

Introduction

ATMPs offer ground-breaking opportunities for the treatment of disease, but value demonstration is often inhibited by data generation challenges in small populations, reliance on single-arm studies, and insufficient follow-up to show a curative effect. The UK has introduced policies to help balance the need for patient access to high value therapies, whilst recognising challenges with evidence generation. These include the ILAP, weighting QALYs by disease severity, the IMF, and the HST programme.

Objective

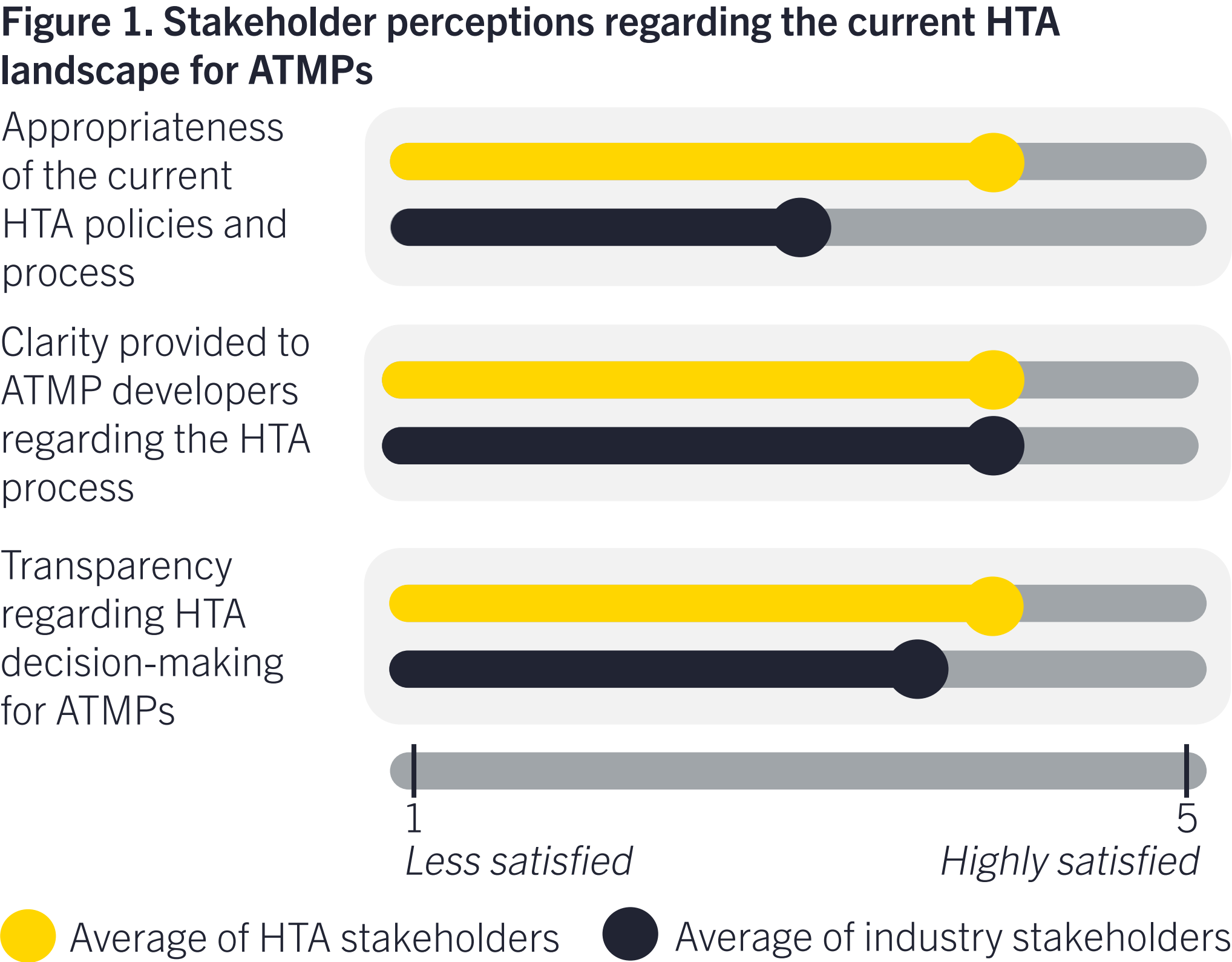
This research explores the impact of four UK policies (the ILAP, HST programme, IMF and disease severity modifier) on evaluation of ATMPs in the UK, including key challenges and future recommendations.

Method

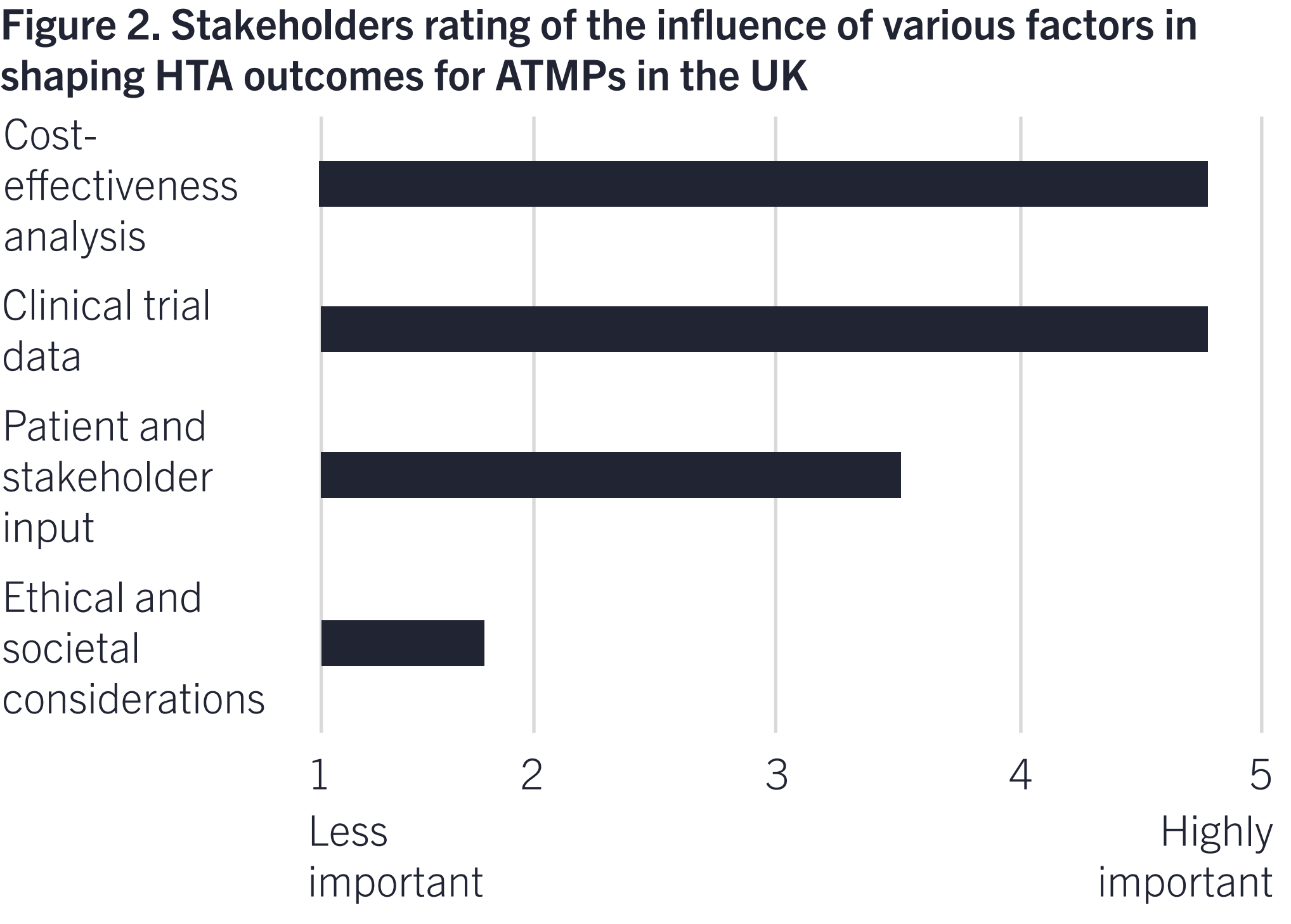
A comprehensive review of relevant literature and policy documents informed the evolving ATMP policy landscape in the UK. Primary research was conducted with three former HTA members and three industry stakeholders from the UK. Interviews were conducted from September to October 2023.

Results

Overall perceptions of the HTA landscape for ATMPs were broadly aligned between HTA and industry stakeholders (Figure 1). The largest divergence was in terms of appropriateness, where HTA experts reported more satisfaction than industry stakeholders.



As shown in Figure 2, clinical data and cost-effectiveness are recognised as the key drivers of HTA outcomes for ATMPs in the UK. Importantly, cost-effectiveness is the most important arbiter of reimbursement decisions, which can present significant challenges for ATMPs launching with high levels of uncertainty in long-term incremental clinical/economic value, despite patient advocacy and the ethical drivers for new treatments.



 You could have great clinical trial data, but if your cost effectiveness was [not] what NICE expected, it wouldn't get through. So, cost effectiveness has to be right.

Former NICE Appraisal Committee member, UK

 So much rests on the ability to model the disease, capture the relevant clinical and QoL impact of the drug, and then extrapolate the costs and benefits across the lifetime horizon.

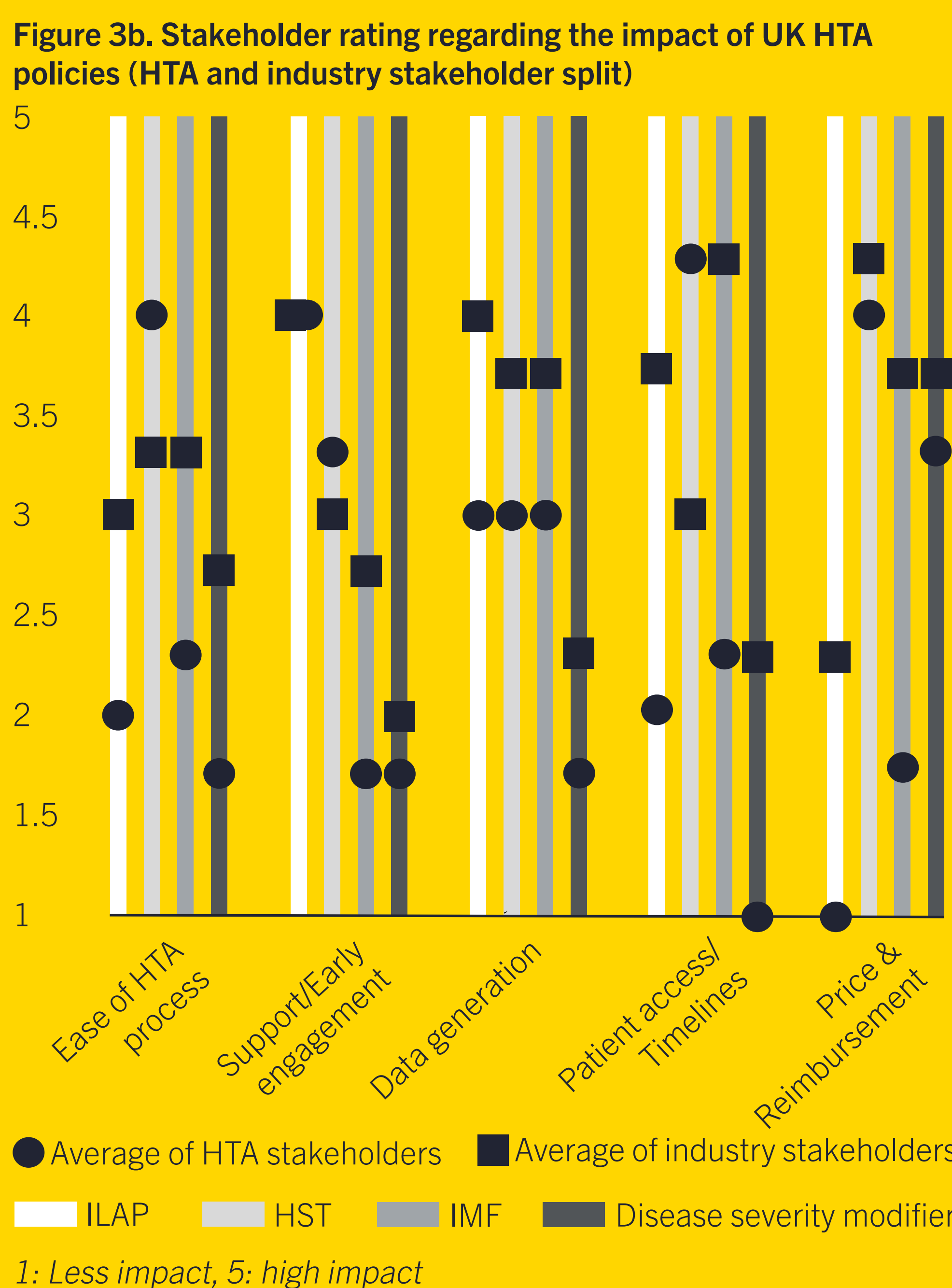
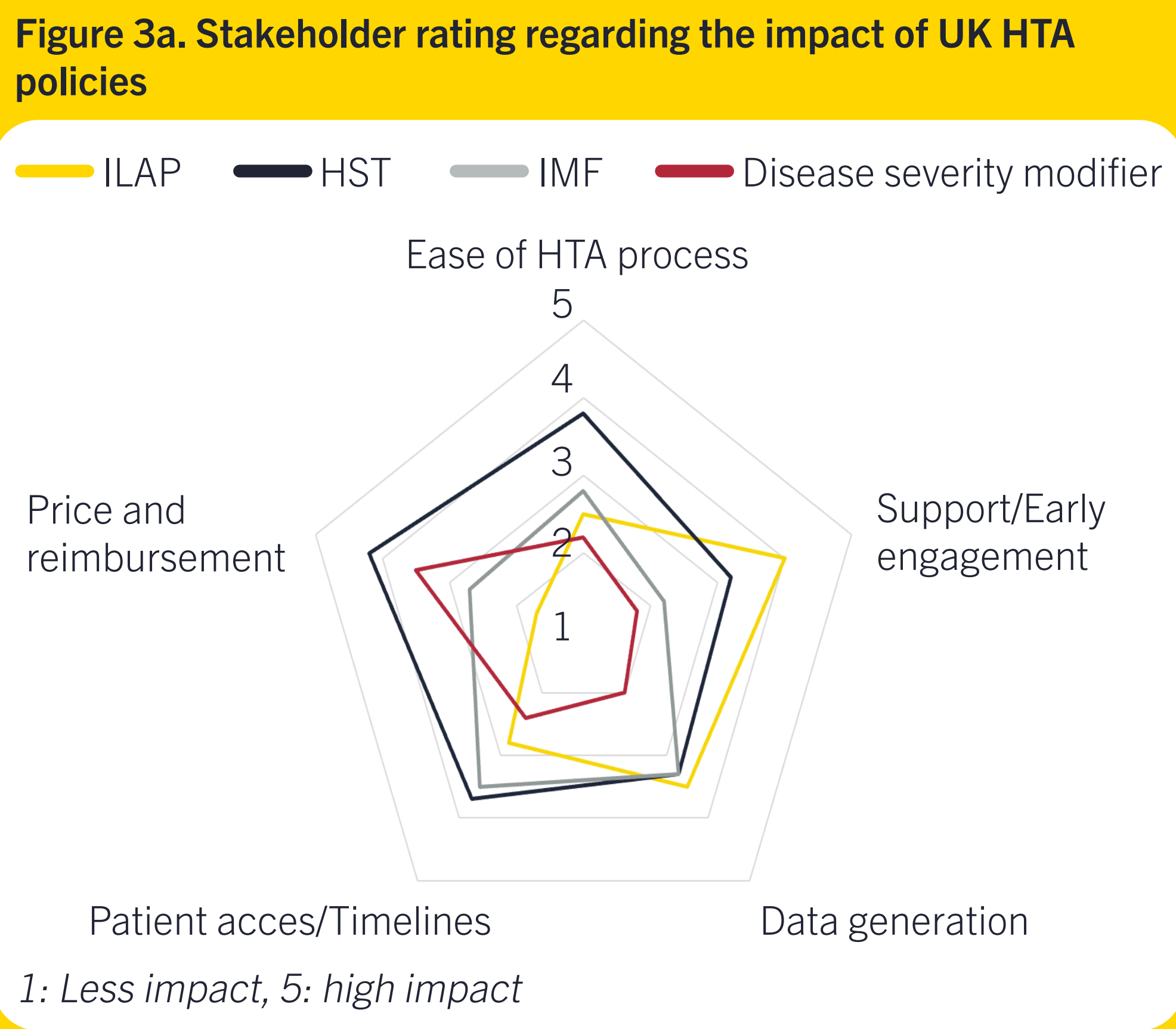
Industry Stakeholder

As shown in Figure 3, the ILAP, HST, IMF, and disease severity modifier have varying potential impact for the evaluation of ATMPs. ILAP provides early guidance for manufacturers and facilitates engagement with senior NHS stakeholders, which is particularly valued for SMEs navigating the UK access landscape. Furthermore, this can enhance investor interest through the Promising Innovative Medicine designation.

The NICE HST programme provides an increased ICER threshold for medicines for very rare, and often very severe, diseases that need specific considerations and flexibilities as part of the evaluation process. The IMF provides conditional reimbursement from the NHS for new therapies with the potential to demonstrate cost-effectiveness, whilst additional evidence is generated to inform further evaluation. The disease severity modifier assigns additional weight to QALY gains for severe diseases (thereby increasing willingness to pay), based on thresholds for estimated QALY shortfall.

 Most of the common diseases we think about like musculoskeletal diseases, diabetes, heart failure, don't qualify for the severity status in the disease severity modifier. So, it has to be quite an outlier. In oncology, the old end of life modifiers would have got you a weighting of 1.7x now most things are getting 1.2x. They've got less generous in UK, it's been good for finances, but not good for access.

Former NICE and SMC member, UK

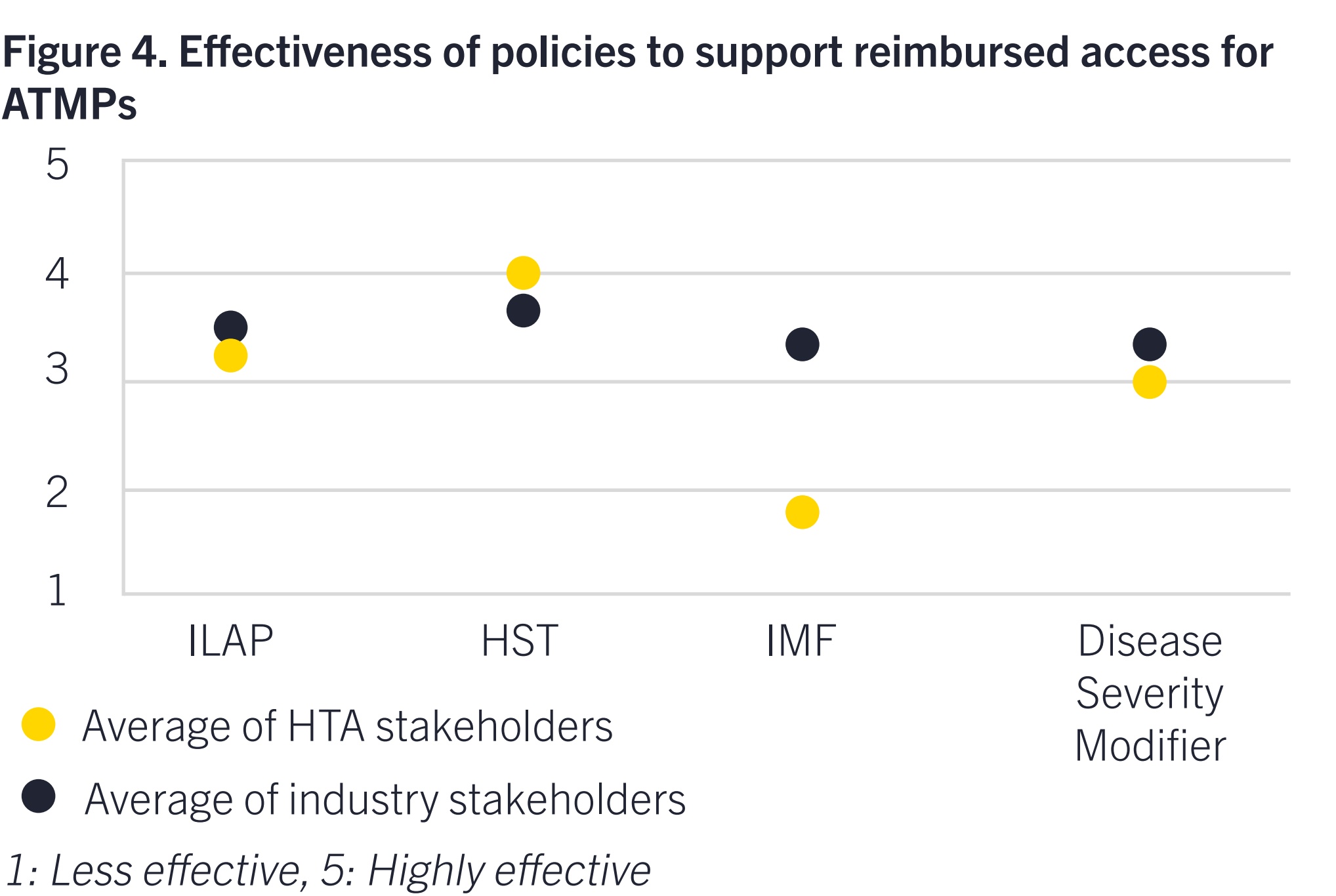


Based on the relative strengths of each policy and their practical impact, both industry stakeholders and former HTA members agreed that the HST programme is the most effective mechanism for supporting the evaluation of ATMPs in the UK (Figure 4).

 Due to HST, there is an overall recognition of the need for a separate pathway for such therapies, it's a signal that the healthcare system...attaches high value to ATMPs and is willing to make allowances to accommodate those therapies.

Industry Stakeholder

Industry stakeholders emphasised the potential role of the IMF in promoting accelerated reimbursed access to promising non-cancer therapies where further evidence is required to confirm cost-effectiveness for the NHS. They regarded the disease severity modifier as the least influential, largely owing to the uncertainties surrounding evaluation of disease severity. In contrast, HTA stakeholders remained sceptical regarding the IMF, highlighting that no drug has successfully navigated this pathway to date.



The policies considered in this research do support the UK HTA landscape for ATMPs; however, stakeholders identified several persistent challenges:

- The need for innovative pricing models to meet the commercial requirements for manufacturers whilst ensuring value and mitigating risks for the NHS
- Aligning the ethical drivers for making potentially high value innovative therapies available, with the practical challenges of data generation in highly rare disorders
- Understanding acceptable methods for addressing data gaps in rare disorders, including proxy QoL values for relevant health states, synthetic control arms, and extrapolating predicted long-term clinical and cost outcomes
- Incorporating the high societal value of ATMPs into the assessment framework (including reduced carer burden and improved productivity for patients and their families)

The stakeholders expressed the need for further improvements:

- Use of different approaches for HTA and managed entry depending on the type of ATMP (e.g. cell therapies with repeated administration vs. single administration gene therapies)
- Early guidance for manufacturers on acceptable methods to address data gaps where a comparative trial, QoL data generation and/or long-term follow up will not be feasible
- An increase in IMF funding should to support expanded use of conditional access for ATMPs with high levels of uncertainty regarding clinical/economic value at the time of initial appraisal
- Streamline the regulatory process by minimising disparities between the MHRA and EMA
- Develop innovative funding models for ATMPs for common conditions (where products may be cost-effective, however budget impact may not be sustainable)

Table 1. Stakeholder recommendations for specific policies

Policy	Recommendation
ILAP	- Utilise ILAP as a centralised engagement platform with NICE, NHS England and MHRA - Increase advocacy and public awareness regarding early engagement with the ILAP process
HST	- Ensure manufacturer understanding of HST eligibility criteria and potential routing early in the clinical development process - Within early engagement, support companies to understand a feasible net pricing range based on the estimated QALY gains - Provide guidance on acceptable methods for addressing data gaps in complex rare disorders, including generating proxy QoL values, synthetic control arms, and extrapolating long-term outcomes
IMF	- Provide clearer guidance for appraisal committees on when IMF inclusion is appropriate (to avoid under-utilisation) - Consider increased funding for expanded conditional access for ATMPs where there is limited evidence at launch - Enhance the transparency of eligibility criteria for IMF inclusion to increase confidence for manufacturers on the feasibility of this access route
Disease severity modifier	- Provide increased support for manufacturers to determine their likely eligibility for QALY weights according to disease severity - Increase the weighting (and WTP) for QALYs in severe disorders, thereby incentivising clinical development and earlier UK launches for therapies targeting severe indications

Conclusion

Overall, the study highlights the importance of a balanced approach that ensures robust evaluation of ATMPs while considering the challenges faced by manufacturers. Continued evaluation and refinement of policies based on feedback of industry stakeholders is crucial for optimising the evaluation and adoption of ATMPs in the UK.