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EDITORIAL

# European union regulation of health technology assessment: what is required for it to succeed?

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## Background

After considerable discussion and debate, the European Commission (EC) proposal for the regulation of health technology assessment (HTA) was finally adopted by the European Union on December 15th 2021 and entered into force on January 11th 2022 (Regulation (EU) 2021/2282). The regulation is designed to formalise and make mandatory some of the activities, such as horizon scanning and clinical assessments of health technologies, that have been pursued over several years on a voluntary basis, through joint actions such as EUnetHTA. In short, the Regulation focuses on the 'clinical domain' of HTA, which includes the estimation of relative clinical effectiveness, and relative clinical safety, of health technologies as compared with existing ones, since in principle this is the component that is more generalisable from setting to setting. Specifically, Member States' HTA bodies are expected to conduct Joint Clinical Assessments (JCAs) of new medicines and certain high-risk medical devices. In addition, they will also engage in Joint Scientific Consultations (JSCs) to advise manufacturers on clinical study designs for generating appropriate evidence. Finally, joint "horizon scanning" exercises at EU level will identify, at an early stage, promising health technologies, to help Member States' health systems prepare for them.

Once JCAs are conducted, individual Member States must take them into consideration but may supplement them with additional clinical analyses that are needed in their national HTA process and/or in their own context. In addition to this mandatory scope of the HTA Regulation, Member States may also engage in further voluntary cooperation, in the assessment of health technologies other than medicines and medical devices. The 'non-clinical domain' of HTA, which includes the assessment of cost-effectiveness or value for money, will remain the responsibility of individual member states.

In principle, the Regulation could improve the efficiency of HTA within the EU, as Member States will be able to pool their HTA resources and expertise and avoid duplication of efforts. The assessment of relative clinical effectiveness usually involves a systematic review of the literature, which can be resource intensive and time-consuming. It is therefore potentially wasteful for several member states to undertake this exercise independently. In addition, the costs of such reviews may have acted as a barrier to entry for those member states with lower levels of resources for HTA and could explain why HTA is not widely practised in some parts of the EU.

The Regulation could also benefit other stakeholders. Patients and clinicians will benefit from a new, transparent assessment framework that will help address inequalities across EU countries and facilitate access to innovative medicines and some high-risk medical devices. Manufacturers of health technologies will benefit from more clarity and predictability concerning the clinical evidence requirements and from efficiency gains when submitting clinical evidence for HTA, as there will be only a single EU-level submission for JCAs, rather than multiple parallel submissions to the different national HTA bodies.

To make the EU-centralised HTA work, the Regulation will establish a Member State Coordination Group of members designated by each country. The Coordination Group will oversee the joint technical work carried out by subgroups of national representatives for specific types of work (e.g. JCA, JSC, or methodological guidance documents). A Stakeholder Network will also be established to facilitate a regular dialogue between European umbrella stakeholder organisations and the Coordination Group. The EC will

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serve as secretariat to the cooperation, ensuring that joint work is produced in a timely and transparent manner and will facilitate the exchange of information with other relevant EU agencies and bodies (e.g. the European Medicines Agency).

## What issues need to be addressed?

While promising, if the implementation of the new regulation is to be successful in the expected timeframe (by January 2025), there are several issues that need to be addressed, and a common approach agreed. We highlight the following issues for consideration by the Coordination Group that will be in charge of the process.

### Differences in current standard of care

For the purposes of HTA, the relative clinical effectiveness of the new treatment or technology is assessed in comparison with the current standard of care. Although we might expect some similarities across the EU in the current standard of care, there may be some differences, particularly if we consider the central and eastern European (CEE) member states [1]. The JCA will have to accommodate this variation. A related issue is that the broader the range of possible alternatives to the new technology of interest, the lower the likelihood of there being head-to-head clinical studies.

Therefore, it seems inevitable that the JCA will have to include a network meta-analysis (NMA) [2], as well as a conventional meta-analysis of head-to-head clinical trials. The use of indirect and mixed treatment comparisons, as implied by an NMA, currently divides opinion among the Member States. Therefore, an attempt should be made to determine the conditions under which develop a NMA would be acceptable, and guidelines for how it should be carried out. If not, it may be necessary to produce two assessments for the JCA, one using the head-to-head studies only for a sub-set of the comparisons, and an NMA using a broader set of clinical data.

### Lack of randomised clinical studies

It is possible that for some new therapies, such as those for very rare conditions, or those where it is difficult or unethical to conduct randomised studies, the available clinical data may comprise only single-arm studies or non-randomised comparisons. One would hope that these situations are kept to the minimum, with the JSCs playing an important role in this regard. Nevertheless, such situations will exist, especially for some gene therapies and some high-risk medical devices [3, 4].

Therefore, it will be important to establish standards for the selection of comparator cohorts of patients, the analysis of observational and non-randomised data, and the role of in silico modelling and synthetic patient cohorts. This is an active area for research at present [4, 5] and the outcomes of this research would need to be considered at the JSC stage for individual therapies and in the agreed methods for conducting JCAs.

### Use of surrogate endpoints

As more new therapies are approved by the EMA through accelerated access programmes, the available clinical data for HTA will become increasingly immature in terms of length of follow-up and the use of surrogate outcomes (such as progression-free survival) will increase and the use of final endpoints (such as overall survival) will decline [6]. The use of surrogate outcomes is also common in the case of treatments for rare diseases where there is less understanding of the epidemiology of disease and disease progression [7].

In principle, the use of surrogates and the length of follow-up in clinical studies could be a topic in the JSCs, but experience shows that if early approval is granted by the EMA, the opportunity and motivation for a further clinical study is lessened [8]. Therefore, if surrogate endpoints are to be used in JCAs, approaches for their validation need to be agreed on. There is currently varied opinion concerning the use and validation of surrogates [9]. If they are to be used in JCAs, common standards need to be developed.

### Real-world data generation

Under the current HTA regulation, the production of JCAs is essentially based on the clinical data available at the time. However, the discussion above suggests that in many ways the available clinical data may be insufficient for adequate HTAs at the time initial reimbursement decisions are made. Those conducting the JCA can ask the manufacturer to gather more data, but some of the data required for a final reimbursement decision may take several months or years to generate. Therefore, assessments must be made over the lifecycle of health technologies as more data are generated [10].

Under the current arrangements in the EU, individual member states make their own decisions about the additional clinical data required and how these data are used in decisions about reimbursement of technologies (eg through outcome-based managed entry agreements) [11, 12]. It may be that this will remain the case, but it will imply that those member states for whom JCAs are potentially the most useful may still not have adequate data to make an informed reimbursement decision. Therefore, it might be worth reflecting on what the new HTA regulation can contribute to the generation of additional clinical data. For example,

could supplemental data needs be determined during the JSC, or could the JCA specify the additional clinical studies that should be conducted? Under the terms of the regulations, these activities in post-launch data collection can be conducted jointly by member states on a voluntary basis, particularly in the case of rare disease treatments where enrolment in studies needs to be on a multi-country level. However, ignoring the key role of real-world data gathered post-launch would constitute a missed opportunity in the implementation of the new EU regulations.

## Conclusion

The new EU Regulation represents an important milestone that is expected to change the HTA landscape in Europe, after decades of voluntary coordination efforts. It can also become a unique example of increased centralisation of HTA activities that can be used in other geographical areas as well. But for it to be successful, all these critical issues should be tackled, with the awareness that the chain will only be as strong as its weakest link.

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