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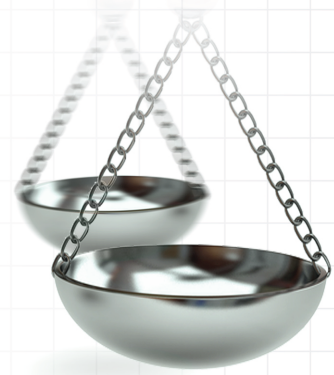

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R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 7

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This month we focus on papers that provide insights into the potential for target trial emulation to be used in health technology assessment, the role of real-world evidence (RWE) in informing additional elements of value and the importance of RWE to European joint clinical assessments.

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Target trial emulation (TTE) is an increasingly familiar concept to those working in real-world evidence (RWE) and comparative effectiveness research; however, there has been limited focus on its potential use in the health technology assessment (HTA) setting to-date. A recent paper authored by employees of National Institute for Health and Care Excellence (NICE) and academic centers across the UK seeks to address this gap in the literature [1]. The paper introduces the concept of TTE to those unfamiliar with the approach and highlights four key areas of HTA where they believe TTE can support the better use of real-world data (RWD). These include comparisons between single-arm trials and external controls, indirect treatment comparisons, HTA reassessments and the evaluation of complex treatment strategies.

While the authors see much potential for TTE in these areas the article does highlight a number of barriers to the use of TTE in HTA; these focus on the challenges in accessing data of sufficient quality to support TTE approaches and the need for those working in HTA to develop an understanding of RWD sources and of potentially complex causal inference methods. These factors may explain the limited use of TTE methods in HTA to-date.

The presence of an employee from NICE as an author on the paper is notable, and indeed NICE appear to be the HTA body that has thus far provided the greatest indication of their intention to advocate for the use of TTE methods with two recent documents published by NICE recommending the approaches [2,3]. While we are not aware of any other HTA bodies directly recommending the use of TTE methods at the moment, some may indirectly do so by recommending that best practice guidelines in observational research/pharmacoepidemiology are followed. For example, recent guidance on RWE by Haute Autorité de Santé (HAS) recommend a number of guidelines are followed including those of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP), which recommend TTE approaches [4,5]. Greater discussion of TTE methods by stakeholders in HTA, as is provided in this recent article, should stimulate the greater consideration of the methods by HTA bodies in general and their greater use by the industry.

A recent paper in 'Value in Health' reflects on the progress of initiatives which have sought to characterize additional, often overlooked elements of value in drug assessments [6]. The article focuses largely on the ISPOR value flower, a framework for conceptualizing these additional elements of value under a number of categories and according to the extent to which they are captured in current value assessment frameworks. The article highlights that while the value flower has stimulated some progress in considering concepts such as: severity of illness, the

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value of hope, option-value and equity, there remains much to be done to align on whether these concepts should be incorporated into value assessment frameworks and how best that might be done.

In the article the authors describe a number of pieces of methodological and empirical evidence that have been generated around these additional elements of value, in a number of which RWE plays a key role. For example, a large amount of the empirical evidence the authors cite supporting the importance of option-value has been generated using RWD. In one such study, Li and colleagues utilized RWD from Truven Health Analytics MarketScan databases to demonstrate that the disclosure of Phase II results for ipilimumab in metastatic melanoma resulted in a twofold increase in the probability of surgical resection relative to no treatment as physicians wanted patients to survive long enough to be eligible to receive ipilimumab if approved [7]. Further, when discussing equity, many of the methodological developments the authors refer to would be heavily reliant on the availability of high-quality RWD on the variable(s) across which equity is being assessed. While the role of RWD in supporting other elements of value is less evident from the article, RWD undoubtedly has a key role in supporting the demonstration of elements such as severity of illness, productivity and adherence-improving factors.

The authors acknowledge that more empirical work is needed to support the greater consideration of these additional elements of value in standard HTA frameworks. While not noted by the authors, it may also be helpful for the importance of RWD to such activities to be better emphasized as it's role in these overlooked elements of value is often itself overlooked. This would also provide further support for the need to continue to build infrastructure for RWD, and ensure variables relevant to broad value assessment activities are considered as new RWD sources are set up and linked.

Finally, a recent paper in the 'European Journal of Health Economics' reflects on the recent adoption by the European Commission of a proposal for the regulation of HTA which will mandate joint clinical assessments (JCAs) [8]. The article highlights a number of potential practical issues which will need to be addressed in order to realize successful implementation of JCAs.

One of the issues the authors raise is 'real-world data generation', under which they focus specifically on the generation of real-world data on new health technologies in the post launch phase. The authors note that real-world data collection requirements are currently set nationally/regionally in a decentralized manner and reflect on whether this will continue to be the case under a JCA. They highlight that a failure to consider opportunities to jointly define, design and/or execute post launch real-world studies may represent a missed opportunity, particularly in rare diseases and in markets/countries where RWD activities are currently limited by issues of experience and scale.

Notably, RWD/RWE was mentioned as being central to each of the three other points the authors raise reflecting on the need for alignment on methods and policies for indirect treatment comparisons, single-arm data and surrogate end points. While RWE can potentially help to address each of these issues [9], the acceptance of RWE for these purposes across Europe is unclear. Therefore, significant alignment would be needed to support the greater use of RWE.

As the methods and policies of JCA are defined and refined it will be important for RWD/RWE stakeholders to engage and ensure the potential role of RWD/RWE is appropriately considered for the benefit of patient access to medicines.

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