POSTER
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Interpreting the Non-Inferiority Evidence in NICE Streamlined Cost-Comparison Appraisals

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INTRODUCTION

- Streamlined cost-comparisons (sCCAs) are an efficient route of submitting cost-comparison appraisals that are considered low risk to the National Institute for Health and Care Excellence (NICE) in the UK.[1] They have been introduced to decrease the burden of appraisals on all stakeholders involved in health technology assessment (HTA) submissions
- In these sCCAs, demonstrating the non-inferiority or the equivalence of a new technology against comparators is pivotal and should follow rigorous and transparent methods[2]

OBJECTIVES

We investigated the methodological challenges and interpretation of the non-inferiority assumptions in NICE sCCAs.

METHODS

We reviewed all NICE HTAs published between January 2023–September 2024 and screened the available documentation to identify sCCAs. Our review focused on the methodology of the indirect treatment comparisons (ITCs), the interpretation of the ITC results, its uncertainties, the External Assessment Group (EAG) critique and the NICE Committee's final appraisal decision.

RESULTS

- From the 126 HTAs that were not terminated, fifteen appraisals (12%) were sCCAs, as summarized in Table 1, and all sCCAs received positive recommendations

Table 1. List of sCCAs reviewed

Reference number	Title	Non-inferiority statement
TA1007[3]	Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer	'There were no statistically significant differences between rucaparib and olaparib or niraparib regardless of BRCA mutation status in any of the comparisons, supporting the equivalent efficacy/effectiveness of this group of PARP inhibitors both in clinical trials and in clinical practice.'
TA1004[4]	Faricimab for treating visual impairment caused by macular oedema after retinal vein occlusion	'The EAG believes that the company has demonstrated that faricimab is equivalent to at least one of the other technologies in the treatment of macular oedema secondary to retinal vein occlusion, aflibercept, and therefore a cost-comparison case is appropriate.'
TA999[5]	Vibegron for treating symptoms of overactive bladder syndrome	'The efficacy and safety data that informed the assumption of non-inferiority between the drugs was derived from the aggregated data from the EMPOWUR trial and equivalent trial data for mirabegron…'
TA998[6]	Risankizumab for treating moderately to severely active ulcerative colitis	'Across all of the NMAs conducted, risankizumab was associated with comparable efficacy and safety in terms of clinical response, clinical remission, endoscopic improvement, serious infections and serious AEs compared with ustekinumab. Based on this, a cost comparison approach was considered suitable for this submission'
TA990[7]	Tenecteplase for treating acute ischaemic stroke	'Compared with alteplase, tenecteplase is associated with non-inferior efficacy and equivalent safety outcomes.'
TA985[8]	Selective internal radiation therapy with QuiremSpheres for treating unresectable advanced hepatocellular carcinoma	'Although no robust, high quality, comparative evidence is available for QuiremSpheres, nor to inform direct or indirect treatment comparisons between QuiremSpheres, SIR-Spheres, and TheraSphere, the EAG believes that these interventions are likely to be broadly similar in terms of overall health outcomes and that the case for a cost comparison has been met.'
TA956[9]	Etrasimod for treating moderately to severely active ulcerative colitis in people aged 16 and over	'In the absence of non-inferiority or equivalence testing, the EAG considers that only statistically significant NMA results favouring etrasimod can provide conclusive evidence that etrasimod is likely to provide similar or greater health benefits versus comparator treatments.'
TA953[10]	Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema	'No significant differences were observed between the two therapies across any of the examined efficacy and safety endpoints. In the absence of a head-to-head comparison, the findings of this report can be used to inform pharmacoeconomic assessments of the most cost-effective treatment for patients with diabetic macular oedema who are unsuitable for, or insufficiently responsive to non-corticosteroid treatment.'
TA929[11]	Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction	'The EAG notes that while results for CV mortality and AC mortality were both non-significant, the point estimate for CV mortality suggests a benefit of empagliflozin vs placebo but for AC mortality the value of 1.00 suggests equivalence.'
TA925[12]	Mirikizumab for treating moderately to severely active ulcerative colitis	'We also note that the similarity of the treatment effects and safety of mirikizumab versus ustekinumab and vedolizumab is based on findings of statistical significance in the NMA. Non-inferiority and equivalence have not been statistically assessed in the available evidence in the company submission (e.g. through an equivalence or non-inferiority trial).'
TA918[13]	Bimekizumab for treating axial spondyloarthritis	'The EAG considers non-inferiority between bimekizumab and secukinumab 150 mg or ixekizumab plausible based on the evidence presented, albeit caveated by a number of uncertainties.'
TA916[14]	Bimekizumab for treating active psoriatic arthritis	'All the relevant trials are included in the submission. No head-to-head trials of bimekizumab and ixekizumab have been undertaken so the assumption of clinical equivalence is based on the results from NMAs.'
TA871[15]	Eptinezumab for preventing migraine	'The key uncertainty in the current model is associated with the relative effectiveness, as none of the NMA outcomes applied to the model showed any statistically significant difference between the different anti-CGRPs. For that reason, cost-comparison results were also provided.'
TA868[16]	Vutrisiran for treating hereditary transthyretin-related amyloidosis	'In a within-trial comparison, vutrisiran demonstrated non-inferiority compared to patisiran in terms of pharmacodynamics activity, as the median treatment difference in TTR percent reduction from baseline (vutrisiran – patisiran), the lower limit of which was above the prespecified noninferiority margin of a 10% worsening.'
TA863[17]	Somatrogon for treating growth disturbance in children and young people aged 3 years and over	'The Phase 3 pivotal study met the primary efficacy objective. Somatrogon administered once weekly was non-inferior to Genotropin® (somatropin) administered once daily as measured by mean annual HV after 12 months of treatment in prepubertal children with GHD.'

Key: AC, all-cause; AEs, adverse events; CGPR, calcitonin gene-related peptide; CV, cardiovascular; GHD, growth hormone deficiency; EAG, External Assessment Group; HV heigh velocity; NMA, network meta-analysis; PARP, poly ADP ribose polymerase; sCCAs, streamlined cost-comparisons; TA, technology appraisal; TTR, time-to-response.

Limited evidence is often a cause of uncertainty; as in TA918, where too few trials and small populations caused uncertainty around the indirect treatment comparison (ITC) estimates. In this case, equivalent efficacy and safety were still supported, even with limited evidence.

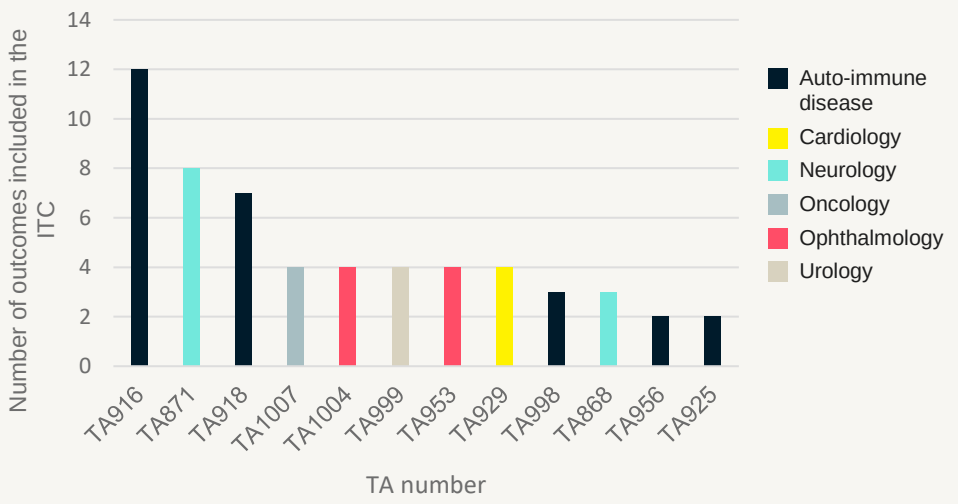
In TA956, the non-inferiority evidence for one subgroup was inconclusive, and the EAG suggested a cost-utility analysis. However, considering clinical expert opinion, non-inferiority evidence in the other subgroup, and experience with other treatments used for this population with the same mechanism of action, the committee subset decided that etrasimod was likely to be an effective and welcome additional treatment option, leading to a positive recommendation

- Two HTAs used direct head-to-head comparison[7,17], while twelve used ITC data for comparative evidence, given the lack of direct comparative evidence. One medical device was assumed to be similar to comparators without robust comparative evidence or ITCs available[8]
- The ITCs included the full population (n = 2)[11,16], only subgroups (n = 3)[9,12,13] and both (n = 7)[3,4,5,6,10,14,15]
- ITC networks were aligned (n = 8) or included other comparators beyond the decision problem defined by the submitting companies (n = 4). However, the latter was not deemed to bias the results
- All ITCs included multiple efficacy endpoints alongside safety. In the studies including an ITC, there were between two and 12 outcomes included, where the highest number of outcomes related to an autoimmune disease

Figure 1. Population or subpopulation included in the ITC

Key: ITC, indirect treatment comparison.

Figure 2. Efficacy endpoints included in the ITCs



Key: ITC, indirect treatment comparison; TA, technology appraisal.

CONCLUSIONS

- More guidance is needed to support the assessment of non-inferiority in sCCAs
- Terminology should be standardized: 'similarity', 'non-inferiority' and 'equivalence' are used interchangeably
- Non-inferiority margins need to be defined and reflect changes in outcomes that are clinically relevant for the patient to make the assessment of non-inferiority clearer
- A framework and criteria to seek clinical expert opinion might reduce decision-making uncertainty, especially when a limited evidence base poses challenges to a conclusive ITC interpretation

REFERENCES

1. NICE. 2022–23. www.nice.org.uk/Media/Default/About/what-we-do/PATT/PATT-final-report-2022-23.pdf Accessed: September 2024.
2. NICE. 2022 (updated: 31 October 2023). www.nice.org.uk/process/pmg36/chapter/committee-recommendations. Accessed: September 2024.
3. NICE. 2024. www.nice.org.uk/guidance/ta1007 Accessed: October 2024.
4. NICE. 2024. www.nice.org.uk/guidance/ta1004 Accessed: October 2024.
5. NICE. 2024. www.nice.org.uk/guidance/ta999 Accessed: October 2024.
6. NICE. 2024. www.nice.org.uk/guidance/ta998 Accessed: October 2024.
7. NICE. 2024. www.nice.org.uk/guidance/ta990 Accessed: October 2024.
8. NICE. 2024. www.nice.org.uk/guidance/ta985 Accessed: October 2024.
9. NICE. 2024. www.nice.org.uk/guidance/ta956 Accessed: June 2024.
10. NICE. 2024. www.nice.org.uk/guidance/ta953 Accessed: October 2024.
11. NICE. 2023. www.nice.org.uk/guidance/ta929 Accessed: June 2024.
12. NICE. 2023. www.nice.org.uk/guidance/ta925 Accessed: June 2024.
13. NICE. 2023. www.nice.org.uk/guidance/ta918 Accessed: June 2024.
14. NICE. 2023. www.nice.org.uk/guidance/ta916 Accessed: June 2024.
15. NICE. 2023. www.nice.org.uk/guidance/ta871 Accessed: June 2024.
16. NICE. 2023. www.nice.org.uk/guidance/ta868 Accessed: June 2024.
17. NICE. 2023. www.nice.org.uk/guidance/ta863 Accessed: June 2024

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