HTA325
THE PERILS OF TREATMENT CROSSOVER IN CLINICAL TRIALS

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Objectives: Treatment crossover can confound the estimation of a therapy's true effect on overall survival (OS). While various statistical methods exist to adjust for this bias, how health technology assessment agencies consider crossover in decision-making remains unclear. This study compared the approaches taken by agencies in oncology assessments, focusing on whether they consider results adjusted for crossover. ***Methods:*** Oncology appraisals, published by the National Institute for Health and Care Excellence (NICE) between 2001 and April 2025 (n=386), were reviewed to identify those discussing statistical methods to adjust for crossover. Corresponding evaluations (same drug, indication, and clinical trial) conducted by the Haute Autorité de Santé (HAS) and the Gemeinsamer Bundesausschuss (G-BA) were retrieved for comparison. ***Results:*** Of n=18 NICE appraisals identified which discussed adjustments for crossover, corresponding assessments were found for all n=18 from HAS and for n=15 from G-BA. Adjustment methods were mentioned in only two HAS, and six G-BA assessments. Two NICE appraisals showed a shift from non-statistically to statistically significant hazard ratios for OS after crossover adjustment. In both cases, NICE accepted the adjusted OS results. In the equivalent submissions to HAS and G-BA, the adjusted OS results were statistically significant in only one case. Notably, HAS provided no commentary on the adjusted data in either case, and G-BA commented in only one case, expressing scepticism regarding the use of a non-pre-specified adjustment method. ***Conclusions:*** NICE considered the results from adjusted analyses using several different methodologies across multiple assessments, with adjustments influencing the interpretation of OS outcomes in some cases. In contrast, crossover adjustments had limited impact on the HAS and G-BA decision-making process. This difference highlights the importance of planning to mitigate for crossover and another challenge for methodological alignment required for the Joint Clinical Assessment framework, where harmonizing evidentiary standards is essential.

HTA326
THE PHANTOM MENACE: HOW CONSULTATIONS AND APPEALS DURING NICE HST APPRAISALS CONTRIBUTE TO DELAYS IN PATIENT ACCESS

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Objectives: NICE's Highly Specialised Technology (HST) programme evaluates treatments for ultra-rare conditions, aiming to provide timely patient access. However, delays from consultations, appeals, and additional committee meetings can delay final guidance. This study evaluated the impact of these events on the time to final guidance in completed HST appraisals. ***Methods:*** Publicly available HST appraisal data (programme inception to May 2025) were extracted and analysed for appraisal duration (Final Scope to Final Evaluation Determination) and number of consultations, appeals, and committee meetings. ***Results:*** Of 30 published HST appraisals, 2 technologies were not recommended. Mean duration of recommended appraisals was 81 weeks (range: 39-318). Of the 28 appraisals that ultimately resulted in a positive recommendation, 4 had no consultations or appeals and 24 underwent ≥1 consultation. Four of these HST appraisals required 2 consultations before final guidance was issued. Appeals were less frequent; 3/24 appraisals had ≥1 appeal. Where reported, the number of evaluation committee meetings ranged from 2 to 5. The duration of the HST appraisal process was substantially longer when additional events such as consultations and appeals were held, when compared with HST appraisals for which no consultations or appeals were observed (mean [range] duration, 86 [39-318] vs. 51 [44-58] weeks). ***Conclusions:*** Delays in the HST appraisal process can push back patient access to rare disease therapies by many months, sometimes years. For the submitting company, this can increase both operational costs and financial burdens from lost revenue. Our findings relating to delays in patient access in rare diseases support the case for better preparation for submission, which should include increased engagement with HTA bodies and the clinical and patient community, coupled with well-thought-out evidence collection and value messaging. These steps can mitigate risk and increase the chances of a smooth, timely appraisal that benefits all parties.

HTA327
THE PREFERENCES FOR ADVANCED THERAPY MEDICINAL PRODUCTS: A MULTICRITERIA DECISION ANALYSIS FRAMEWORK

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Objectives: Advanced therapy medicinal products (ATMPs) represent revolutionary treatments for previously untreatable or inadequately managed conditions. However, ATMPs present unprecedented challenges for healthcare systems due to their exceptional costs, limited long-term efficacy data, complex manufacturing requirements, and uncertain durability of effect. The study aims to deliver an ATMP-specific MCDA framework that balances affordability, clinical effectiveness, and long-term value considerations. ***Methods:*** Our study employs a mixed-methods approach beginning with a systematic literature review examining established MCDA frameworks in healthcare, specifically analyzing EVIDEM, Advanced Value Framework, Hungary's National Framework, and VALIDATE for their applicability to ATMPs. We also reviewed recent HTA decisions for approved ATMPs to identify evaluation patterns and challenges. A comprehensive criteria list will be developed and refined through a 2-round modified Delphi process involving a multidisciplinary panel of 25 experts (clinicians, health economists, patient representatives, payers, industry specialists, and bioethicists). Finally, the Analytic Hierarchy Process (AHP) was applied to establish stakeholder preferences for the refined framework. ***Results:*** After comprehensive reviews, we identified five core value domains relevant for ATMPs: disease burden, therapeutic outcomes, economic impacts, innovation level, and evidence quality, with 18 potential criteria. After experts reviewed the definitions of each factor, we kept 15 criteria and deleted the last three with the lowest scores. The rankings are as follows: 1. Improvement of efficacy/effectiveness 2. Unmet Medical Needs 2. Improvement of adverse events and tolerability 4. Evidence on Efficacy and Comparative Effectiveness 5. Disease severity 5. Size and Design of Trials 5. Disease Progression and Long-Term Effect 8. Public health interest 9. Affordability 10. Ethical analysis 11. Cost-effectiveness 11. Innovation 13. Family and Societal Impact 14. Equity 15. Budget impact. ***Conclusions:*** AHP was further applied to establish stakeholder preferences for the refined framework. We expect this framework to provide decision-makers with a structured approach to evaluate ATMPs.

HTA328
THE RISE OF OPTIMIZATION IN NICE GUIDANCE: A TWO-DECADE REVIEW WITH A FOCUS ON PREVENTION

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Objectives: The National Institute for Health and Care Excellence (NICE) assesses the clinical and cost-effectiveness of medicines for NHS use in England. Recommendations may be full or optimised, the latter restricting use to a subpopulation rather than the full licensed indication. The proportion of optimised recommendations has increased in recent decades. This study describes patterns in NICE's use of optimised recommendations, with a focus on preventive medicines. ***Methods:*** Data on all optimised recommendations issued by NICE over the last twenty years were extracted from published Technology Appraisals (TAs). Trends were analysed by year, therapeutic area, and preventive vs non-preventive classification. Descriptive statistics were used to evaluate patterns. ***Results:*** Optimised recommendations have grown at an average annual rate of 6.7% over the last twenty years, outpacing the overall growth in TAs, and greatly surpassing the average annual growth rate of 1% seen in full recommendations. Musculoskeletal therapies received optimised recommendations in 64% (n=70) of appraisals over the last twenty years - one of the highest proportions - whereas, cancer received optimised recommendations for only 18% (n=65). Other disproportionately affected areas include diabetes, endocrine and metabolic conditions, and neurological disorders. Preventive medicines were found to be 1.83 times more likely to receive an optimised recommendation than non-preventive medicines, based on analysis of 85 preventive and 1,110 non-preventive medicines. 44% of preventive medicines had their recommendations optimised between 2004/05-2024/25, versus only 29% of non-preventive medicines. ***Conclusions:*** NICE is increasingly using optimisation, but the implications for patient access remain unclear. While optimisation may be seen as restricting access, it could alternatively enable access to treatments that might otherwise be rejected outright. Preventive medicines and certain therapeutic areas appear disproportionately affected. Optimisation may unintentionally undermine public health strategies reliant on widespread preventive treatment, and further research is needed to assess its broader impact.

HTA329
THE ROLE OF ENVIRONMENTAL EVIDENCE IN HTA: COMPARATIVE INSIGHTS INTO GLOBAL ASSESSMENT FRAMEWORKS

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Objectives: With environmental sustainability becoming a key focus in healthcare, the first step toward meeting environmental commitments is to measure the impact of health interventions and integrate insights into decision-making frameworks. Environmental impact is a relevant domain for health technology assessment (HTA) agencies; however, there currently lacks an agreed or harmonious approach on a decision-making framework, the evidentiary standards needed to support claims of reduced environmental impact, and how decision outcomes will be influenced. This research aimed to explore the role of environmental impact within key global HTA agencies' decision-making frameworks. ***Methods:*** A targeted search of national HTA agencies was conducted between January and June 2025 to identify relevant policies, position statements, or guidelines that addressed environmental impact or