A targeted review of methods for effect modifier (EM) and prognostic factor identification in population adjusted indirect comparisons (PAICs) in NICE oncology submissions

Miranda Cooper[1], Robert Hettle[2], Miguel Miranda[3], Charlie Rymer[2]

AstraZeneca Macclesfield, UK[1], AstraZeneca Cambridge, UK[2], AstraZeneca Luton, UK[3]

HTA92

Abstract

- This is a review of the methods used to identify prognostic factors and effect modifiers within population adjusted indirect comparisons (PAICs) both in recent technology appraisals and published literature on suggested methodology.
- In reimbursement submissions, a variety of methods are currently being used to identify relevant factors, the majority use expert opinion in some way.
- Published literature suggests using a combination of methods, although does not provide a clear process to follow.
- This review highlights the need for further guidance on how to reliably identify these covariates and therefore improve consistency across submissions.

Introduction

- The use of PAIC in reimbursement submissions has substantially increased.
- In the case of anchored PAICs, guidance recommends adjusting for EMs only, and adjusting for all EMs and prognostic factors for unanchored PAICs; hence the accurate identification of relevant factors is essential.
- This research investigates methods that are currently being applied in PAIC to identify EMs and prognostic factors, and proposes a suggested methodology for factor identification.

Methods

NICE technology appraisal review

- Due to the comprehensive information the National Institute for Health and Care Excellence (NICE) provides[1], a targeted review of technology appraisals (TA) in 5 chosen oncology indications was performed.
- The search included appraisals that used some form of population adjustment, published between January 2019 and May 2023.
- Methods for prognostic factor and effect modifier identification were extracted and grouped into three broad categories: literature informed, use of expert opinion and conduct of trial data analysis.

Supplementary Literature Review

- To supplement this review, publications relating to PAIC methodology were identified from Google Scholar, and reviewed for information on methods of covariate identification.

Results

Methods used in HTA

- Figure 1 summarises the appraisals selection process.
- Approximately one third of reviewed appraisals used some type of PAIC. Of which, 25% of appraisals used anchored PAIC, 71% used unanchored PAIC. One appraisal (4%) considered both.
- Three quarters of appraisals made use of expert opinion (Figure 2), this was often done in combination with one or more of the other methods.

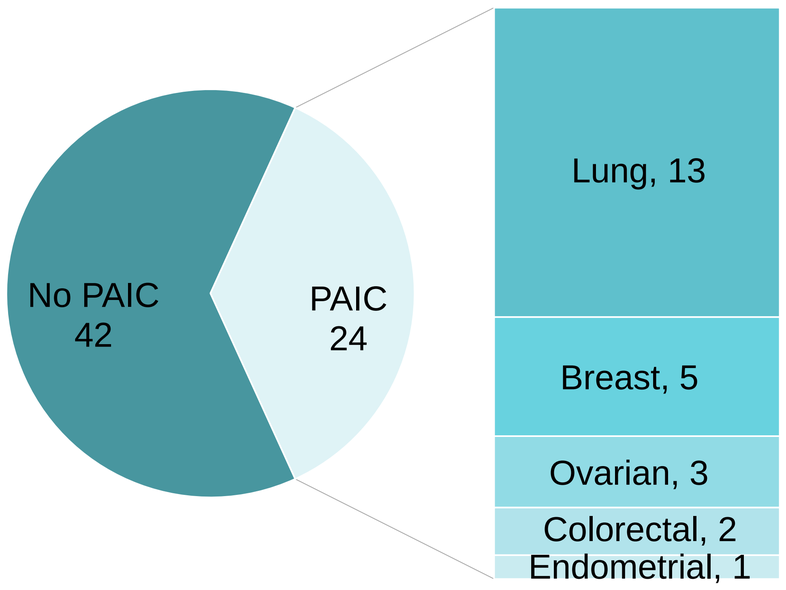

Figure 1 Pie chart showing the number of technology appraisals identified including those that used PAIC, split by the chosen indications

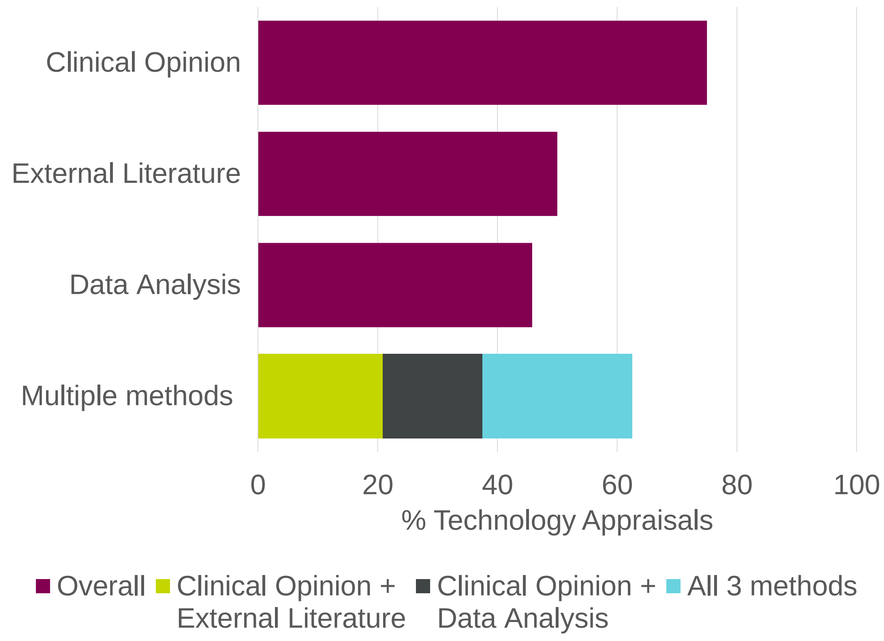

Figure 2 Proportion of appraisals using each method and combination of methods used in appraisals

- Use of clinical opinion in the matching variable selection process could involve advice from internal and/or external medical teams, dependent on the appraisal. Furthermore, the stage at which clinical opinion was sought varied, used either as the main approach to identify a list of relevant covariates or to validate those identified by another method.
  - ➢ Expert opinion was relied on solely in three appraisals (TA770, TA784, TA789)
  - ➢ 5 appraisals validated selection via clinical opinion using data analysis (TA628, TA670, TA693, TA779, TA716)
  - ➢ The other 10 appraisals used clinical opinion as a validation technique (TA571, TA611, TA643, TA704, TA781, TA812, TA836, TA850, TA855, TA866)
- The use of Cox regression models was the most common method of data analysis (8/11 TAs: TA611, TA628, TA653, TA670, TA693, TA716, TA779, TA866), however, there was variation in how results were interpreted for the selection of matching variables.
- There was minimal variation in the literature searches within appraisals. Published literature within the relevant indication was searched to identify known prognostic factors.

Supplemental literature review

- PAIC guidance identified included materials developed by EUnetHTA and NICE[2,3]. Both advocate for the use of clinical guidance and literature reviews to identify EMs and prognostic factors, and prefer pre specification of selected factors though timing of pre specification is unclear.
- Limitations of using data driven approaches for the selection of matching factors identified[3,4] were related to the lack of power available to identify relevant factors. In addition, the challenges that data driven methods face due to multiplicity were raised.
- A previous methodology review of PAICs submitted to NICE between 2010 and 2018 was identified in the supplementary review[5]. This review reported that the most common method of covariate selection in unanchored comparisons was to adjust for all available baseline data. Three of 18 appraisals incorporated expert opinion, and two applied data analysis techniques, suggesting that more emphasis is placed on variable selection methods in more recent TAs.
- A more recent review of the application of PAIC methodologies has also been published since the original review covering a broader range of sources available from 2010 to 2023[6]. Covariate selection methods are grouped as per this review, with the addition of a category for availability of covariates. Of these, the most common justification for inclusion is expert opinion and the proportions using data analysis and literature reviews are similar, which align with the observations from this targeted review.

Discussion

- Across the NICE TAs and literature reviewed the use of expert opinion, published literature and data analysis were the main methods considered.
- Of the NICE TAs identified, clinical opinion was the most common method utilised for matching variable selection. This aligned with both the findings of the most recent review of PAIC literature and with recommended approaches specified in recent PAIC guidance.
- The available guidance on PAIC provides general recommendations on variable selection. This may contribute to the substantial variation in the combination, and specific application, of the selection methods across both TAs and literature.
- Overall, our findings suggest that further guidance on how to identify these adjustment variables would be beneficial to improve consistency in the methods used in NICE appraisals.

Summary

- Building on the preferences from existing PAIC guidance would suggest that generating a candidate list of matching variables using a combination of expert clinical opinion and external literature may be a viable approach.
- Data analysis approaches may be more appropriate used in combination with the other methods given the challenges identified with this method.
- All methods should likely play a role in the selection process, however the influence of each may vary depending on the specific situation, including the disease area and available evidence.

References

1. National Institute for Health and Care Excellence (NICE, 2013) https://www.nice.org.uk/guidance/conditions-and-diseases/cancer (access: 25/10/23).
2. Phillippo, D et al. (2016) Med Decis Making, doi: 10.1177/0272989X17725740. 3. EUnetHTA 21 (2022) www.eunethta.eu/wp-content/uploads/2022/12/EUnetHTA-21-D4.3.1-Direct-and-indirect-comparisons-v1.0.pdf (access: 25/10/23).
4. Remiro-Azócar et al. (2020). arXiv preprint arXiv:2012.05127 5. Phillippo, D et al. (2019) Int J Technol Assess Health Care. doi:10.1017/S0266462319000333. 6. Truong B, et al. (2023). Res Synth Methods. doi: 10.1002/jrsm.1653. Epub ahead of print.

Supported by AstraZeneca

Presented at ISPOR Europe 2023, Copenhagen, Denmark, 13 November 2023