

Perspective Paper

Proposal for a Regulation on Health Technology Assessment in Europe – opinions of policy makers, payers and academics from the field of HTA

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(Accepted for publication Expert Review of Pharmacoeconomics and Outcomes Research – Please keep CONFIDENTIAL)

Abstract

Introduction: In January 2018 the European Commission published a Proposal for a Regulation on Health Technology Assessment (HTA): ‘Proposal for a Regulation on health technology assessment and amending Directive 2011/24/EU’. A number of stakeholders, including some Member States, welcomed this initiative as it was considered to improve collaboration, reduce duplication and improve efficiency; there were however a number of concerns including its legal basis, the establishment of a single managing authority, the preservation of national jurisdiction over HTA decision making and the voluntary/mandatory uptake of joint assessments by Member States. Areas covered: This paper presents the consolidated views and considerations on the original Proposal as set by the European Commission of a number of policy makers, payers, experts from pricing and reimbursement authorities and academics from across Europe. Expert commentary: The Proposal has since been extensively discussed at Council and while good progress has been achieved, there are still divergent positions. The European Parliament gave a number of recommendations for amendments. If the Proposal is approved, it is important that balanced, improved outcome is achieved for all stakeholders. If not approved, the extensive contribution and progress attained should be sustained and preserved, and the best alternative solutions found.

Key words: EUnetHTA; joint collaboration on HTA; cross border agreements; Member States; European legislation

1. Introduction

This paper presents the consolidated views and considerations of a number of policy makers, payers, experts from pricing and reimbursement authorities as well as academics from across Europe regarding the ‘Proposal for a Regulation on health technology assessment and amending Directive 2011/24/EU’ hereafter referred to as the ‘Proposal’. For the purpose of this paper, “payers” refer to those persons and institutions responsible for public financing of healthcare, including reimbursement decisions, such as social insurances, government agencies or health authorities. We are aware that whilst several groups of payers (AIM Association Internationale de Mutualite; ESIP - European Social Insurance Platform and MEDEV - Medicines evaluation Committee) have been discussing the Proposal [1-3], there currently appears no consolidated view from payers and their advisers from across Europe to enhance future discussions as this important initiative evolves. The contributing authors come from different Member States and from different bodies and institutions.

This paper was based on the original Proposal before the discussions in the Council and the European Parliament took place. When the Proposal was published, the potential multifaceted impact of the Proposal and its deliberations on the future health technology assessment (HTA) and policies among EU Member States and their citizens, brought about an urgent need to analyse and discuss the strengths and concerns of the Proposal, as well as possible alternative considerations to stimulate ongoing debates now and in the future. By the time this review paper is published, the discussions at the Council and Parliament will have progressed significantly. We are also aware that there have been, and still are ongoing, detailed discussions of the Proposal and changes are under consideration. There have also been debates at the European Parliament's Committee on the Environment, Public Health and Food Safety (ENVI) on the Proposal [4,5], and amendments were adopted at the Parliament Plenary on the 3rd of October 2018. A number of the points brought up by the authors in this paper were discussed, debated, and also proposed for amendments during the discussions at the European Parliament as well as the Council. This paper will not go into the details of the recommendations and the discussions from this debate. In spite of the progress being achieved in the co-legislative process, the discussion and the updates are still ongoing; consequently, we believe the publication of this paper is still relevant.

While the Proposal covered HTA for different modalities including medicinal products, medical devices and in-vitro diagnostics this paper will focus mainly on HTA for medicinal products.

2. The current EU legislative framework

HTA, pricing and reimbursement of medicinal products, which incorporate both clinical and economic aspects of technologies [6,7], are established on the basis of Article 168 of the Treaty of the Functioning of the European Union (TFEU), and are within the competence of Member States. Article 5(2) of the TFEU sets the principles of conferral (which governs the limits of EU competences) and the principle of subsidiarity whereby the EU does not take action (except in the areas that fall within its exclusive competence) unless it is more effective than action taken at the national level. The European Union, the European Parliament, and the Council, can adopt measures for setting high standards of quality and safety for medicinal products. The TFEU specifies that it is fully the competence and responsibility of Member States to decide which medicinal products are reimbursed and at what price [8,9]. The Treaties mandate the European Commission to encourage cooperation between Member States in the field of public health and, if necessary, lend support to their actions. According to Article 6 of the TFEU, in the field of protection and improvement of human health, the Union has the competence to carry out activities aimed at supporting, coordinating or supplementing the actions of Member States. The Union's competences do not replace the States' competence in this area, and EU acts must not lead to harmonization of the Member States' laws and regulations (Article 2 (5) TFEU).

Pricing and reimbursement are regulated by the 'Transparency Directive' (Directive 89/105/EEC). This Directive lies at the interface between EU responsibilities for the internal market and national competences in the area of public health in accordance with Article 168(7) of the TFEU. Its provisions affect national policies on price setting and the organisation of social security schemes just as far as it is necessary to achieve transparency. In March 2013, the European Commission adopted an amended proposal to amend this Directive but the amendment was officially withdrawn in March 2015 [10].

3. Historical background on initiatives for HTA

For over 20 years, there have been various initiatives to strengthen collaboration on HTA across Europe. This started with the EUR-ASSESS project funded by the European Commission during 1994-1996 [11]. This project aimed to promote coordination of HTA in Europe by improving methods of assessment, priority setting, and the use of HTA results through better dissemination and use of HTA in coverage decisions. Thereafter, two other research projects were funded by the European Commission to improve collaboration between HTA institutions in Europe. These were HTA Europe (1997–1999) and the ECHTA/ECHAHI (European Collaboration for Assessment of Health Interventions) project (1999–2001) [11,12]. These projects laid the foundation for the European Network for Health Technology Assessment (EUnetHTA). EUnetHTA is a network of government appointed organisations combined with a large number of regional agencies and not for profit organisations. The first EUnetHTA project (2006 – 2008) was followed by the EUnetHTA

Collaboration (2009) [11,13]. This was followed by three EU Joint Action projects JA1 (2010-2012), JA2 (2012-2015) and the ongoing JA3(2016-2020) [13,14]. The main objectives of EUnetHTA included support of the efficient production and use of HTA in decision making across Europe, provision of an independent and science-based platform, an access point for communication and the development of research. Over the last three years, Member States have also developed regional co-operations, e.g. BeNeLuxAlr, the Valletta Declaration, FINOSE and Visegrad projects, to undertake joint activities such as HTA, price negotiations especially for new medicines for orphan diseases, horizon scanning and information sharing [15-18].

The Health Technology Assessment Network (HTA Network) was established by the European Commission in line with Article 15 of Directive 2011/24/EU. This Network includes a representative from all EU countries and aims to (i) support cooperation between national authorities or bodies, (ii) support Member States in the provision of objective, reliable, timely, transparent, comparable and transferable information on the relative efficacy as well as on the short- and long-term effectiveness, when applicable, of health technologies, (iii) enable an effective exchange of this information; (iv) support the analysis of the nature and type of information that can be exchanged; and (v) avoid duplication. The first meeting of the Network took place in October 2013 [19]. In 2014, the HTA Network published its strategy for EU cooperation on HTA [20]. The report supported cooperation on HTA between Member States, Iceland, and Norway, and presented possibilities for this cooperation without being specific on any particular methodology. This strategy was totally based on the principle of voluntary cooperation [20]. The Council Conclusions of different Presidencies of the Council of the European Union advocated for voluntary cooperation on HTA. The conclusions consider cooperation between groups of Member States that share common interests in relation to pricing and reimbursement, support exchange of HTA methodologies and assessment of outcomes as well as voluntary cooperation to improve access to health technologies [8,21].

In 2016, the European Commission embarked on an initiative to strengthen EU cooperation on HTA beyond 2020 since in 2020, the current EU funding from the EU Health Programme 2014 – 2020 will end and no permanent funding can subsequently be established according to EU Financial Regulations. This initiative adopted the process for Commission Better Regulation [22]. The Commission claimed that this initiative was undertaken in response to calls from Member States, the European Parliament, and other key stakeholders, to ensure the sustainability of EU HTA beyond 2020. It was intended to address the shortcomings identified by the Commission with regards to EUnetHTA, i.e. low uptake of joint assessments, differences in HTA frameworks and differences in technical capacities among the Member States, significant differences in national HTA methodologies and the lack of financial sustainability of the current model of HTA cooperation at the EU level [23].

In September 2016, the Commission published an Inception Impact Assessment for Strengthening of the EU cooperation on HTA. This Impact Assessment defined HTA on the basis of the EUnetHTA Core Model in terms of 'core domains' [24]. These included a Relative Effectiveness Assessment (REA) covering the health problem and the current use of a given technology incorporating its safety and clinical effectiveness, as well as 'other domains' including costs, an economic evaluation, ethical analysis, organisational aspects, patient and social aspects, as well as legal aspects. The Impact Assessment specifically excluded pricing and reimbursement decisions, which were considered 'of national prerogative'; however, quoted studies which demonstrated the potential benefits from HTA [25]. In October 2016, the European Commission issued a public consultation, with meetings also held with key stakeholders. The public consultation presented different options for HTA which considered outputs (voluntary or mandatory participation and uptake), different models of implementation (level of EU input and input from an EU agency – existing or new) as well as potential funding mechanisms and scope. The responses of the public consultation were published by the European Commission. An Impact Assessment was published by the Commission later in 2017 [23].

On the 31st of January 2018, the European Commission issued a legislative proposal: Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU [26]. During 2018, the Proposal was discussed by the co-legislators: the Council and the European Parliament. ENVI published a draft report and put forward more than 170 amendments to the Proposal [5]. The Parliament Plenary adopted the amendments on the 3rd of October 2018 and referred the proposal back to ENVI. By the end of 2018 the Proposal was still being discussed at the Council. The current discussions at the European Parliament and the Council have

managed to achieve an agreed position on a number of aspects, although there are still contentions over other aspects of the Proposal and the final approval has not yet been achieved.

4. Consolidation of the opinions of the authors on the original Proposal as set by the European Commission

As mentioned above, this consolidation of opinions concerned the original Proposal as set by the European Commission and took place before the Proposal started being discussed by the co-legislators. There have been divergent opinions on different aspects of the Proposal. This section reflects the different opinions of the authors. These are not in any way linked to the position of the different Member States as being expressed at Council.

The Proposal suggested a framework for joint HTA assessment for different health technologies including medicinal products and medical devices. For the scope of this section only medicinal products will be considered. In the case of medicinal products, the Proposal covers only Relative Effectiveness Assessment (REA) for new centrally authorised medicinal products.

It is recognised that there are currently differences in access to medicines for patients across Europe as seen with medicines for cancer and orphan diseases [27-31]. This goes against the EU principles that all patients within the EU should have a right to equal access to medicines. Some stakeholders consider that the Proposal will increase access to medicines, particularly in those countries with low access. In a number of countries, the major reasons for differences in access and availability are issues of affordability, especially for new biological medicines [32,33]. The Proposal does not address prices of medicines and affordability as these are within the competence of each Member State. Another concern with access to new medicinal products is the lack or delay by marketing authorisation holders to place new medicinal products onto the market of individual Member States. This issue is also not addressed by the Proposal. For this hurdle to be overcome, the Proposal should oblige the marketing authorisation holder to place the product on the market in all Member States who decide to reimburse the product without delay.

In principle, a number of stakeholders, including Member States, support the concept of collaboration on HTA, as this is considered to ensure that all countries benefit from HTA conducted in accordance with an agreed standard and high level methodology. Countries have different levels of capacity for HTA and adopt different models for its utilisation. Some countries have adopted a 'heavy' model whereby analyses are largely carried out by the national HTA agency, whilst others utilise a 'light' model whereby the national HTA agency mainly evaluates HTA analyses supplied by the pharmaceutical industry for pricing and reimbursement considerations. Some countries apply mixed models. The skills needed for HTA should include critical review of the clinical and economic data behind the models used to determine the cost-effectiveness of different technologies. Some Member States have not yet made use of HTA in their pricing and reimbursement decisions to the same extent as others, for example, they mainly base pricing decisions on the perceived level of innovation of the new medicine [34-37]. The experience of EUnetHTA has led to the development of tools and methodologies for HTA. These will allow joint assessment using agreed methodologies. The Member States with limited resources, systems and expertise for HTA are considered to benefit most from joint assessment.

Member States acknowledge the challenges posed by the different methodologies, tools, and models used for the utilisation of HTA across countries, and generally consider the standardisation of approaches positively. Currently, there are different HTA requirements across countries and any REA undertaken by EUnetHTA may be considered of limited relevance in certain countries which have their national methodology for HTA. Having a joint submission and assessment could potentially address this. Joint assessment can be accompanied by different demand-side measures in each pertinent Member State to ensure that new medicines are only prescribed in those patients where their value is greatest in that country, with usage subsequently monitored [36,38-40], which could also be part of any managed entry agreement (MEA) [41-43].

Benefits of HTA collaboration include unification and implementation of common criteria for Member States and companies, streamlining of activities, avoidance of duplication, more effective use of resources through the development of joint methodologies, synergies between experts and the authorities, availability of best expertise to cover future challenges, the possibility of having a common

framework to support the process and the possibility of one joint submission [44]. The establishment of a joint HTA organisation can bring about improvements in methodologies and scientific standards, particularly with increased expertise and specialisation requirements for new medicines [44]. It is important that any HTA is undertaken by competent experts, and that the various HTA agencies can trust the work and competence of each other. Proposals for collaboration should preserve best practices and well-functioning solutions, which have been developed through collaborations across Europe since the early nineties as well as in some Member States [7,45]. There could also be benefits through possible funding of joint research projects, payment for assessment work as well as for consultation and expert advice. Some reimbursement authorities, and possibly also some individuals, may see the Proposal as a possible avenue for further specialisation in specific areas of HTA. Current models for HTA utilisation in many national healthcare systems have provided a positive and stimulating impact on the development of HTA as a relatively new and interdisciplinary science, and this should continue.

The Proposal addresses the problem of variable access to clinical data from the marketing authorisation submission to be used as part of any REA by making this information accessible for HTA; thus, this ensures that this information will be available for all HTA agencies.

However, a number of concerns were expressed with the Proposal. The Proposal is not clear about the true role and power of the Commission to shape and determine the final conclusion of any joint assessment (REA). More detail was designed to be included in the delegated and implementing acts, and this creates uncertainty. Due to the way that the Proposal was set out, the Commission could potentially be in a position of conflict of interest. As the Commission is responsible for issuing the marketing authorisations for centrally authorised products, the Commission will be in an awkward position to support payers if during HTA they question, or do not agree with, any part of the marketing authorisation process or decision.

Whatever the current HTA model within a country, the Proposal will impact on individual countries, their methods of HTA evaluation and their HTA and pricing and reimbursement agencies. This is generally considered negatively by countries which have well established systems for HTA and would therefore like to preserve their well established HTA processes based on years of experience. Alternatively, less advanced countries may consider collaboration on HTA as an opportunity for learning, standardisation and sharing of work. There is concern that particular requirements, which are not yet known and will be established later, could upset existing national and well-functional HTA models through European legislation and possibly impact the quality of assessment and reduce the speed of well developed HTA organisations and systems [44].

There is also belief that transferring the authority to conduct comparative benefit assessments (i.e. REA) of medicinal products to a single body with a binding effect on Member States is a violation of primary law, and this could have severe consequences among national pricing authorities in ensuring the cost-effective (pricing) provision for their medicinal products. The Proposal is shifting part of the HTA process (REA) to a European institution, but the responsibility for the other domains, including the economic, social, legal, ethical and the organizational context, remain within national healthcare systems. The Proposal may well have a significant impact on national processes and national legislation, and the final Regulation will supersede all overlapping national legislation. This is a particular concern if undue pressure is placed on the body undertaking the initial (joint) assessment. We already see high prices for new cancer medicines, and those for orphan diseases, with often limited health gain due to pressures resulting from the emotive nature of these diseases [36, 46-52].

One way forward is to have realistic price expectations especially with the low cost of goods (e.g. low cost for ingredients and manufacturing compared to price of the product on the market) of some new cancer medicines [53]. This follows increasing calls for moderation in the pricing of new cancer medicines for long term sustainability [54-56], with world-wide sales of medicines for cancer at \$107billion globally in 2015 and rising with more than 500 companies actively pursuing new oncology medicines [57]. There is a similar situation for new medicines for orphan diseases with EURORDIS having as one of its key objectives that by 2025 there should be 3 to 5 times more therapies for rare diseases approved per year in Europe than currently; however, prices up to three to five times cheaper to enhance access and affordability [29]. We are also aware of the general considerations regarding issues of fairer pricing and value based pricing as seen for instance with the WHO launching the 'Fair Price Forum' [58,59]. In addition, there are ongoing discussions with the WHO and

others to address concerns with the availability and affordability of medicines for patients with cancer [51,55].

Other major concerns with joint assessment include potential comparators for clinical effectiveness analyses, with different requirements and attitudes among Member States including the use of placebo [34,36,60]. Different standard treatments are available in different countries. Will the selected comparator(s) be treatments recommended in national, Pan-European or International clinical guidelines? Alternatively, will there be a consensus on the different medicines currently reimbursed among Member States? Different selections could appreciably impact on potential prices despite external reference pricing across Europe [61-64]. This can potentially be addressed with comprehensive REA information being used to improve deliberations regarding the potential value of a new technology, and hence potential prices.

A concern emphasised by Kalo et al (2016) [65], and also shared by some of the authors of this paper, is that HTA roadmaps cannot be fully transferred among Central and Eastern European (CEE) countries, due to national peculiarities such as country size and gross domestic product per capita. In addition to technical factors, there are also ethical and cultural considerations for HTA, including major differences in social values, public health priorities and models of healthcare financing among CEE countries. The clinical part of HTA is crucial to prepare the economic models and a number of authors consider that these cannot be separated. Moreover, different health technologies may challenge moral or cultural values and beliefs, and their implementation may also have significant impact on people other than the patient. These are essential considerations for health policy, and are important considerations as the Proposal is debated and potentially implemented.

The possible restriction on payers' jurisdiction over the methodology for HTA, and the position that Member States cannot implement any updates to the evaluation without the permission of the Commission, caused major reservations among the authors. There is concern that the Proposal will be a way of stopping payers and their advisers from developing new methodologies, and will be a means for controlling the 'fourth hurdle'. One of the major challenges for HTA has been how to adapt the methodology for HTA to consider evolving issues such as the uncertainty from conditional approval, the evolution of new methods of payment including MEAs, as well as consideration of the technical specificities of the products which are always developing, e.g. with the introduction of different advanced therapy medicinal products (ATMPs) including gene therapies [66-70]. If these restrictions also cover factors such as the choice of comparators, update of the evaluation with new clinical data, information from registries, information to fill the gaps and uncertainty for medicines authorised through conditional approval and observational data, or outcome based risk sharing data after the joint assessment, then the REA assessment will just be based on the original marketing authorisation information. Restrictions in the methodology of HTA may propagate and increase the gaps in knowledge and prevent payers from using evidence-based evaluation approaches particularly for emerging principles such as value-based pricing, price negotiations, and novel models for payment. With increasing use of a new medicine in clinical practice, new effectiveness data may show that a medicine is less efficacious than originally established [71]. Alternatively, initial safety concerns become less of an issue in clinical practice as seen with the TNF alpha inhibitors in rheumatoid arthritis and psoriasis following registry studies among countries to fully assess issues of infection and cancer in reality [52,72,73]. Payers already face great challenges to pay premium prices for new medicines with uncertain effectiveness due to a lack of data or immature data, lack of proven cost-effectiveness, and concerns with the budget impact as seen with some new medicines for cancer and orphan diseases and lately ATMPs such as gene therapy [35,38,48,69], and this will intensify and will threaten the sustainability of national healthcare systems, given the number of new medicines in development.

The Proposal stipulates that the joint assessment must be finalised at the same time as the marketing authorisation decision. A growing number of new medicines are being granted a marketing authorisation without data from randomised clinical trials and with approval being based on the results from non-randomised, single arm open trials. Real world data evidence (observational and registries) is increasingly welcomed based on actual outcomes rather than surrogate data [74]. Incomplete data from marketing authorisation decision could compromise the HTA especially if there is no clear link between the surrogate markers and long term patient outcomes [75-77].

Once the legislation is approved, the position of the Member States in the power balance will change. Article 8 of the Proposal includes an obligation for Member States to inform the European Commission on how the HTA evaluation was undertaken as well as an obligation to inform on any changes. There will no doubt be considerable questioning by industry and by the Commission on the right of Member States to consider different and potentially new aspects of the evaluation during pricing and reimbursement decisions. For example, if payers would be restricted from defining unmet medical need according to their perspective and to consider the uncertainty in effectiveness during HTA evaluation, they could be blocked from including these considerations in their deliberations and negotiations.

The Proposal advocates for greater involvement of patients and other stakeholders in decision making. Authors expressed different experiences with the involvement of patients, patient organisations, and other stakeholders. The authors generally considered patient participation positively as a means to increase buy-in, include the patient perspective, and for pointing out missing aspects when considering new medicines. On the other hand, there is the possibility that patient participation can put pressure on decision making. There are already examples where particular diseases have been treated differently from others in certain countries, leading to difficulties with equity in the allocation of limited resources [51]. This includes special funding schemes for the reimbursement of orphan diseases and cancer as well as higher cost per QALY considerations for new medicines in these disease areas [35,36,46,48,49]. There is also some concern that joint assessments might be used to put pressure on countries to reimburse certain medicines, where these medicines otherwise would not be reimbursed due to financial constraints.

The 'legal basis' has been one of the main criticisms relating to the Proposal. TFEU sets the mandate for the pharmaceutical framework. Article 168 of the TFEU specifies that a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities. Under Article 168(4) (c) of the TFEU, the European Parliament and the Council can, in order to meet common safety concerns, adopt measures setting high standards of quality and safety for medicinal products and devices for medical use. The main legal basis for the Proposal is the single market and not public health, in particular Article 114 of the TFEU, whose objective is the establishment and functioning of the internal market.

5. Consolidation of other relevant opinions and recommendations from the authors

Significant progress has been achieved in the agreement on joint standardised methodologies and tools through EUnetHTA and other recent EU-funded projects on HTA methodologies, including MedTechHTA and INTEGRATE-HTA, with education, establishing methodologies for medicinal products and medical devices, dealing with complex health technologies, as well as instigating new methods for assessment [78-80], and this work should be expanded.

EUnetHTA identified that the processes of application for reimbursement are started at different times in different Member States, with different criteria for the level of evidence required by different European countries [79], thereby making further integration challenging. Other key issues, as mentioned, include consensus over comparators and treatment approaches [34]. If the Proposal were to specify the evaluation but factor out appraisal and comparison with treatments as well as their applicability (or external validity of the new pharmaceutical), this could compromise its applicability.

The Proposal could improve collaboration between HTA bodies and payers, medicines regulators, and marketing authorisation holders (MAHs). Regulation (EC) No 726/2004 allows joint regulatory and HTA scientific advice for applicant MAHs at an early stage of development of a medicinal product, and this experience is generally considered positively [81]. However, there is currently a lack of collaboration between medicines regulation and HTA, as well as pricing and reimbursement authorities, in monitoring the effectiveness of new medicines during the post-authorisation phase, although this is increasingly happening at a national level [52,72,82-86]. With the introduction of conditional approvals, there is a shift in responsibility for effectiveness from the marketing authorisation to the post-authorisation phase [87], and this also brings added burden on the financing of new medicines by national healthcare systems.

Regulators should clearly identify and document the gaps in data at the time of the marketing authorisation decision, and transparently include these requirements as part of the conditional

marketing authorisation approval, together with time-lines for presentation of this data for granting of a non-conditional approval. There have been challenges and concerns among some stakeholders with the current system for conditional approval. These include difficulties with delisting medicines from conditional schemes if their value is not shown in routine clinical practice [88], coupled with concerns with the strength of evidence at approval [89]. Regulators should enforce the requirements for non-conditional approval and update the effectiveness data as part of variations to the marketing authorisation, including variations or withdrawal of marketing authorisation where lack of effectiveness becomes evident. There should also be similar activities among payers and companies if the value of the new medicine is not shown in routine clinical care.

Currently the marketing authorisation holder collaborates with payers on reimbursement conditions and pricing through for instance MEAs and other mechanisms [41-43,90]. This collaboration could include consideration of conditions for the marketing authorisation holder to be able to collect the required effectiveness information for the granting of the non-conditional approval such as through the upkeep of registries with the increasing use of electronic health records [91], as well as initiatives such as GetReal, which is a three-year project involving the Innovative Medicines Initiative (IMI), pharmaceutical companies, academia, HTA agencies, payers, regulators, patient organisations as well as commercial organisations in generating patient level data [92]. Such collaborations will no doubt change the relationship between marketing authorisation holders and payers, and the power of each, during price negotiations and any update of prices. This should not be compromised.

Overall, whilst the Proposal on HTA gives a framework for cooperation on REA, the Proposal specifies that details of the HTA process and methodology will come through the delegated acts and the implementing acts. Some authors are concerned with this. While the assessment for marketing authorisation of medicinal products is based on guidelines which are subject to interpretation, the HTA appraisal will be directed by a strict and detailed methodology imposed through legislation which will restrict the assessment process and adaptation. It will be difficult to keep updating this legislation with every change that is warranted. The experience of the Falsified Medicines Directive (Directive 2011/62/EU) is a good example of how requirements set through legislation will be difficult to implement [93].

6. Opinions of the authors on the model for collaboration on HTA between Member States

In spite of the efforts made by a number of Member States and the Commission, and the resources invested, Member States have not achieved the point where they effectively fully collaborate together on HTA voluntarily. Their approach is still typically country specific. This has made a legislative proposal seem the only remaining alternative to achieve full HTA collaboration among Member States. The experience of EUnetHTA has shown that Member States are not willing to cooperate voluntarily on HTA. However, there have been some initiatives for cross border and regional collaborations concerning key aspects of pricing and reimbursement in recent years.

Within the current pharmaceutical framework, there are aspects which are considered to be within the jurisdiction and rights of specific stakeholders. Companies are considered to have full rights on the setting of prices for their new medicines, the right to set conditions for lack of transparency on prices and for negotiation of prices, and the right to refuse to get into joint price negotiation and MEAs with Member States at their discretion. The Proposal on HTA will impinge on none of these rights of the companies.

Member States currently have jurisdiction over the HTA evaluation within their healthcare systems, as well as reimbursement decisions including managed entry agreements (within the framework of Directive 89/105/EEC). Currently Member States also have the right to decide to whether and how to collaborate between themselves on these activities. The Proposal will affect the level of voluntary collaboration on HTA. In the field of HTA, pricing and reimbursement, the Member States have considered and proposed Member State driven voluntary cooperation, and there have been the experiences of EUnetHTA, the HTA Network and regional cross border collaborations, all of which are voluntary. The cooperation stipulated in the Proposal follows a more coercive model. There are divergent opinions between the authors regarding HTA cooperation regulated by legislation.

In the field of medicines regulation, there are a number of Member State collaborations such as the role of Member States in the various procedures of the European Medicines Agency [94], which is

governed by Regulation (EC) No 726/2004, and the Heads of Medicines Agencies, which is a voluntary network of heads of the national competent authorities (NCAs) for medicines regulation [95].

There are different models for the formation of networks and for international coordination. These arrangements may vary in complexity. Examples of such models include trans-national regulators setting 'soft law' standards, supra-national legal requirements, application of regulatory instruments, professional self-regulators and certification bodies. Coordination is a major challenge in such networks. Not all regulators will have the same substantive or normative conceptions of 'good'. They also have varying capacity, skills and resources, and these differences are likely to affect their preferred approach to regulation as well as their responsiveness. Some regulators are flexible and able to cope with change and others are not. There are also differences in regulatory cultures, and these are reflected in regulatory interventions. Moreover, different regulators will occupy positions and status within the broader political and legal infrastructures and may be controlled by other governmental institutions [96]. There may be other factors and interests including sources of funding and financial governance of institutions.

Baldwin et al. (2011) describe five different modes of coordination within government networks [96]. These are:

- Hierarchies which involve a top-down arrangement in which a central body lays down rules and policies that provide direction to inferior institutions within the network.
- The second mode is coordination of a network, whereby a stable group of peers engages in mutual recognition of membership and where there is sharing of a common set of interests.
- A third approach to coordination is network management which involves a lead party or 'manager' body taking positive steps to facilitate concerted network actions by fostering collective behaviour through building levels of consensus to enable actions to be taken.
- Distinctly, the fourth approach is based on rituals, which may be adopted voluntarily or imposed.
- Fifthly, coordination can be left to markets, and is in the interests of participants who are willing to exchange resources and conclude agreements in order to attain mutually beneficial solutions and higher levels of collective welfare.

EUnetHTA and the Regional Cooperations for HTA are most closely represented by the third approach, i.e. where there is a lead party and an organisation of initiatives under different leadership models. The Proposal on HTA as proposed by the Commission presents a hierarchical model (the first model), whereby the Commission will lay the rules and Member States will have to follow these (both for the assessment - REA - and the re-assessment). If this model is adopted, the legislation will 'force' Member States to cooperate on the REA.

Logically, it is difficult to understand how currently Member States have difficulties to fully cooperate voluntarily within EUnetHTA but could end up all happily and voluntarily coordinating together within a hierarchical model. Some Member States with limited capabilities, expertise and resources are very happy to collaborate in order to avoid issues such as duplication and to benefit from the resources of other countries [44]. We recognise though that within the network of voluntary cooperation, there are still elements of hierarchy and power struggle, and those who feel less strong may rather be at par with other Member States under a third party than feel "bullied" by certain more powerful Member States. Ideally Member States should agree to cooperate between them in a framework which is set and managed by them. In the meantime, Member States could build on current cross border collaborations and other arrangements with existing co-operation around key activities such as horizon scanning as well as pricing and reimbursement considerations [15-18,97,98].

7. Conclusions

Currently, there are different opinions, perspectives and interests on the Proposal both within and between key stakeholder groups.

There seems to be a high level of support for collaboration on HTA across Europe as collaboration increases the efficiency of HTA by avoiding duplication as well as maintaining or improving the quality of assessments. Alongside this, it is important to safeguard the needs of individual Member States and to take the local context into consideration. Success in producing European HTA's of high quality which can be used by all Member States without compromising their healthcare systems can be a catalyst for further cooperation.

Payers may benefit from the possibility of regional cooperation for joint horizon scanning, negotiations, pricing and the possibility of transparency in pricing at their discretion. This is happening to a limited extent. Collaboration is considered to result in increased strength and negotiation power, which are especially important for new premium priced medicines. These are also key principles of the single market.

A number of changes have been put forward by ENVI regarding proposed methodologies. The thrust of these are to make the process more transparent and expert-based. These are welcome developments [4]. However the idea to list the stakeholders to be consulted without mentioning payers in Amendments 33,75,108, 116, 121, 136 and 149 has been a major concern as payers typically have budget responsibility in their countries [5].

It is up to Member States to decide whether and how much the Proposal affects their jurisdiction over HTA and what the implications of the legislation would be. The Proposal is shifting the process of HTA outside national jurisdiction, but the responsibility for pricing and reimbursement remains among national healthcare systems. If Member States truly support the objective of increasing collaboration on HTA, they need to find a way for collaborating between them, preferably fully within their power.

Once the Proposal is approved, then the Member States will need to embark on its implementation. A lot of good work has already been done, and this should be used as the foundation for future developments of HTA. In terms of working together and collaboration, much needs to be learnt and to be put into practice. If the Proposal is not approved through the co-legislative process, it is important that all that has been invested through EUnetHTA and other work, particularly the methodologies and tools which have been developed, as well as the consolidations which would have been attained through the discussions of the Proposal, are utilized to find the best way forward.

The co-authors will be critically following the developments with the Proposal, and commenting on any future developments.

8. Expert Commentary

Thoughtful compromises and proactive ways forward highlighted in this paper are necessary to achieve a model for cooperation on HTA which will benefit all European citizens. This especially given the current considerable differences that exist between Member States in terms of issues of access and affordability of new medicines, including those for cancer and orphan diseases, which is likely to intensify with the launch of more complex technologies including gene therapies. Whichever model is finally decided upon, healthy discussion and debate regarding any Proposal is essential to enhance future support.

If there is support for collaboration by a number of Member States, which is likely, then irrespective of the model chosen for collaboration, i.e. whether voluntary or through Regulation, there should be support by the Commission to make this model a success. This includes sufficient funds for any joint activities such as horizon scanning, assessment and other associated activities.

9. Five year review

There will be increased HTA collaboration across Europe over the next five years whether this is voluntary or governed by regulations. European countries will benefit in different ways from increased collaboration. Some will benefit more substantially than others addressing key issues such as availability of resources and personnel to fully undertake HTA evaluations. Methodologies will also improve as a result of joint collaborations, and there will be increased funding for joint research projects.

However, it is likely that issues such as access, affordability and availability of medicines throughout European countries will remain in spite of collaboration on HTA due to continued differences in affordability between different European countries and the lack of impact of collaboration on HTA on the prices of medicines.

10. Key Points

- There have been concerns with variable collaboration on health technology assessments (HTA) among European countries, as well as use of assessments from European groups, despite a number of initiatives over twenty years across Europe to address this.
- With current funding coming to an end, the European Commission has published a Proposal for joint assessments of HTA incorporating Relative Effectiveness Assessments (REAs) to address these concerns.
- Some benefits of collaboration on HTA include reduced duplication, improved efficiency and improved quality of evaluation, particularly for countries with limited national resources.
- There are concerns with the Proposal including adequately addressing issues of different methodologies, tools and models for HTA across Europe, the potential binding of assessments and restrictions with adopting methodologies for HTA which address issues such as the lack of evidence following marketing authorisation and uncertainty,
- The Proposal has generated ongoing debate and a great deal of alternative considerations in an attempt to achieve an agreed position. This will continue

Conflicts of interest and funding

The majority of co-authors either work for health authorities or health insurance agencies or are advisers to them. However, there are no additional conflicts of interest to declare. There was no funding for this paper.

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