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Investigator-choice comparator arms in oncology clinical trials: implications for HTA/reimbursement assessments

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Introduction and objectives

The rise in the use of investigator-choice comparator (ICC) arms in clinical trials is driven by issues including the routine use of multiple treatment options and the lack of a clear single comparator. Although ICC arms may support pragmatic and individualized treatment choices for patients, they also add variability compared with having a defined standard comparator arm, making interpreting results and establishing comparative clinical benefit more challenging. Although ICCs are accepted by regulators, they may be challenged by health technology assessment (HTA) agencies.

This study considered how different HTA agencies reviewed ICC-based trials and identified the challenges and criticisms raised.

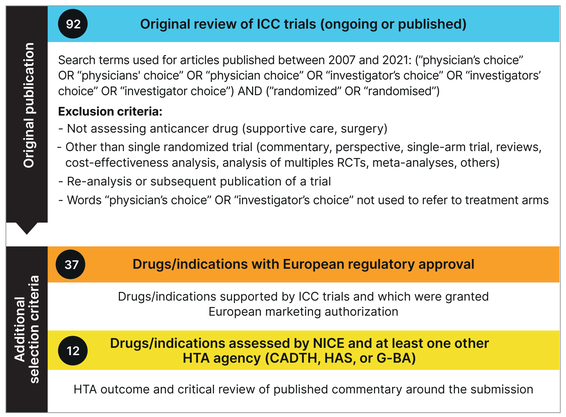
Methods

A published literature review of studies conducted between 2007 and 2021 identified 92 oncology randomized trials with an ICC. The included articles reported trials of anticancer interventions that included the phrases "physician's choice" or "investigator's choice" within the title or the abstract.[1]

This study was selected as the basis of the research as it was the most recent literature review on the topic and provided a comprehensive list of published and ongoing relevant clinical trials.

For each drug/indication included in the literature review, those with a European regulatory approval and a subsequent assessment in the UK (National Institute for Health and Care Excellence, NICE) and additionally in either France (National Authority for Health, HAS), Germany (Federal Joint Commission, G-BA), or Canada (Canadian Agency for Drugs and Technologies in Health, CADTH) were identified (Figure 1). Each HTA outcome and published commentary on the submission were reviewed to identify any payer concerns and criticisms.

Figure 1: Methodology for the selection of clinical trials for review



Results

Of the drugs/indications studied in the 92 trials identified by the published literature review, 37 had received European regulatory approval. A total of 12 drugs underwent HTA by NICE between 2016 and 2023 and, of those, 12 had also been reviewed in Canada, 9 in France, and 6 in Germany (Table 1). However, there was little consistency across agencies.

Table 1: HTA outcomes of oncology drugs

Drug Indication	NICE	CADTH	HAS	G-BA
Nivolumab (melanoma)	Recommended in full[2]	Recommended with restrictions[14]	Not assessed	Recommended in full[35] (Additional benefit not proven)
Pembrolizumab (non-small cell lung cancer)	Recommended with restrictions[3]	Recommended in full[15]	Recommended in full[26]	Not assessed
Brentuximab vedotin (T-cell lymphoma)	Recommended with restrictions[4]	Recommended in full[16]	Not assessed	Not assessed
Encorafenib (colorectal cancer)	Recommended in full[5]	Recommended in full[17]	Recommended in full[27]	Not assessed
Pembrolizumab (colorectal cancer)	Recommended with restrictions[6]	Recommended in full[18]	Recommended with restrictions[28]	Not assessed
Pembrolizumab (urothelial cancer)	Not recommended[7]	Recommended in full[19]	Recommended with restrictions[29]	Not assessed
Nivolumab (head and neck cancer)	Recommended with restrictions[8]	Recommended in full[20]	Not assessed	Recommended in full[36] (Additional benefit not proven)
Sacituzumab (breast cancer)	Recommended in full[9]	Recommended in full[21]	Recommended in full[30]	Recommended in full[37](Significant additional benefit)
Pembrolizumab (breast cancer)	Recommended with restrictions[10]	Recommended with restrictions[22]	Recommended in full[31]	Recommended in full[38] (2 subgroups: additional benefit not proven and considerable additional benefit)
Abemaciclib (breast cancer)	Recommended in full[11]	Recommended with restrictions[23]	Not recommended[32]	Not assessed
Lenvatinib (endometrial cancer)	Recommended in full[12]	Recommended with restrictions[24]	Recommended in full[33]	Recommended in full[39] (Considerable added benefit)
Olaparib (prostate cancer)	Recommended in full[13]	Recommended in full[25]	Recommended with restrictions[34]	Recommended in full[40] (Hint of considerable added benefit)

NICE: "Recommended with restrictions" includes outcomes with specified restrictions + recommendation for use through the Cancer Drugs Fund; CADTH: "Recommended with restrictions" includes outcomes with specified restrictions on the patient population; HAS: "Recommended in full" = SMR (actual medical benefit): sufficient + ASMR (improvement in medical benefit) 1-3; "Recommended with restrictions" = SMR: sufficient + ASMR 4 (overall or for any subpopulation); "Not recommended" = SMR insufficient or SMR sufficient + ASMR 5; G-BA: Includes only outcomes of HTA; all are noted as "Recommended in full" but level of additional benefit is captured.

A number of concerns and criticisms were raised by the HTA agencies (Figure 2), centering on two key themes:

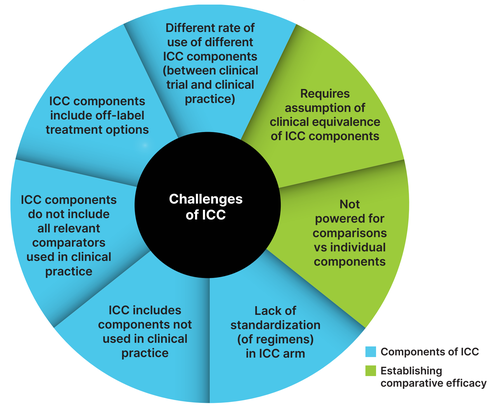
1. Components of ICC: whether the components of the ICC aligned with which treatments were used in clinical practice in the specific market, and how these treatments were used. For example:

- **NICE/G-BA:** ICC arm included specific combinations not used,[5] used off-label[35] or used in a different way[13] from current practice.
- **NICE/CADTH:** ICC did not include all relevant comparators that represented usual care or standard of care.[7,18]
- **HAS:** ICC was not considered optimal for all patients included in the trial given the heterogeneity of the study population.[27]

2. Establishing comparative efficacy: whether the efficacy of the individual components was considered consistent, and whether the study was designed with sufficient power to support the relevant comparisons for the specific HTA agency. For example:

- **NICE:** ICC components were not clinically equivalent, raising concern about conclusions drawn from a blended comparator.[5]
- **NICE:** High use of one ICC element (70% patients) was expected to influence estimation of overall clinical benefit (given potential differential efficacy between ICC components).[6]
- **CADTH:** Treatments included in the ICC arm may have biased the overall results.[19]

Figure 2: Themes identified in HTA critiques of ICC trials



Implications

- The choice of ICC components needs to consider heterogeneous clinical practice across markets.
  - Where a single trial supports regulatory/reimbursement assesments, it will always be challenging to accurately reflect all relevant elements in the comparator arm for all countries.
  - With the advent of joint clinical assessments in Europe, this issue will be exacerbated by a single central EU assessment of clinical efficacy based on a minimal set of PICO elements (population, intervention, comparators, outcomes).
- Manufacturers should provide evidence to support the choice of ICC.
  - Several manufacturers provided evidence of country-specific treatment patterns to support their approach.
  - In several cases, the ICC arm was known to be supported by clinicians within that country (established through expert consultation by manufacturers or HTA agencies).
- Manufacturers can conduct analyses to mitigate some key challenges, but they also have limitations.
  - Subgroup analyses excluding non-relevant components of ICC: Although this provided a comparison with relevant treatments, the analysis was recognized to potentially introduce bias and there was a lack of power for this comparison.
  - Post hoc analyses vs individual ICC components: Although this provides a comparison with only the relevant treatments, is not a randomized comparison, lacks power for the comparisons, and raises issues about sample size in each ICC component.

Conclusions

The increasing use of ICCs is driven by the availability of multiple treatment options and lack of a clear single comparator. However, challenges specific to HTA are evident, with implications for the analyses required to support assessments.

HTA agencies differed significantly in their acceptance of treatments with pivotal trials that included ICC arms, but little evidence showed a direct link between restricting access and the use of ICC arms.

Market-specific generalizability issues will be exacerbated by the introduction of European joint clinical assessments and subsequent market assessments, with an increasing focus on demonstrating how trials align with local clinical practice.

Manufacturers conducting trials with ICCs will need to anticipate potential objections and implement mitigation strategies where they can; however, no clear strategies have emerged that address HTA concerns, and assessment outcomes may be impacted.

References

1. Olivier T, et al. Reporting of Physicians' or Investigators' Choice of Treatment in Oncology Randomized Clinical Trials. JAMA Netw Open. 2022;5(1):e2144770; 2. TA384 (Feb 2016); 3. TA531 (Jul 2018); 4. TA577 (Apr 2019); 5. TA668 (Jan 2021); 6. TA709 (Jun 2021); 7. TA692 (Apr 2021); 8. TA736 (Oct 2021); 9. TA819 (Aug 2022); 10. TA801 (Jun 2022); 11. TA810 (Jul 2022); 12. TA904 (Jun 2023); 13. TA887 (May 2023). Further references can be provided on request.

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