Editorial

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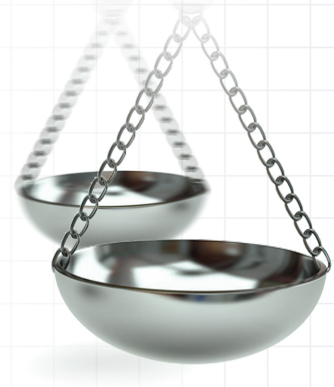

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EU HTA Joint Clinical Assessment: are patients with rare disease going to lose out?

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"The EU HTA guidance should strike a balance between evidential uncertainties and patient access, aligning with the pragmatic approaches of some member states."

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The EU Regulation on Health Technology Assessment (EU HTA)aims to create a framework for cooperation between EU member states in joint clinical assessment (JCA). However, initial guidance on indirect comparisons appears to dismiss the use of real-world evidence (RWE) and external control arms, which are often the only available evidence for rare disease treatments. This approach may lead to inequalities in patient access to these treatments across the EU. While RWE has limitations, health technology assessment agencies such as NICE and CADTH have developed frameworks to minimize bias and enable the use of RWE in decision-making. The EU HTA guidance should strike a balance between evidential uncertainties and patient access, aligning with the pragmatic approaches of some member states. Failure to consider RWE in JCAs may result in countries conducting their own assessments, potentially increasing inequity for rare disease patients.

The EU HTA is attempting to create a framework for cooperation between EU member states in joint clinical assessment (JCA), expected to take effect in 2025 [1]. We are now beginning to see initial guidance for JCA being published. The first such guidance outlines methodological considerations for indirect comparisons [2]. Despite stating, "*For some interventions, single-arm or non-randomised evidence may be the only evidence available for consideration*" the guidance goes on state that "*it may well be that this evidence is insufficient for estimation of the relative treatment effectiveness in the context of JCA*". This guidance therefore appears to be idealistic rather than pragmatic when considering the likely limited evidence base that can be generated for rare disease treatments.

Developing treatments for rare disease is inherently difficult [3]. The European Medicines Agency (EMA) defines a disease as rare if it afflicts fewer than 5 people in 10,000. Despite being rare, there are many of these diseases, with more than 7000 recognized, and each needing medicines being developed. Given their rarity, researchers often opt for a single-arm trial design to test new therapeutics. There are several compelling reasons to do so. First, when a new therapy holds significant promise for a rare disease, it may be considered unethical to withhold a potentially life-changing or life-saving intervention, particularly when alternative treatment options are limited or non-existent. Second, recruiting participants for rare disease trials can be challenging due to the small patient population and inability to find eligible patients. Additionally, patients may be reluctant to enroll in trials that include a placebo arm, fearing that they might be randomly assigned to the control group and receive an inactive treatment, further exacerbating recruitment challenges. In order to provide comparative evidence for regulatory approval and health technology assessment, the use of real-world data (RWD) external control arms is increasing [4]. However non-randomised comparisons have the potential for bias and therefore until recently have had limited acceptance by HTA decision makers [5].

Acknowledging the need to be pragmatic to enable patient access to medicines, a number of HTA agencies such as England's National Institute for Health and Care Excellence (NICE) and Canada's Drug and Health Technology Agency (CADTH) have developed real-world evidence frameworks providing guidance on best methodological practice to minimize bias when generating real-world evidence (RWE) to be used as an external control arm, notably suggesting the target trial emulation approach [6,7]. Further, negative controls and quantitative bias analysis can be used to quantify and correct for any potential residual confounding [6,8]. These frameworks are already having an impact on decision making, with NICE's framework allowing for the acceptance for an RWE external control arm [9].

It is therefore disappointing that given the pragmatic guidance from HTA agencies already in existence, as well as the continued development in analytical methods and quality of real-world data sources, the EU HTA guidance has taken a largely negative approach to RWE and external controls. This perhaps reflects the opinion of some EU countries on the value of RWD (notably Germany [10] who have been vocally dismissive of RWD) as compared with others. The French HTA agency, Haute Autorité de santé (HAS) [11] has stated that to balance rapid access for patients with evidential uncertainties, external comparisons following best methodological practice are a reasonable form of comparative data. A similar view comes from the Danish Medicines Council [12].

The EU HTA regulation aims to establish a collaborative framework for the coordinated assessment of health technologies, promoting transparency, efficiency, reducing duplication of work and the exchange of information among member states aiming to improve patient access across the EU. The guidance released on indirect treatment comparisons may not allow this to be achieved. While it is true that RWE has greater potential to include material bias and that decisions based on uncertainty lead to concerns such as patients using products for which the benefits remain unknown, a balance needs to be made to allow for patient access. Choosing not to consider RWE and not perform a JCA when single arm trials are being evaluated may lead to inequalities in patient access to rare disease treatments. Countries may choose to perform their own clinical assessments to enable patient access if they do not feel that EU HTA aligns with their national process. We hope that as JCAs are performed inequity is not increased for those with rare disease.

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