was met and standard NMAs were conducted for 48.1% of appraisals that assessed survival outcomes (**Figure 5**).

Figure 3. Statistical frameworks used in I-O NMAs (n=27)

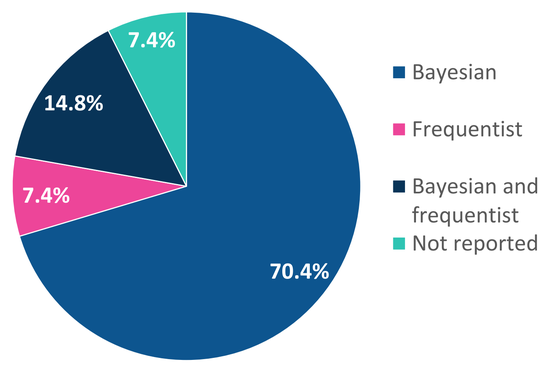


Figure 4. Type of models used in I-O NMAs (n=27)

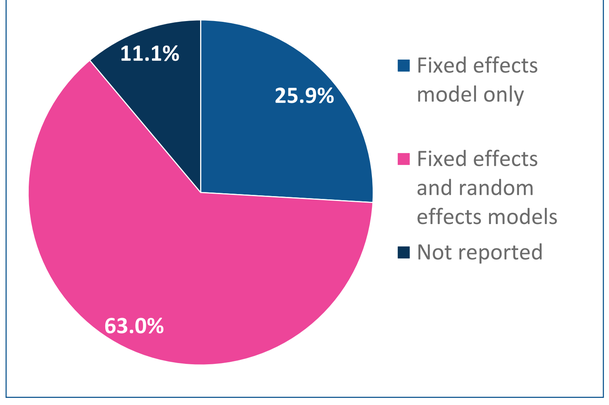
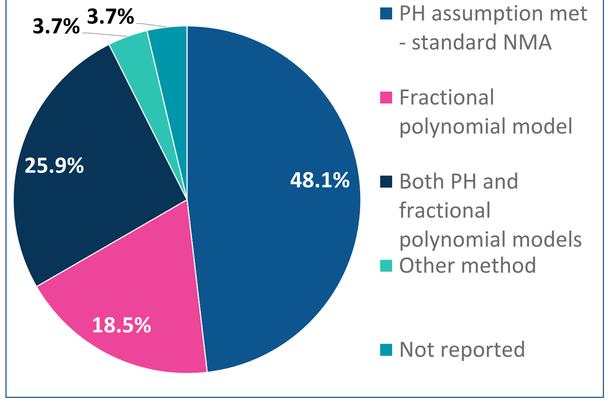


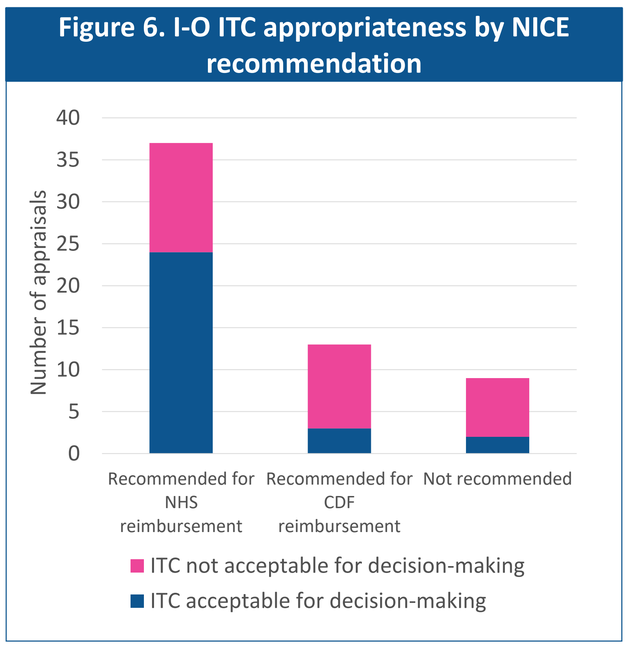
Figure 5. Survival models used in I-O NMAs (n=27)



I-O ITCs and NICE recommendations

- In 49.2% of appraisals, NICE found the ITC acceptable for decision-making: 82.8% were recommended for UK National Health Service (NHS) reimbursement, 10.3% were recommended for Cancer Drugs Funds (CDF) reimbursement and 6.9% were not recommended.
- In 50.8% of appraisals, NICE did not consider the ITC acceptable for decision-making: 43.4% were recommended for NHS reimbursement, 33.3% were recommended for CDF reimbursement and 23.3% were not recommended (**Figure 6**).

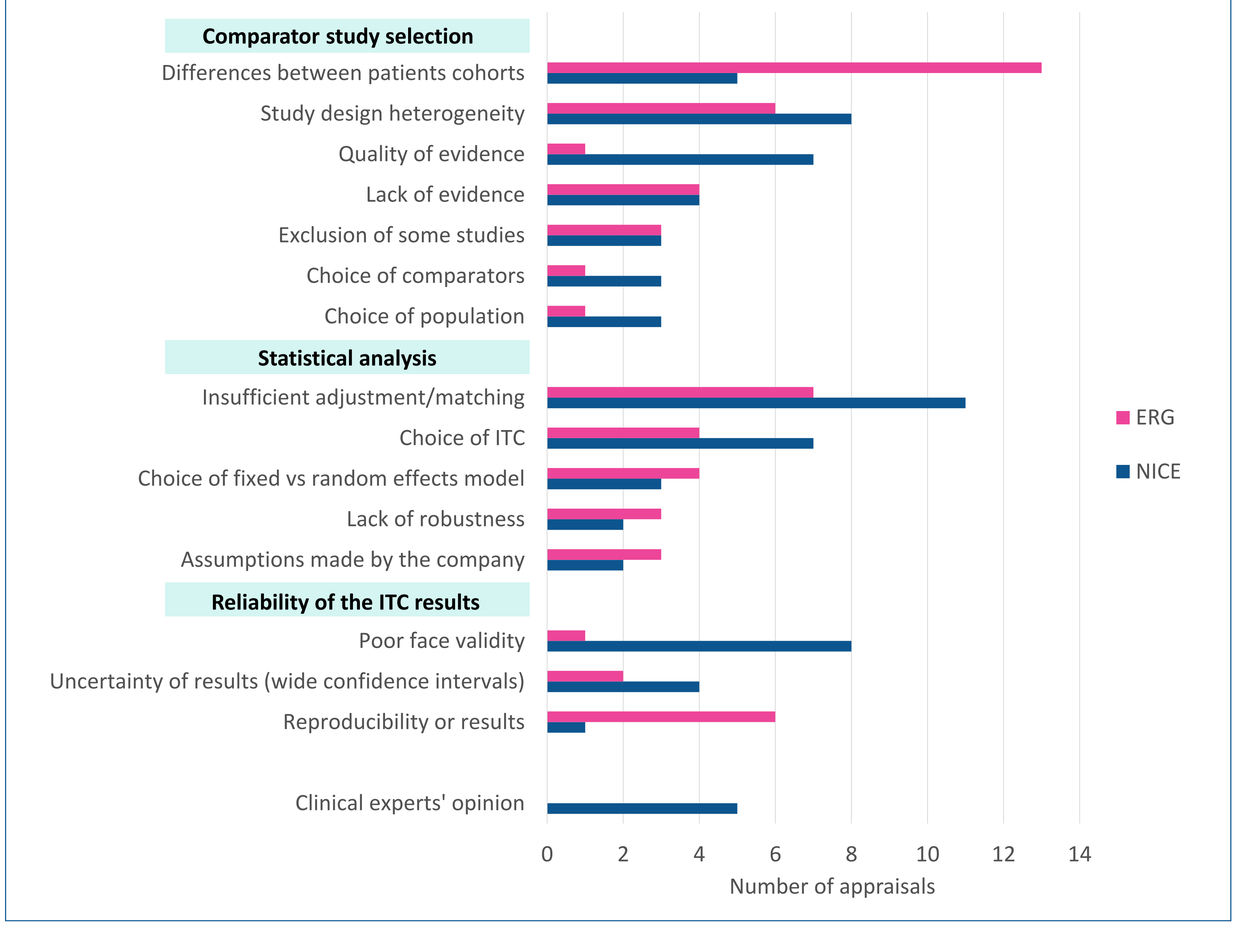
Figure 6. I-O ITC appropriateness by NICE recommendation



Critiques to I-O ITCs

- The ERG/NICE committees' main criticism of I-O ITCs included (**Figure 7**):
  - Comparator study selection (NICE: 44.1%; ERG: 37.3%)
  - Statistical analysis (NICE: 37.3%; ERG: 32.2%)
  - Reliability of the ITC results (NICE: 20.3%; ERG: 13.6%)
  - Clinical experts' opinion (NICE: 8.5%)
- The most common criticism concerned substantial differences between patient cohorts of the studies included in the comparison and insufficient adjustment/matching (for MAICs).

Figure 7. ERG/ NICE committees' criticism to I-O ITCs



Opportunities for Further Work

- The evidence explored was limited to publicly available data contained in the FADs. Additional evidence contained in other available NICE documents (e.g. manufacturer's submission, ERG report) was not systematically examined.
- NICE appraisals were carried out by several ERGs and appraisal committees; critiques may vary depending on the ERGs and committees' internal discussions.

Conclusions and Implications

- Only half of the I-O ITCs were considered acceptable by NICE for reimbursement decision-making, with NMA being the most widely used and acknowledged method. Most of these treatments were recommended for reimbursement (82.8%).
- Substantially fewer treatments were reimbursed when an ITC was considered unsuitable for decision-making (43.3%).
- The main criticism highlighted by the ERGs and NICE committees concerned the comparator study selection (e.g. patient cohort differences, study design heterogeneity), the statistical analyses performed (e.g. choice of ITC method, choice of NMA model, insufficient matching of effect modifiers in MAICs), and the reliability of the ITC results (e.g. poor face validity and lack or reproducibility).

Key message: Manufacturers should ensure the methodological validity and clinical plausibility of their ITCs to increase their chances of I-O treatment approval.

References: (1) https://www.cancerresearch.org/immunotherapy/treatment-types (2) Kaufman HL, et al. The promise of Immuno-oncology: implications for defining the value of cancer treatment. J Immunother Cancer. 2019 May 17;7(1):129. (3) Campbell CM, et al. Health Technology Assessment Decisions in Immuno-Oncology Therapies: Results, Rationales, and Trends. Value in Health. 2017 October 1;20(9):PA401. (4) https://www.nice.org.uk/guidance (5) National Institute for Health and Care Excellence Decision Support Unit. TSD 18: Methods for population-adjusted indirect comparisons in submissions to NICE 2016.

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