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Assessing the wider benefits of the EU's proposal on strengthening cooperation on health technology assessment from the industry perspective

Final report

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Executive summary

EFPIA asked Charles River Associates (CRA) to undertake an assessment of the impact of the European Commission's (EC) proposals to strengthen cooperation on health technology assessment (HTA). To do so, CRA:

- Undertook a literature review on the problems associated with a fragmented system of HTA
- Facilitated a workshop and follow-up interviews with individual pharmaceutical companies to understand the overall value that cooperation on HTA could deliver from the industry's perspective
- Conducted an economic impact assessment focusing on the "wider" costs and benefits of the Commission's proposal, supported by targeted interviews with groups of patients and clinicians.

This study is intended to complement the findings from the consultation process currently being undertaken by the Commission, which is supported by a series of consultancy projects investigating the benefits and impacts of the different options. Whilst the Commission's study is focusing on the immediate costs and benefits of the submission and HTA processes, this analysis is intended to cover the wider range of potential costs and benefits. We assess the value of cooperation on the different outputs set out by the EC in its roadmap: (1) the collection, sharing and use of common templates, tools and data, (2) early dialogues, (3) the production of joint relative efficacy assessment (REA) reports, (4) the production of joint full HTA reports.

Findings

There are a variety of potential benefits from improved cooperation, as set out in Table 1.

Table 1: Possible long-term benefits of strengthening cooperation on HTA

Dimension	Potential benefits to society
Consistency of the assessment requirements	• Reduced variability in the scope of assessments (the population and subpopulations), comparators and outcomes • Efficiency in the generation and synthesis of evidence due to choice of comparators, types of evidence required and/or accepted in the assessment, selection of outcomes and subpopulations, post-marketing evidence
Predictability of evidence synthesis, timelines and interpretation	• Increased predictability of the timelines (due to proposed predictability of the process) • Increased predictability of evidence interpretation in national appraisals (particularly those that have less established processes)

Quality of governance and processes to improve quality of assessment	• Increased scientific quality of assessment by having consistent assessment processes and governance, with particular focus on transparency, validation and engagement opportunities • Reduced heterogeneity of expertise across HTA agencies and hence improved quality assessment across member states (MS) • Holistic approach to assessment including patients' perspectives • More evidence-based national decision-making processes across Europe • Increased ability to appeal decisions
Speed of decision-making process at national level	• Increased speed of the clinical assessment processes • Increased speed of payer negotiations, as informed by an objective evidence base • Increased efficiency of information exchange with the European Medicines Agency (EMA) and hence of overall process, as EMA would be required to share information with one agency instead of multiple national agencies (avoid "queueing" for information) • Increased opportunities for early and fast access, reducing inequality of access for EU patients

We discuss in turn how the different outputs from cooperation as set out by the EC would contribute in delivering these benefits.

Consistency of the assessment requirements

Common tools and templates. **Regarding consistency, common tools and templates would provide some benefits.** In particular, common submission templates and methodology documents will be useful for countries that do not have these today and will prevent, to a degree, additional requirements being introduced.

Early dialogue. **Strengthened coordination on early dialogue would also bring benefits**. Early dialogue only occurs in seven markets today, so could be extended to cover 28 countries. Parallel scientific advice has occurred between EMA and health technology assessment bodies (HTABs) (although typically only 3-4 HTABs are involved in any one pilot and there are concerns about the sustainability of this model) but this would provide a more sustainable approach involving a wider set of HTABs.

Joint REA. **The most significant benefits occur from a process that incorporates early dialogue with joint REA**. Although it is unlikely to reduce the cost of evidence generation significantly, given that evidence generation occurs globally and requests for post-authorisation evidence collection occur for a range of reasons, this will deliver a more coherent European voice on evidence requirements with the result that evidence is better targeted to the needs of the REA process.

Full HTA. **We do not find joint full HTA would improve consistency**. On the contrary, it would lead to a delay in the provision of REA information,[1] negating its value in terms of consistency. It is also likely to lead to countries adopting different approaches to undertaking their own economic assessment, which could further reduce consistency. Joint full HTA reduces the autonomy countries have to undertake their own national evaluations. Member States are therefore likely to disregard these joint assessments in order to preserve some degree of autonomy, especially regarding their assessment of economic considerations.[2] This may lead to a system where although formally Member States will adopt joint full HTA, in practice they will conduct independent evaluations, implying a greater inconsistency (as there is greater ambiguity about the methodology that is being used in practice).

Predictability of evidence synthesis, timelines and interpretation

Common tools and templates. In terms of predictability, the outcome of the assessment depends critically on the process of evidence assessment and the methodological choices, **so the impact on common tools on the predictability of the resulting assessment is small.**

Early dialogue. Turning to the value of early dialogue, based on our interviews, the process represents an opportunity for companies to receive a clear 'red light' message on certain aspects of medicine development. Therefore, this exercise can increase predictability and guide applicants to invest resources in viable developments from both a regulatory and a reimbursement perspective, to provide the required evidence to support regulatory and reimbursement decision-making. This could lead to timely access to the market in the interest of patients. The evidence shows that early dialogue with HTABs is valuable as the perspective of HTABs and regulators differ and the early dialogue reduces these differences. It could also lead to greater agreement amongst HTABs. However, these benefits should not be over-stated as these studies show HTAB views, at least among the subset of participating HTABs to date, are not as fragmented as might have been considered. **So there is a modest benefit from early dialogue**.

Joint REA. In terms of strengthened cooperation on REA, it is very unlikely that adoption of EU REA would increase the number of products being reimbursed or have a significant impact on prices. The reason is that the link between the HTA and the reimbursement decision is complex and the reimbursement decision takes into account the value for money of the medicine and the budget impact. Given it is ultimately the reimbursement decision that affects the investment decisions of a company this will also not be affected by strengthened cooperation on REA. However, it seems reasonable to conclude that although this will not remove variation in subsequent reimbursement decision across countries it could reduce it, and this could lead to greater convergence for particular products (both in terms of assessment of added value and in terms of those assessed as

1 This assumes that the full HTA report will take longer than the joint REA report to be produced, and therefore REA information in the full HTA report will be delivered later than it would have been delivered in a joint REA report only.

2 On the contrary, joint REA does not represent the same challenges to national autonomy. It is an input into an economic assessment and the appraisal process.

offering less significant benefit). **The improvement in predictability resulting from strengthened cooperation on EU REA would still be valued by industry and by patients** as it could reduce inequality in access.

Full HTA. **We find that cooperation on full HTA is unlikely to improve predictability, for the same reasons that is unlikely to improve consistency.**

Quality of governance and processes to improve quality of assessment

The question is whether greater cooperation (1) will increase transparency, (2) will increase the role and the contribution of stakeholders (e.g. patients), and (3) will lead to better decisions from a societal perspective.

Common tools and templates. **The use of common templates implies that elements of value for patients are also adopted in countries where they are not currently captured**. However, there is no guarantee this would be used in the subsequent assessment.

Early dialogue. Although the exact role of patients in a strengthened early dialogue process is unclear, they have been more involved in early dialogue at the EU level (in parallel advice, Shaping European Early Dialogues for health technologies (SEED) and European network for Health Technology Assessment (EUnetHTA) pilots) than at the national level. **So early dialogue would bring benefits in countries without an early dialogue process (21 countries) and in the seven countries with a process but with little patient involvement today**.

Joint REA. **In terms of cooperation on REA, this would increase patient involvement in the assessment in about 16 markets.** The limited evidence that exists suggests that incorporating patient views is helping to deliver evidence that satisfies the needs of the HTA processes, to the benefit of patients and society.

Full HTA. In terms of cooperation on full HTA, our findings are that it would, on the face of it, increase transparency regarding the process, but **in reality the countries will still want to undertake their own economic assessment, potentially in the negotiating process, reducing transparency overall** (and patient's input to full HTA may be disregarded)**.**

Speed of decision-making process at national level

Common tools and templates / early dialogue. **We do not find any evidence that common tools or templates or early dialogue lead to a faster decision-making process**.

Joint REA. Strengthened cooperation on REA could accelerate the national assessment process, but this varies depending on the speed of the current process and the type of HTA process. We distinguish between different processes that can finish before or at marketing authorisation (where the benefits would materialise through synergies in the submission process), those with parallel and sequential REA and CEA processes finishing after marketing authorisation, and those that only start after marketing authorisation. As to whether it would also speed up decision-making, it is possible that countries delay reimbursement (even with an accelerated REA process) or that companies delay submitting products to countries. Based on our interviews with national associations and with companies, it remains reasonable to conclude that some time savings would be

passed on to patients. **We therefore conclude that EU REA could lead to some faster patient access but only in some markets**.

Full HTA. **We do not find that strengthened cooperation on full HTA delivers any benefits because the process will delay the communication on the REA (reducing the benefits discussed in the previous section).** The countries will also find other ways to conduct their own economic evaluation and so this will not lead to any acceleration in the process.

Summary

The findings of our study are summarised in Table 2 below. It is clear that common tools could deliver some benefits, but greater benefits are delivered by early dialogue and Joint REA. Joint REA with early dialogue delivers the largest societal benefits. Joint full HTA offers few benefits.

Table 2: Summary of degree to which different outputs of cooperation would deliver societal benefits

EU Output	Consistency	Predictability	Governance	Market access
Common tools and templates	+	+	+	0
Early dialogue	++	++	+	0
Joint REA	++	++	++	0/+
Joint full HTA	-	-	-	0

Source: CRA analysis. Key: + positive societal impact, - negative societal impact, O no impact

1. Introduction

EFPIA asked Charles River Associates (CRA) to undertake an assessment of the impact of the European Commission's (EC) proposals to strengthen cooperation on health technology assessment (HTA). To do so, CRA:

- Undertook a literature review on the problems associated with a fragmented system of HTA
- Facilitated a workshop and follow-up interviews with individual pharmaceutical companies to understand the overall value that cooperation on HTA could deliver from the industry's perspective
- Conducted an economic impact assessment focusing on the "wider" costs and benefits of the Commission's proposal, supported by targeted interviews with groups of patients and clinicians.

This study is intended to complement the findings from the ongoing consultation process being undertaken by the Commission, which is supported by a series of consultancy projects investigating the benefits and impacts of the different options. Whilst the Commission's study is focusing on the immediate costs and benefits of the submission and HTA processes, this analysis is intended to cover the wider range of potential costs and benefits.

1.1. Background

Since 2005, there have been increasing efforts to promote collaboration between European HTA agencies. A key facilitator has been the EC and its support for the European network for Health Technology Assessment (EUnetHTA). To date, EUnetHTA has developed an HTA Core Model to promote best practice of joint technology assessments at the European level[3] and has piloted relative efficacy assessments (REA) in two previous Joint Actions (JA).[4,5] EUnetHTA is currently undertaking JA3, a four-year project ending in 2020, with the aim to establish and implement a "sustainable model for HTA cooperation in Europe".[6] In parallel, the EC is making plans to strengthen EU cooperation on HTA. It is important to note that the innovative pharmaceutical industry has supported the development of EU

3 EUnetHTA (2015), "Methods for health economic evaluations – A guideline based on current practices in Europe" Final version, May 2015. Available at [last access 3 July 2017]: http://www.eunethta.eu/sites/default/files/sites/5026.fedimbo.belgium.be/files/Methods%20for%20health%20economic%20evaluations%20A%20guideline%20based%20on%20current%20practices%20in%20Europe_Guideline_Final%20May%202015.pdf

4 EUnetHTA website [last access 3 July 2017]: http://www.eunethta.eu/about-us

5 EUnetHTA website [last access 3 July 2017]: http://www.eunethta.eu/national-uptake

6 EUnetHTA website [last access 3 July 2017]: http://www.eunethta.eu/activities/joint-action-3/jointaction31/eunethta-joint-action-3-2016-2020

REA provided that joint reports remove some work currently conducted at national level (which was not the case in the previous JAs).[7]

In 2016, the EC set out the potential benefits of HTA cooperation for different stakeholders – from health professionals, public health organisations and patient organisations to the pharmaceutical industry – in an inception impact assessment after concluding that the current fragmentation of HTAs in Europe (the dominance of national HTA procedures and methodologies) has led to:[8]

- Duplication of efforts
- Diverging patient access and health inequality within the EU
- Business unpredictability, thereby adversely influencing investment in life sciences.

The EC has created a roadmap to determine how to address this problem. Specifically, it has set out options focused on different outputs:

- The collection, sharing and use of common templates, tools and data
- Early dialogues
- The production of joint REA reports
- The production of joint full HTA reports.

The EC is looking to assess the impact of strengthening EU cooperation on HTA and has issued a public consultation[9] and commissioned a study.[10] Importantly, this study has particularly emphasised collecting evidence on the cost of developing submissions for health technology agencies and the costs falling on the health technology assessment bodies (HTABs) themselves.[11] We define these as "narrow" benefits of the proposals. Less attention has been given to collecting evidence on the wider benefits to patients, the healthcare system or the industry.

To this end, CRA has developed this report to complement the data being collected by the EC's consultants. CRA has focused on documenting and then testing the potential benefits

7 EFPIA (2017), Response to the questionnaire provided by Gesundheit Österreich Forschungs- und Planungs GmbH (GÖ FP), London School of Economics (LSE Health) and SOGETI: "Study on impact analysis of policy options for strengthened EU cooperation on HTA". Internal document

8 European Commission (2016), "Inception Impact Assessment - Strengthening of the EU cooperation on Health Technology Assessment (HTA)". Available at [last access 3 July 2017]: http://ec.europa.eu/smart-regulation/roadmaps/docs/2016_sante_144_health_technology_assessments_en.pdf

9 European Commission website [last access 3 July 2017: http://ec.europa.eu/health/technology_assessment/consultations/cooperation_hta_en.

The results of this consultation were recently published. European Commission website [last access 3 July 2017]: https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/20161020_frep_en.pdf

10 The Austrian Public Health Institute (GÖ FP) and the London School of Economics (LSE Health) are jointly responsible for developing a report based on a survey on the impact of the policy options and case studies of a sample of health technologies: "Study on impact analysis of policy options for strengthened EU cooperation on HTA. 2017. Sogeti, Austrian Public Health Institute, London School of Economics".

11 For example, in the Austrian Public Health Institute survey, 18 questions explicitly focus on costs.

to all stakeholders from strengthening cooperation on HTA, beyond its impact on the cost of developing and submitting the HTA submission.

1.2. The challenges arising from a fragmented approach to HTA

Before considering the impact of proposed policy changes, it is important to consider what would happen in the absence of policy change - in other words, what is the problem that the policy seeks to address. The challenges that result from a fragmented HTA system have been set out by the European Commission in its Inception Impact Assessment.[12] There is also a large existing literature on the use of the HTA today in European Member States and ongoing trends. This documents the following:

- Currently there exists a wide variety of approaches to undertaking HTA, with different approaches being applied in different countries and even on a regional basis. Looking to the future, it seems likely that the number of different approaches to HTA will continue to increase, particularly with new approaches being developed in smaller European markets.[13] Evidence on the extent to which HTABs are willing to rely on the assessment undertaken by other national HTABs remains weak.
- The focus on different outputs of HTA will vary significantly. Early dialogue will occur in some markets as it does today, but its application will vary from country to country and not be undertaken on a consistent basis.[14]
- The variation in the methodology applied and the process followed will continue to exhibit a high degree of variation. There are ongoing initiatives to collaborate between countries, with some "clusters" of HTA agencies working together, but evidence on the impact of these initiatives is weak and hence there is still

12 European Commission (2016), "Inception Impact Assessment - Strengthening of the EU cooperation on Health Technology Assessment (HTA)". Available at [last access 3 July 2017]: http://ec.europa.eu/smart-regulation/roadmaps/docs/2016_sante_144_health_technology_assessments_en.pdf

13 Compared to a decade ago, there has been a significant increase of activity related to HTA for decision-making purposes in Central and Eastern Europe (CEE) and this trend is expected to expand to other countries. Gulacsi L, Rotar AM, Niewada M, Loblova O, Rencz F, Petrova G, Boncz I and Klazinga NS (2014) "Health technology assessment in Poland, the Czech Republic, Hungary, Romania and Bulgaria", *European Journal of Health Economics* 15:S13-S2

14 OECD (2017) "New Health Technologies – Managing Access, Value and Sustainability". Available at [last access 3 July 2017]: http://www.oecd.org/health/managing-new-technologies-in-health-care-9789264266438-en.htm

uncertainty on how these will develop. It seems likely that these will only mitigate the fragmentation to a small degree.[15,16,17,18]

- The multiple processes and inconsistent timelines will delay patient access. The level of resources dedicated to HTA varies significantly from one country to another contributing to the length of the process and the resulting delay. The pressure on resources and delays will be exacerbated in the future by the number of medicines in development and the resulting number of technology assessments imposing significant burden on current approaches.[19,20]
- In terms of process and governance, there will be improvements in transparency and patient involvement, but the way this is implemented and its effectiveness will continue to vary considerably from country to country.[21]
- There is increasing interest in the use of real-world evidence (RWE), and HTABs are commonly asking for additional data to be collected following the initial assessment. The approach to RWE generation will continue to develop, with differing requirements arising from different HTA processes.[22,23]

If no action is undertaken to strengthen cooperation on HTA, it is very likely that the post-2020 landscape will be even more fragmented than today's. This is summarised in Table 3.

15 European Parliament website [last access 3 July 2017]: http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+REPORT+A8-2017-0040+0+DOC+XML+V0//EN

16 Nordic Innovation website [last access 3 July]: http://www.nordicinnovation.org/no/prosjekter/innovative-nordic-health-and-welfare-solutions/nordic-medtech-growth-2/

17 Kalo Z, Gheorghe A, Huic M, Csanadi M and Kristensen FB (2016), "HTA implementation roadmap in Central and Eastern European countries", Health Economics 25S1:179-192.

18 PMLive website [last access 3 July 2017]: http://www.pmlive.com/pharma_intelligence/market_access_in_europe_balancing_access_and_affordability_1184275

19 Other studies highlight differences in HTA outcomes across markets that lead to differences in access. For instance: Kawalec P, Sagan A and Pilc A (2016), "The correlation between HTA recommendations and reimbursement status of orphan drugs in Europe", *Orphanet Journal of Rare Diseases* 11 (122).

20 Pavlovic, M "Challenges for Relative Effectiveness Assessment and Early Access for immunotherapies in Europe," *Frontiers in Medicine*, November 2016, Volume 3, Article 56.

21 Scott AM and Wale JL (2017), "Patient advocate perspectives on involvement in HTA: an international snapshot", *Research Involvement and Engagement* 3:2.

22 Makady et al. "Policies for Use of Real-World Data in Health Technology Assessment (HTA): A Comparative Study of Six HTA Agencies," *Value in Health* (2017) 520–532, http://dx.doi.org/10.1016/j.jval.2016.12.003

23 Lipska et al. "Does conditional approval for new oncology drugs in Europe lead to differences in health technology assessment decisions?" *Clin Pharmacol Ther*. (November 2015) 98(5):489-91. doi: 10.1002/cpt.198. Epub 2015 Sep 8.

Table 3: Potential implications of a scenario without strengthened cooperation on HTA

Areas	Conclusions
Number of HTA processes	The number of HTA processes will increase, as new markets without HTAs (mostly in Central and Eastern Europe (CEE)) will introduce them and markets that are using HTA will continue to develop national rules. Some processes allowing cooperation could emerge, but their impact is uncertain.
Different approaches to early dialogue	The number of HTAs offering early dialogue will increase, but this will still vary in terms of formality and effectiveness.
Variation in the methodology, process and conclusions	Methodology, process and conclusions will vary considerably across HTABs, increasing the burden of inconsistency and unpredictability.
Multiple processes and inconsistent timelines	Multiple processes with different timelines will contribute to inequality in access across Member States.
Different approaches to governance of HTA process will persist	Patient involvement will continue to increase, but the way this is implemented and its effectiveness will continue to vary considerably from country to country.
Real-world evidence	The interest in RWE will continue to grow. Different HTA agencies are adopting different approaches, which is likely to increase going forward.

Source: CRA analysis

1.3. Methodology

The project assessed the impact of the EC's options in the EU Member States through a literature review, a facilitated workshop and targeted interviews.

1.3.1. A literature review

CRA first reviewed the literature on the challenges from a fragmented HTA system in Europe and then examined the academic and grey literature on the potential impact of strengthened cooperation on HTA. Search terms included different combinations and variations of terms such as "European Health Technology Assessment", "relative efficacy", "relative effectiveness", "harmonisation", "duplication", "fragmentation" and "impact". There

is a vast literature on the current HTA landscape and the challenges this creates.[24] We have reviewed 52 reports focused on different elements of the environment today.

Several studies recognise the value of cooperation, but there is very limited or no evidence about its quantification. The notable exception is the ECORYS report for the Executive Agency for Health and Consumers, which in 2013 estimated €152 million of net cumulative benefits deriving in 2022 from the implementation of a cooperation model based on the production of joint assessments in Europe (but focused on direct cost savings).[25] However, there have been no recent updates to this assessment, and the literature mostly notes that HTA cooperation can

- Allow for better business predictability and improve the quality of assessments[26]
- Increase the speed to access innovative medicines[27]
- Improve the common understanding of requirements, facilitating the appropriate design of clinical trials.[28]

In total, we reviewed 12 reports focused directly on EU cooperation. However, with the exception of the ECORYS report, these do not provide any quantification of the potential impact.

24 We understand there is an ongoing landscape assessment (a study on mapping of HTA national organisations, programmes and processes in EU, by Julia Chamova, and a study on mapping of HTA methodologies in EU, by Prof. Finn Boerlum Kristensen) so we do not attempt to summarise this literature in detail.

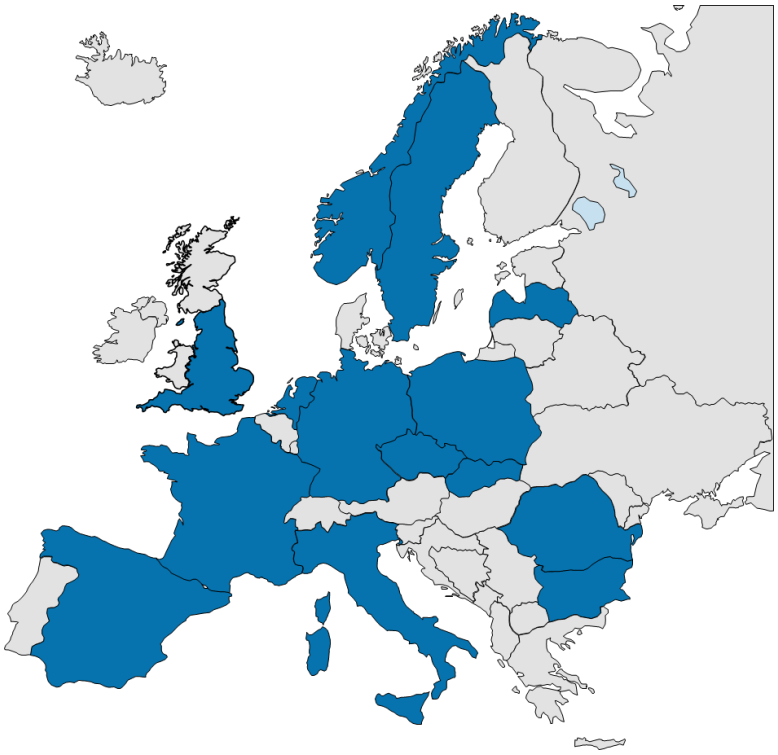
25 ECORYS (2013), "European Cooperation on Health Technology Assessment, Economic and governance analysis of the establishment of a permanent secretariat". Available at [last access 3 July 2017]: http://ec.europa.eu/health/sites/health/files/technology_assessment/docs/study_ecorys_european_cooperation_hta_en.pdf

26 Nachtnebel A, Mayer J, Erdos J, Lampe K, Kleijnen S, Schnell-Inderst P and Wild C (2015), "HTA goes Europe: European collaboration on joint assessment and methodological issues becomes reality", *The Journal of Evidence and Quality in Health Care* 109(4-5): 291-299.

27 I-Com (2017), "Health Technology Assessment in the European Union: State of art and future scenarios", February 2017. Available at [last access 3 July 2017]: http://www.i-com.it/wp-content/uploads/2017/02/Studio_Health_Technology_Assessment-in-the-State-of-Art-and-Future-Scenarios1.pdf

28 Ciani O and Jommi C (2014), "The role of health technology assessment bodies in shaping drug development", *Drug Design, Development and Therapy*.

Figure 1: Geographic scope of project



Notes: These are: Bulgaria, Czech Republic, England, France, Germany, Italy, Latvia, the Netherlands, Norway, Poland, Romania, Slovakia, Spain, and Sweden.

In terms of geographic scope, our project focused on data in 14 Member States (Figure 1). These countries were selected to represent a comprehensive geographic scope and a varied sample of HTA systems (in terms of maturity).

1.3.2. A facilitated workshop to articulate the societal benefits from strengthened cooperation on HTA

CRA facilitated a workshop with 18 representatives from the industry and six representatives from national trade associations.[29] In the workshop, CRA described the preliminary findings from the literature review on the extent of HTA fragmentation in Europe, the consequences of the fragmentation, and the theoretical benefits of HTA cooperation discussed in the literature. Participants provided their critical views on the challenges from the environment and the potential *societal* benefits from the industry perspective. Their feedback was used to develop a structured framework on how to quantify the benefits of strengthened cooperation, and this was validated through a series of targeted interviews with relevant stakeholders.

1.3.3. Targeted interviews

We undertook 16 detailed interviews, to test and validate preliminary findings, with a variety of stakeholders including industry experts, patient organisations and clinical groups. Table 4 lists the interviewed stakeholders.

29 These were representing the following countries: England, Germany, Norway, Portugal, Sweden and Switzerland.

Table 4: Interviewed stakeholders[30,31]

Stakeholder type	Organisation
Patient groups	• European Federation of Neurological Associations (EFNA)
Consumers	• European Public Health Alliance (EPHA)
Clinical Groups	• Senior experts from two international societies (Leukemia & Lymphoma Society, European Hematology Association)
Trade associations	• CEE industry associations (Bulgaria, Czech Republic, Slovakia, Poland)
Pharmaceutical companies	• Seven pharmaceutical companies (BMS, Celgene, Eli Lilly, J&J, Merck, MSD, Roche)

Source: CRA analysis

Finally, CRA used the collected and validated information on wider benefits accrued under each of the EC options to determine the impacts of those options.

1.4. Structure of the report

The rest of this report is structured as follows:

- Chapter 2 describes the theoretical societal benefits that accrue to all stakeholders from strengthened cooperation on HTA.
- Chapter 3 assesses the degree to which these benefits would be achieved through cooperation on different outputs (based on the assumption of take-up).
- Chapter 4 sets out the implications for the Commission's proposals.

30 The interviews undertaken gathered the views of the individuals rather than representing the organisation. A much wider group of stakeholders was invited to participate in interviews (over 20 requests for interviews were sent) but many did not wish to participate during the Commission's consultation period.

31 In addition to the public response to the Commission's consultation provided by EFPIA, CRA also reviewed the responses published by: European Public Health Alliance (EPHA), Representation of the French Social Security (REIF), Prescrire, Health Action International (HAI), European Social Insurance Platform (ESIP), European Cancer Patient Coalition (ECPC); Dutch Ministry of Health, Welfare and Sport (VWS).

2. The benefits of strengthening cooperation on HTA to different stakeholders

The first step in the project was to understand the benefits to the innovative pharmaceutical industry and to other stakeholders that could result from a strengthened cooperation on HTA. In the following chapters we test whether this is consistent with the views of other stakeholders and with the evidence.

To develop this position, CRA facilitated a workshop with industry participants on how the benefits of cooperation (beyond the reduction in duplication) would materialise. The benefits of the strengthened approach to HTA were articulated along four dimensions: consistency of assessment requirements, predictability of evidence synthesis, quality of governance, and speed of assessment. To each of these groups a series of potential benefits was articulated. The description of the potential benefits under each dimension is provided in Table 5.

Table 5: Possible long-term benefits of strengthened cooperation on HTA

Dimension	Potential benefits to society
Consistency of the assessment requirements	• Reduced variability of the scope of assessments (the population and subpopulations), comparators and outcomes • Efficiency in the generation and synthesis of evidence due to choice of comparators, types of evidence required and/or accepted in the assessment, selection of outcomes and subpopulations, post-marketing evidence
Predictability of evidence synthesis, timelines and interpretation	• Increased predictability of the timelines • Increased predictability of evidence interpretation in national appraisals (particularly those that have fewer established processes)
Quality of governance and processes to improve quality of assessment	• Increased scientific quality of assessment by having consistent assessment processes and governance, with particular focus on transparency, validation and engagement opportunities • Reduced heterogeneity of expertise across HTA agencies and hence improved quality assessment across member states (MS) • Holistic approach to assessment including patients' perspectives • More evidence-based national decision-making processes across Europe • Increased ability to appeal decisions

Speed of decision-making process at national level	• Increased speed of the clinical assessment processes • Increased speed of payer negotiations, as informed by an objective evidence base • Increased efficiency of information exchange with the European Medicines Agency (EMA) and hence overall process, as EMA would be required to share information with one agency instead of multiple national agencies (avoid "queueing" for information) • Increased opportunities for early and fast access, reducing inequality of access for EU patients

It was clear from the workshop and subsequent interviews with industry participants that there are differences of opinion on the relative importance of these benefits and the likelihood they will be delivered, both between companies and across countries, specifically:

- The value of early dialogue versus the production of joint REA reports, with some countries placing significantly more value on early dialogue than the production of REA reports and vice versa
- The degree to which the benefits can be quantified. In particular, it was argued that the magnitude of benefits in terms of predictability could be much greater than, say, market access delays, but the benefits much more difficult to quantify
- The countries where the benefits of strengthened cooperation will have the most significant benefit
- The magnitude of the cost savings from efficiencies in evidence generation
- The role that patients should play at different stages in the HTA process and the magnitude of the benefits this would bring (with some arguing that their role more naturally occurs at a national level after the assessment of clinical evidence, while other argue that the role is pivotal at the early scientific advice stage).

However, there was general agreement that the potential benefits of HTA to all stakeholders were encompassed by greater consistency, more predictability, improved governance and faster decision-making.

3. Assessment of the wider impact of cooperation on HTA (and benefits to all stakeholders)

In this chapter, we review the degree to which strengthened cooperation would deliver the benefits set out in the previous chapter, focusing particularly on the degree to which these benefits are supported by the existing evidence, the extent to which they can be quantified, and the conditions under which they are most likely to materialise. We assume, for the basis of this discussion, uptake of the outputs of EU cooperation.[32] In the next chapter, we use this analysis to consider the European Commission's five options.

3.1. Consistency of the assessment requirements

Strengthened cooperation on HTA could bring more consistency of the requirements for assessment in a number of ways. We consider in turn how more consistency would materialise in the different outputs of EU cooperation (common tools and templates; early dialogue; joint REA; joint full HTA).

Common tools and templates

In terms of the use of common tools (e.g. use of submission templates) and methodologies (e.g. the HTA Core Model developed by EUnetHTA), EUnetHTA JAs have supported the development of common submission templates that are being used today in JA3. If these were used across national HTA processes to harmonise the HTA landscape, this could reduce complexity (tools aim to provide a common methodology, suggesting a standard for conducting and reporting HTA); however, there is only weak evidence that this will increase consistency in evidence requirements:

- The templates are an agglomeration of existing requirements and therefore cannot lead to greater consistency.
- The application of the methodology is determined by HTA authors; for example, the templates do not determine the choice of comparators, types of evidence or population.
- As with the JA2 pilots, the way the methodology is applied is only determined through discussions during the assessment, with the scoping meeting being particularly important in this process.
- There will still be the need to have national submission templates to provide local data for national reviews.

Other common tools also have been established to support cooperation. For instance, the EUnetHTA Planned and Ongoing Projects (POP) database was established in 2009 to facilitate collaboration among European HTA agencies and reduce duplication of work. To achieve this aim, EUnetHTA POP database provides EUnetHTA partners a tool allowing them to share information on planned, ongoing or recently published projects of participating agencies. However, while the POP database has the potential to reduce duplication of effort, this has not been realised during the three-year period of the EUnetHTA Joint Action Project Framework, 2010-2012.

32 The issue of whether the outputs are used on a voluntary or mandatory basis is discussed in the next chapter.

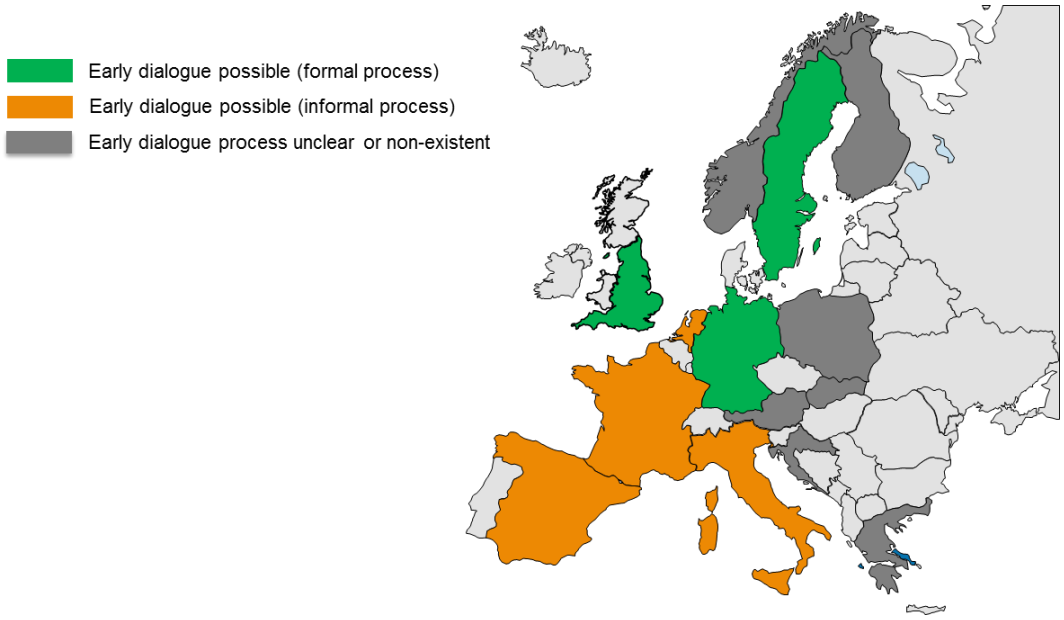
Based on our interviews, common templates and tools are useful in terms of clarifying the types of information that could be used in the assessment, but this does not ensure the same evidence is used consistently in assessment processes that follow. In particular, common submission templates and methodology documents will be useful for countries that do not have these today, and will prevent to a degree additional requirements being introduced.

Hence, this does improve consistency for countries that currently lack a formal submission process / template. In this case, the countries can adopt (and adapt locally) the common EU submission template.

Early dialogue

We consider that an EU process for early dialogue would allow a discussion about the patient population, preferred comparators, and outcomes for all the countries included in the process – rather than the discussion being limited to only the small number of countries that have a formal process today. As Figure 2 shows, there are early dialogue processes for HTA agencies in Germany, France, the Netherlands, Spain, Sweden and the UK, but there are also a number of countries (particularly CEE countries) where early dialogue does not occur. The formality of early dialogue processes also differs: countries such as Germany and Sweden have formal processes, while collaborations are more informal in France, Italy and Spain (as set out in Figure 2).[33,34]

Figure 2: Early dialogue with national HTA agencies across Europe



Sources: CRA analysis of various publications

33 CBParners (2014), "Optimising yield from early advice consultation with HTA and regulatory organisations". Available at [last access 3 July 2017]: https://www.ispor.org/Event/GetReleasedPresentation/191

34 Foxon G and Craddy P (2015), "Early Scientific advice from payers across the EU". Available at [last access 3 July 2017]: http://www.remapconsulting.com/wp-content/uploads/Early-scientific-advice-2_0.pdf

To understand the potential benefits from this, it is useful to look at the benefits that early dialogue with HTABs already delivers. Because early dialogue sessions are confidential in nature (as they are intended to inform companies), there is limited evidence on the benefits of these *national* discussions – neither the industry nor the national HTA makes discussions public. However, companies involved in early dialogue have expressed their satisfaction indicating they are successful from the industry perspective. For example, a pilot early dialogue study by Tapestry Networks reflected that the industry found early dialogue "valuable" and "worthwhile" and that it helped reduce costs via the elimination of unnecessary studies.[35] At the same time, HTABs found the increased interaction useful and educational in terms of public health trends and it allowed early alignment on expected patient reported outcomes.[36,37] However it is evident that there are significant differences in how early dialogue is currently undertaken (Table 6), which cooperation could reduce.

Table 6: Differences in HTA bodies early dialogue[38,39]

	Outline	Usage	Timelines	Number of meetings a year
NICE (England)	Confidential, interactive, professional service Experts selected based on questions in briefing book Thorough, well-considered feedback covering expert critique of clinical development & broader evidence plans	Can help to de-risk phase 2b programme as well as phase 3 Detailed advice with implications also outside the UK	4-5 months	20
GBA (Germany)	Confidential. Reviewed by GBA committee	Prefer interaction based on phase 2	4-5 months	n/a

35 Tapestry Networks (2010), "Pilots of Multi-Stakeholder Consultations in Early-Stage Drug Development Frequently Asked Questions". Available at [last access 30 April 2017]: http://www.tapestrynetworks.com/documents/EHILN-multi-stakeholder%20pilots%20FAQs%20-%2010-19-10.pdf

36 CBParners (2014), "Optimising yield from early advice consultation with HTA and regulatory organisations". Available at [last access 3 July 2017]: https://www.ispor.org/Event/GetReleasedPresentation/191

37 Tapestry Networks (2012), "Pilots of multi-stakeholder consultations in drug development". Available at [last access 3 July 2017]: http://www.tapestrynetworks.com/initiatives/healthcare/upload/Pilots-of-multi-stakeholder-consultations-in-drug-development-6-June-2012.pdf

38 Antonisse A (2015) "Joined regulatory/payer advice". Internal document

39 Deerfield Institute and EuropaBio (2015), "Deerfield Institute – EuropaBio Report on Regulatory and HTA scientific advice for small and medium enterprises" March 2015. Available at [last access 3 July 2017]: https://issuu.com/europabio/docs/deerfield_europabio_survey_regulato

	Clear feedback in line with the law	data but prior to phase 3		
HAS (France)	Confidential Informal interaction	Provide insights on requirement to achieve highest added therapeutic value (ASMR) rating	3-4 months	10

Sources: First four columns from "Joined regulatory/payer advice" A presentation by Ad Antonisse; Fifth column from Deerfield Institute and EuropaBio

Looking at cooperation, EMA initiated parallel HTA-regulatory scientific advice in 2010, with the participation of several HTABs, that allows developers to receive simultaneous feedback from both regulators and national HTABs on their development plans for new medicines.[40] In addition to the parallel advice process, there have been 10 early dialogues involving multiple HTABs under the SEED (Shaping European Early Dialogues for health technologies) project. Furthermore, HTABs have performed several early dialogues in the framework of the EUnetHTA JA1 and JA2. Based on our interviews all of these pilot programmes have been valuable but participants to these projects recognise the need to make it more formal and sustainable. We understand that HTABs want to have a better structured cooperation with EMA, which is currently provided within the EUnetHTA initiative.[41] However, once the EUnetHTA initiative will cease, HTABs would need another sustainable process in place in order to achieve the same results.

As with the national processes, assessing whether *European* cooperation on early dialogues would lead to great consistency on evidence requirements is challenging. The pilots conducted to date are also confidential, and therefore it is difficult to look at published experience of products undergoing early dialogue. However, there is some public evidence from (1) EMA report on pilots, (2) case studies presented by EMA and industry, (3) surveys with companies.

(1) There is some evidence from the European pilots as reported by EMA. This has set out the HTABs involved, with pilot projects typically involving 3-4 HTABs.[42] EMA has investigated the benefits of early dialogue. EMA reports that the industry sees this initiative as "very valuable". It was also reported that "from a company perspective, getting clarity on areas of consensus and divergence means the company can better understand what

40 EMA (2016), "Best practice guidance for the parallel regulatory – HTA scientific advice procedure". Available at [last access 3 July 2017]: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500203944.pdf

41 However, it is important to note that we have not interviewed HTAB for this project and this is based on interviews with companies.

42 Killalea S (2013), "Early engagement between manufacturers, HTA assessors, and regulators: learning from the past to guide the future". Available at [last access 3 July 2017]: https://www.ispor.org/congresses/Dublin1113/presentations/SecondPlenary-Sheila-Killalea-Slides.pdf

changes it has to make and where it might need to consider so-called 'trade-offs'".[43] This is consistent with the workshop and with the interviews conducted for this project. However, it is recognised that regulators and HTA agencies have different objectives, so differences in data requirements may be expected. The experience with the first pilots of parallel regulator–HTA scientific advice, as reported by the EMA, shows that the evidence needs of different stakeholders can be met within one trial design or one development programme in most cases without blurring of remits between regulators and HTABs.[44]

(2) EMA has reported some case studies on the impact of early dialogue involving HTABs.[45,46] It was agreed that a statistically less stringent approach could meet all stakeholders' requirements. One company has also presented public evidence based on their experience of early dialogue process. They found that early dialogue with multiple HTABs worked satisfactorily. Only in one case of rare disease was this problematic (as the meeting became rather crowded) and suggestions and advice were more driven by country-specific requirements or restrictions disregarding specificities of the therapeutic area. When consensus was reached, they reported clear and univocal advice was given on outcomes, comparators, population and trial design, indirect comparison, real-world evidence, and patient stratification. [47] The advice will depend on the specifics of the case study and we only have a small number to draw upon (and these may not be representative as orphan medicines), it is however interesting that in this case the benefits of early dialogue cover both consideration from REA and full HTA.

(3) Survey evidence supports the benefits of early dialogue covering both regulatory and HTA issues. For example: "The companies, HTA bodies, and regulatory authorities interviewed were positive about the idea of joint advice. Some companies strongly supported the concept, noting joint advice and common EMA and HTA guidelines would be game-changing, providing consistency across Europe, and improving the timeliness of the whole process".[48]

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43 EMA (2013), "EMA–HTA workshop – Bringing together stakeholders for early dialogue in medicines development". Available at [last access 3 July 2017]: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/05/WC500166228.pdf

44 EMA (2016), "Report of the pilot on parallel regulatory–health technology assessment scientific advice". Available at [last access 3 July 2017]: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/03/WC500203945.pdf

45 Killalea S (2013), "Early engagement between manufacturers, HTA assessors, and regulators: learning from the past to guide the future". Available at [last access 3 July 2017]: https://www.ispor.org/congresses/Dublin1113/presentations/SecondPlenary-Sheila-Killalea-Slides.pdf

46 For example, EMA has presented the case of Pouchitis (a rare disease). In this case, the company proposed a placebo and an unlicensed comparator. EMA considered superiority to placebo as key to their assessment, but HTABs wanted to be able to compare the value (total cost) of new therapy to what it will replace.

47 Vidal A, Prudhomme M and Caprari F (2015), "Analysis of four early dialogues as part of the SEED (Shaping European Early Dialogues) Pilot: Lessons Learnt and Way Forward – A Sanofi Perspective". November 2015. Available at [last access 3 July 2015]: https://www.ispor.org/research_pdfs/51/pdffiles/PHP262.pdf

48 Deerfield Institute and EuropaBio (2015), "Deerfield Institute – EuropaBio Report on Regulatory and HTA scientific advice for small and medium enterprises" March 2015. Available at [last access 3 July 2017]: https://issuu.com/europabio/docs/deerfield_europabio_survey_regulato

As set out above, there are seven European markets where this is possible (England, France, Italy, the Netherlands, Spain, Sweden) but only three (England, Germany, Sweden) with a formal process. So, depending on the number of countries that participate this could potentially cover many more countries than is currently the case – from seven to 28 countries, potentially. It should also be noted that a form of early dialogue has been possible without strengthened cooperation on HTA. Parallel scientific advice has occurred between EMA and HTABs (although typically only 3-4 in any pilot). However, according to interviews, there are significant concerns about the sustainability of the current process and this is not a satisfactory model going forward.

In terms of the benefits, this could potentially feed into the evidence creation process (we discuss the quantification of this in the next section), helping to design phase 3 trials by minimising divergent data requirements between regulators and HTABs.[49] In addition, EU collaboration on early dialogue would increase the benefits of parallel regulatory/HTA scientific advice as it would reduce the number of EMA / national HTA agency interactions.

EU cooperation on REA

The EU REA process itself would be undertaken according to the EU REA methodology and would allow the scope of the assessment (Population, Intervention, Comparison, and Outcome – known as PICO) to be established with more consistency.

It was emphasised in the interviews that the impact of early dialogue and EU REA need to be looked at together. The value delivered by early dialogue is only realised if this has an impact on the resulting REA, this is much more likely to happen if it is associated with an EU REA process. Specifically, early dialogue and earlier clarification on methodology potentially bring a number of benefits:

1. Reducing the cost of developing unnecessary evidence.
2. The importance of the European "voice" in clinical trial design could be stronger, leading to trials that are more geared to the European market, with the result that the design of the evidence generation process is more likely to deliver evidence that is useful for the REA.
3. They could streamline the requirements to develop RWE post the launch of the product, decreasing costs and the burden on patients, the healthcare system and manufacturers.

We will look at each of these in turn.

In terms of the cost of clinical development, the cost of trial is significant, with phase 3 trials being a large component of overall development costs.[50] Any reduction in the cost of evidence generation (whether in clinical trial costs, the costs of observational or registry

49 EMA (2013), "EMA–HTA workshop – Bringing together stakeholders for early dialogue in medicines development". Available at [last access 3 July 2017]: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/05/WC500166228.pdf

50 Estimates of the cost of phase 3 trial vary but one study showed it is common for these to cost over €50 million. Sertkaya A, Wong HH, Jessup A and Beleche T (2016), "Key cost drivers of pharmaceutical clinical trials in the United States", *Clinical Trials* 13(2), 117–126. This paper is focused on the US but in reality, phase 3 trials are global so it is not possible to differentiate between US and EU phase 3 trials costs.

collection) would offer substantial benefits to companies. It is clearly documented, and validated through the interviews, that the requirements of market access (including the role of REA) are taken into account in the clinical development programme. This occurs in different ways, but commonly with market access and HTA experts feeding into the appraisal of medicines in the pipeline.[51,52] Strengthening cooperation on REA would make this easier for market access specialists within companies to communicate the likely approach to REA to those involved in product development.

There is also little disagreement that the requirements of the regulatory and the HTABs and between HTABs often differ and acknowledging this in the evidence generation process is beneficial.[53] Divergence in data requirements can be seen in the multiple sclerosis example below (Table 7).[54]

Table 7: Differences in EMA versus REA/HTA requirements for a relapsing-remitting multiple sclerosis (RRMS) medicine[55]

Agency	Comparator requests	Additional population data requests
EU (EMA)	Placebo, beta-interferon	Active RRMS
England (NICE)	Asked for other interferons	Asked for subgroup analysis
France (HAS)	Vs natalizumab	Same as EMA
Germany (IQWIG)	Did not accept placebo	Asked for indirect comparison for subgroup
Spain	Same as EMA	Same as EMA
Italy (AIFA)	Same as EMA	Same as EMA

Source: Weber et al.

51 PharmaPhorum website: "Overcoming the market access hurdle through better planning of clinical trials". Available at [last access 3 July 2017]: https://pharmaphorum.com/views-and-analysis/overcoming-the-market-access-hurdle-through-better-planning-of-clinical-trials/

52 Touchot N and Ali O (2012), "The New Role of Payer Advisory Boards in Shaping Clinical Development Preparation, Structure, Outcomes and Key Success Factors". Available at [last access 3 July 2017]: http://www.grouph.com/inspiration/wp-content/uploads/ViewPoints-February-2012-The-New-Role-of-Payer-Advisory-Boards.pdf

53 Ciani O and Jommi C (2014), "The role of health technology assessment bodies in shaping drug development", *Drug Design, Development and Therapy.*

54 EFPIA website: "Assessing the added value of medicines to support access: the benefits of European cooperation". Available at [last access 3 July 2017]: http://www.efpia.eu/relative-efficacy-assessment

55 Weber S, Jain M, Nallangangula TK, Jawla S, Rai N, Dev D, Cook N (2015), "Heterogeneity in Relative Efficacy Assessments(REA) across European HTA bodies: opportunity for improving efficiency and speed of access to patients?"

However, although greater clarity of how REA will be undertaken is valuable, the evidence suggests this would not have a significant impact on the costs of evidence generation. In reality, evidence generation is a global decision, with pivotal trials designed to reflect their use globally, and remains primarily focused on establishing market authorisation.[56] This means that trials are often designed reflecting the largest global pharmaceutical market (the United States). European requirements feed into the global decision-making but, on the basis of the interviews conducted, it is extremely rare for a trial to be designed to reflect just European requirements, and even less common, the needs of a single country.

Currently, the requirements of Germany, France and the UK are taken into account in the global trial programme (in addition to the US and Japan). However, in reality, where new data is required by HTA processes it is normally delivered through further investigation of existing clinical trials. For example, in Germany, the industry has had to generate new and additional evidence for diabetes, antibacterial and oncology products according to IQWiG requests.[57,58,59,60] This was completed using existing clinical trial information. The occasions where companies have been requested to develop new clinical trial data directly attributable to the REA process appear extremely rare. Indeed, based on secondary research we cannot find any public reports of a company developing a new trial directly in response to a request from a European HTA agency to fulfil the initial assessment.

Finally, the methodology for undertaking REA and HTA more widely has evolved to reflect the data that is available; for example, indirect comparisons are used to overcome the problem of a lack of head-to-head trial information (with the result that REA requirements may have a smaller impact on clinical trials design). We can compare the use of indirect comparison across some of the larger HTA agencies (Table 8). Although the application of indirect comparisons varies across the HTA agencies, there is the potential to use it, and this reduces the incentives to invest in country-specific clinical trial information. Indeed, greater cooperation on tools and templates could make it easier to use these methods in other countries, reducing the potential for new evidence creation.

56 HTA Network (2014), "Strategy for EU cooperation on Health Technology Assessment". Available at [last access 3 July 2017]: http://ec.europa.eu/health//sites/health/files/technology_assessment/docs/2014_strategy_eucooperation_hta_en.pdf

57 IQWiG, (2013), "Gliptins: IQWiG assessed data subsequently submitted by the manufacturer". Available at [last access 27 April 2017]: https://www.iqwig.de/en/press/press-releases/press-releases/gliptins-iqwig-assessed-data-subsequently-submitted-by-the-manufacturer.3740.html

58 IQWIG website: "Fidaxomicin: Data subsequently submitted by manufacturer prove added benefit". Available at [last access 3 July 2017]: https://www.iqwig.de/en/press/press-releases/press-releases/fidaxomicin-data-subsequently-submitted-by-manufacturer-prove-added-benefit.3673.html

59 IQWiG website: "Enzalutamide: IQWiG assessed data subsequently submitted by the manufacturer". Available at [last access 3 July 2017]: https://www.iqwig.de/en/press/press-releases/press-releases/enzalutamide-iqwig-assessed-data-subsequently-submitted-by-the-manufacturer.5985.html

60 Financial Times website: "Germany's tough reimbursement rules cause drug companies to consider alternative drug trial solutions". Available at [last access 3 July 2017]: http://www.ft.com/cms/s/2/d458d470-4696-11e1-89a8-00144feabdc0.html?ft_site=falcon&desktop=true#axzz4fSgOb99Q

Table 8: Evaluation of indirect comparisons submitted to IQWiG, HAS, NICE and SMC based on a sample of 24 products [61]

	Acceptance of indirect comparison			
	Germany	France	England	Scotland
Product where indirect comparison was used	Brilique	Zytiga	Trobalt	Eylea, Trobalt, Onglyza

Source: Lebioda et al.

It seems unlikely that greater cooperation on EU REA will significantly reduce the cost of evidence collection or the cost of bringing a product to market.

The second argument is that although EU REA does not change the absolute amount of evidence (and hence the cost), the evidence will be better targeted to the European REA process and therefore more likely to be successful. In other words, the differences in requirements from HTABs make it harder to design studies that deliver evidence relevant for Europe.

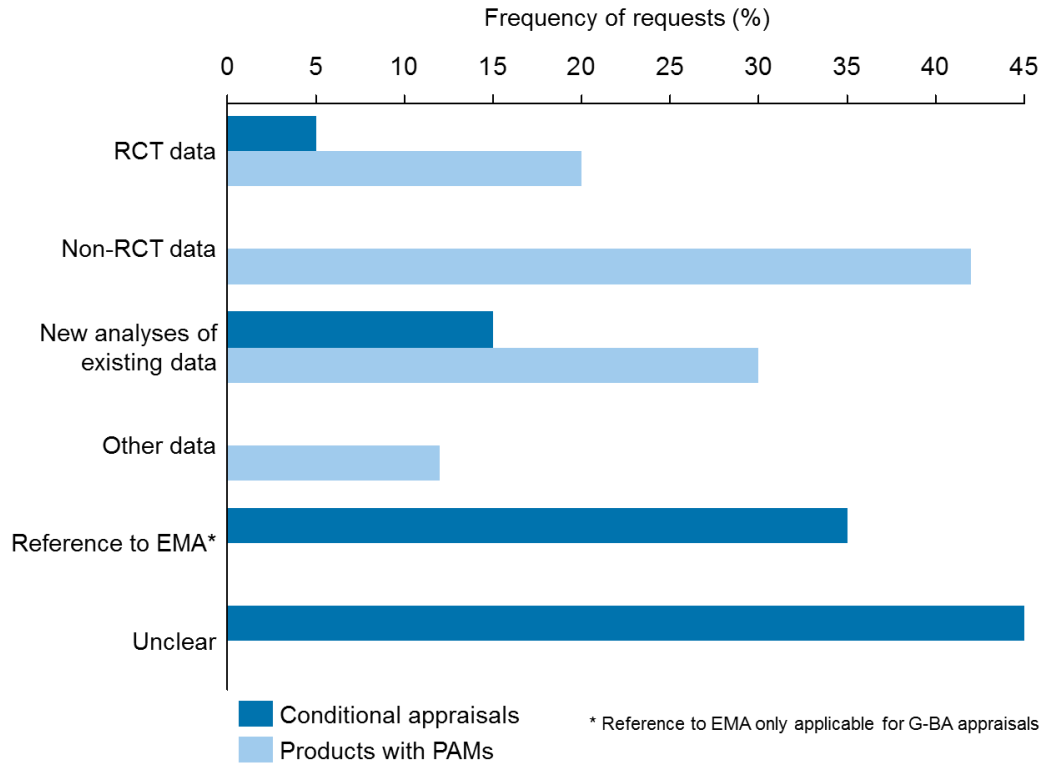
Clearer requirements from the EU REA process in terms of the types of outcomes, the patient population and even the comparators of interest was seen as beneficial from a company perspective. If instead of presenting the different requirements of the largest five European markets (when discussing the phase 2 programme) a single view could be expressed, this would bring greater clarity and influence trial design. (There is little evidence to quantify the impact of European requirements in clinical trial design today.[62]) Theoretically, all interviewed companies agreed this was a benefit; however, they also emphasised that this impact depends on the countries that use the assessment.

Finally, we turn to the requirements of ongoing data collection, which is an increasing requirement globally and within Europe. The information that HTABs require to be generated is different from that required by the regulatory process (Figure 3).

61 Lebioda et al. (2014), "Relevance of indirect comparisons in the German early benefit assessment and in comparison to HTA processes in England, France and Scotland" *Health Economics Review,* 4:31

62 Mestre-Ferrandiz J, Deverka P, Pistollato M and Rosenberg E (2014), "The Current Drug Development Paradigm: Responding to US and European Demands for Evidence of Comparative Effectiveness and Relative Effectiveness". Available at [last access 3 July 2017]: https://www.ohe.org/publications/current-drug-development-paradigm-responding-us-and-european-demands-evidence

Figure 3: Types of additional data requests by the GBA (conditional appraisals) and the EMA (post-authorisation measures, PAMs)[63]**



***Note: Conditional appraisal refer to fixed-termed conditional appraisals of early benefit assessments by the GBA. This is usually done if no reliable conclusions regarding the extent of additional benefit can be drawn from the submitted data. After a pre-specified time frame, the G-BA will review the additionally submitted scientific data and subsequently re-assess a product's additional benefit in a new procedure PAMs are undertaken by EMA, RCT means random control trial. *Reference to EMA is only applicable for G-BA requests and refers to G-BA data requests consistent with PAMs (i.e. there the G-BA request is aligned with the EMA request).*

Source: Ruof et al.

It is clear that EMA and HTA processes are asking for different types of information. The differences across HTA agencies are less clear, and research is required in this area. However, it is the case that requirements from the HTA agencies take a number of forms: (1) to test whether the evidence presented in clinical trials will occur when used in the healthcare system (effectiveness), (2) to look for information about particular subpopulations, and (3) to examine the results in the clinical setting of the host country. This is often the result of the entire assessment process, including requests resulting from cost-effectiveness analysis (rather than just relative efficacy) and therefore requirements to develop post-launch evidence will persist based on the national appraisal even with strengthened cooperation on REA. Given conditional marketing authorisations, some argue, this will increase as new and innovative medicines enter the market with evidence gaps (according to the payers) in their value proposition and there will be an increasing

63 Ruof et al. (2016), "Comparison of post-authorisation measures from regulatory authorities with additional evidence requirements from the HTA body in Germany – are additional data requirements by the Federal Joint Committee justified?" Ruof et al., *Health Economics Review*, 6:46.

number of requests for data to be gathered outside the clinical trial programme. Access to a wide body of relevant data is therefore likely to be increasingly necessary to reduce the uncertainty among payers regarding costs, risks, and patient outcomes.[64]

Cooperation on full HTA

Joint full HTA would include cost and economic evaluation, ethical analysis, organisational aspects, patient and social aspects, and legal aspects. As set out in the Inception Report, full HTA assessments are more linked to the national/regional context than clinical assessments (REA).[65] Drawing on interviews with industry, there are significant concerns that (1) the CEA is naturally country-specific, so benefits in terms of consistency are null, and (2) this will increase the time taken, negating the benefits from strengthened cooperation on HTA. In terms of the evidence:

- All stakeholders, including patient groups and clinicians (and the EC in the inception report) agree that economic assessment is naturally country-specific. There are a multitude of different approaches taken to economic assessment that reflect the structure and nature of the healthcare system.[66] This includes: costs and benefits to be included, the structure of decision-making (i.e. whether it informs, mandates a decision), the structure of costs falling on the healthcare system (cost of hospitalisation, primary care, social care services), the value placed on different types of medicine (including end of life, orphan medicines), the approach to modelling economic assessment, the approach to dealing with uncertainty, and cost and benefits occurring over time. This has implications in that the resources to undertake economic assessment at an EU level would be the same (indeed a rapporteur model could have this being undertaken nationally), as the approach will need to be tailored to country-specific issues. If, on the other hand, the economic assessment is not undertaken on a country-by-country basis and does not reflect national differences, it will not be used in practice.
- The length of time taken could be increased. There are two hypotheses: (1) full HTA takes longer than REA, and (2) cooperating on CEA is intrinsically more challenging that on REA:
    - We do not find evidence that countries adopting a CEA process rather than an REA process are longer. Some of the fastest processes have REA and CEA being undertaken in parallel. Therefore we do not find this argument compelling.
    - However, the requirement to undertake a CEA needs to be tailored to every country. This requires considerable coordination and review at the national level, and the opportunity for national payers to comment on their

64 Valid Insight website [last access 3 July 2017]: http://validinsight.com/payer-centric-post-launch-studies/

65 European Commission (2016), "Inception Impact Assessment - Strengthening of the EU cooperation on Health Technology Assessment (HTA)". Available at [last access 3 July 2017]: http://ec.europa.eu/smart-regulation/roadmaps/docs/2016_sante_144_health_technology_assessments_en.pdf

66 Chalkidou K, Li R, Culyer AJ, Glassman A, Hofman KJ, Teerawattananon Y (2017), "Health Technology Assessment: Global advocacy and local realities", *International Journal of Health Policy Management* 6(4), 233-236.

national circumstances would need to be significantly developed. It seems incredible to most stakeholders (including patient groups and clinicians) that this would not significantly delay the development of the EU REA report substantially beyond the marketing authorisation of the product (if the process started according the current EUnetHTA timelines). As with EUnetHTA JA2 pilots, any delay publishing the report substantially reduces the value of the reports.[67]

Summary

We conclude that regarding consistency, common tools and templates would provide some benefits; however, more significant benefits will occur from a process that incorporates early dialogue with joint REA. This will deliver a more coherent European voice on evidence requirements, but it is unlikely to reduce the cost of evidence generation significantly. Cooperation on Joint full HTA would result in countries developing an alternative approach to economic assessment and reduce consistency: Member States are likely to disregard central assessments in order to preserve some degree of autonomy in national evaluations, especially regarding economic considerations (the CEA part of the HTA). This may lead to a system where although formally Member States will adopt joint full HTA, in practice they will conduct independent evaluations (perhaps informally through the negotiation process), implying a greater inconsistency (indeed this may also prompt Member States to conduct an independent REA).

Table 9: Summary of degree to which different outputs of cooperation would deliver a societal benefit – consistency

EU Output	Consistency
Common tools and templates	+
Early dialogue	++
Joint REA	++
Joint full HTA	-

Source: CRA analysis. Key: + positive societal impact, - negative societal impact, O no impact

3.2. Predictability of evidence synthesis, timelines and interpretation

One of the challenges from a fragmented system of HTA is that the evidence dossier is analysed in a different way in different countries. If strengthened cooperation led to more consistent evaluation of the evidence, it could be valuable for companies in terms of risk associated to whether products will be successful in achieving reimbursement, and it could

67 It should be noted that the later pilots were conducted to the EUnetHTA timeline and the delay resulted from the delayed start to the assessment.

allow companies to prioritise medicines more effectively in the development portfolio. This would also be valuable to patients in understanding the different decisions across countries.

Common tools and templates

Although common tools and templates can lead to greater consistency in evidence reviewed and in the methodology applied, the outcome of the REA depends critically on the process of evidence assessment and the methodological choices. Therefore, the impact of common tools on the predictability of the resulting assessment is small. Based on JA2, the assessment undertaken in the EU REA was understood through the scoping meeting, considering the feedback from the authors, and only to a limited extent by analysing the methodological documents provided by EUnetHTA. Indeed, flexibility of the assessment process (within the boundaries of the EUnetHTA methodology) has proven to be a successful element for joint REA.[68] Equally, databases that share information on assessment undertaken in other markets already exist, but the degree to which they influence the process undertaken in national appraisals is very unclear. Therefore databases, common tools or templates do not in themselves increase predictability (beyond the benefits already discussed in consistency of evidence requirements).

Early dialogue

Turning to the value of early dialogue, the confidentiality of the specific products that have experienced early dialogue (with the exception of those with SEED pilots) at the European level again makes analysing the benefits of this challenging. We can contrast this with evidence from early scientific advice where there are observable benefits in the probability of marketing authorisation.[69,70]

Just because early dialogue occurs, it does not necessarily mean regulators and HTAs will always agree. The evidence as reported by the EMA shows the same questions are being raised by applicants to the regulator and the HTABs in parallel regulator–HTA advice (Figure 4).[71]

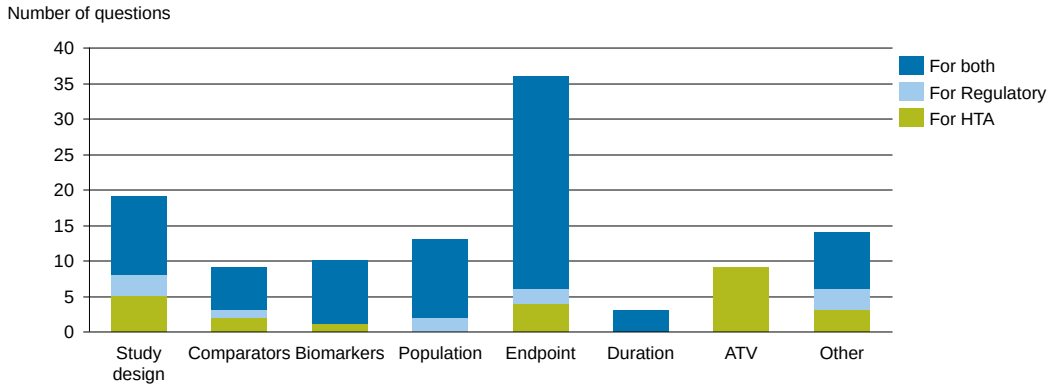
68 CRA (2015), "An analysis of the EUnetHTA pilot assessments". Available at [last access 3 July 2017]: http://www.efpia.eu/uploads/Modules/Documents/cra-efpia---analysis-of-rapid-rea-pilots-final-report-december-2015-stc.PDF

69 Due to confidentiality, it is not possible to undertake analysis that compares what happens to products that use early dialogue to those that do not. There is evidence that early scientific regulatory advice leads to higher probability of success. For early scientific advice by regulatory, analysis has shown that products undertaking early scientific advice have higher probability of achieving regulatory approval. See for example Deerfield Institute and EuropaBio (2015), "Deerfield Institute – EuropaBio Report on Regulatory and HTA scientific advice for small and medium enterprises" March 2015. Available at [last access 3 July 2017]: https://issuu.com/europabio/docs/deerfield_europabio_survey_regulato

70 According to the EMA report on assessing the pilots, there will be a detailed joint publication of the analysis summarised in a peer reviewed journal, but this is yet to be published.

71 Killalea S (2013), "Early engagement between manufacturers, HTA assessors, and regulators: learning from the past to guide the future". Available at [last access 3 July 2017]: https://www.ispor.org/congresses/Dublin1113/presentations/SecondPlenary-Sheila-Killalea-Slides.pdf

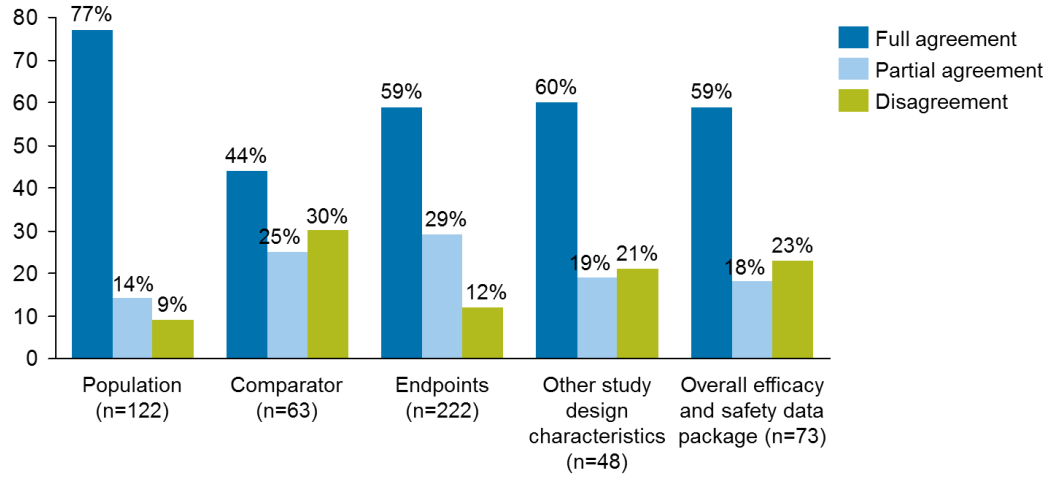
Figure 4: Questions raised by applicants to parallel regulator–HTA advice[72]



Source: Killalea

Recent research has compared the results of early dialogue with HTABs and the EMA. In terms of the outcome of the process, the analysis shows that a high level of overall agreement was reached (see Figure 5). With agreement on some domains close to 80%.

Figure 5 : Level of agreement for each domain: Health Technology Assessment bodies (HTABs) vs regulators[73]



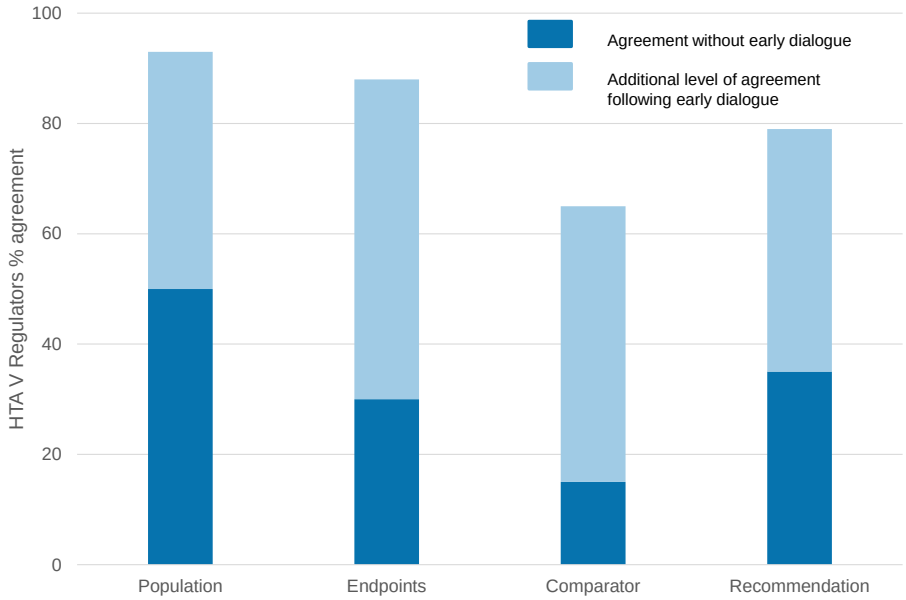
Source: Tafuri et al. n corresponds to the number of questions asked in the early dialogue. The overall sample was 31 products.

72 Killalea S (2013), "Early engagement between manufacturers, HTA assessors, and regulators: learning from the past to guide the future". Available at [last access 3 July 2017]: https://www.ispor.org/congresses/Dublin1113/presentations/SecondPlenary-Sheila-Killalea-Slides.pdf

73 Tafuri et al. (2016), "How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory–HTA parallel scientific advice", *Br J Clin Pharmacol*, 82 965–973.

There is also evidence that the early dialogue process narrowed the areas of disagreement, bringing the regulatory and HTAB perspective closer together.[74] However, we have not been able to assess the methodology used in this analysis.

Figure 6: Commonality of advice following the parallel advice process[75]



Source: Moseley

There is therefore evidence that early dialogue helps companies understand the different perspective and narrow the differences between the regulator and the HTAB. However, it was recognised that even with early dialogue regulators and HTA agencies have different objectives, so some variation in data requirements is to be expected.[76]

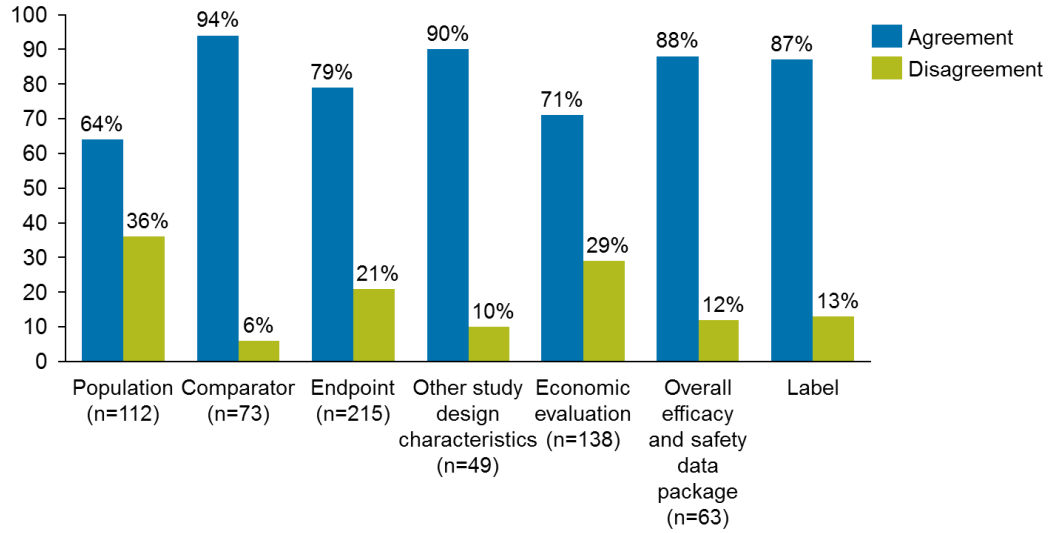
In addition to reducing the variation between HTABs and EMA, the impact of strengthened cooperation on early dialogue could be to reduce the variation across HTABs. However, as shown in Figure 7, the disagreement between HTABs is less than between HTABs and regulatory (for most domains – although not for population). It remains the case that if there were only one assessment of REA we might expect more convergence with the regulatory requirements.

74 The data in Figure 5 and 6 are not entirely consistent. They come from different studies comparing different samples of medicines.

75 Moseley J, ""How can a joint regulatory-HTA-scientific advice process (both pre- and post-launch) help deliver the right evidence?" Presented on 7th April 2016

76 Tafuri et al. (2016), "How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory–HTA parallel scientific advice", *Br J Clin Pharmacol*, 82 965–973.

Figure 7: Level of agreement among Health Technology Assessment bodies (HTABs) for each domain[77]



Source: Tafuri et al.

The process allows guidance on the data that will be valuable, which could make the outcome of the assessment more predictable. To illustrate this point, Tafuri et al.[78] considered the discussion of a primary endpoint, within a different procedure. In such cases, both the regulators and HTABs agreed that the proposed surrogate endpoint was acceptable overall, but some of the HTAB representatives indicated a need to show correlation of the surrogate endpoint with clinical outcomes and quality of life. In this case, the value of early dialogue was clear, as during the discussion meeting, the applicant proposed a new composite key secondary endpoint in support of the primary endpoint, as a means to accommodate patient heterogeneity and quality of life, and this was considered acceptable by HTABs. It is unclear, however, if this was subsequently developed and used in the way the early dialogue suggested (and whether the HTAB involved used the data as suggested in its assessment). Guidance from early dialogues is not binding.

However, based on our interviews, the process represents the opportunity for companies to receive a clear 'red light' message on certain aspects of medicine development. Therefore, this exercise can increase predictability and guide applicants to invest resources in viable developments from both a regulatory and a reimbursement perspective, to provide the required evidence to support regulatory and reimbursement decision-making, and to have a timely access to the market in the interest of patients.

The analysis shows that early dialogue with HTABs is valuable in terms of predictability. If strengthened cooperation delivers a sustainable system incorporating views beyond 3-4 HTABs this will be beneficial (even though HTAB views are not as fragmented as might

77 Tafuri et al. (2016), "How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory–HTA parallel scientific advice", *Br J Clin Pharmacol*, 82 965–973.

78 Tafuri et al. (2016), "How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory–HTA parallel scientific advice", *Br J Clin Pharmacol*, 82 965–973.

previously have been considered).[79] Even more importantly, strengthened cooperation can increase alignment between the EMA and the HTABs.

Cooperation on EU REA

EU REA also will mean a single presentation of the evidence and assessment of the relative efficacy information. This could in principle reduce the variation in the subsequent national appraisal of therapeutic value (i.e. this might be observable in terms of to reduced variation in the Added Therapeutic Value (ATV) scores across countries that use ATVs), which could reduce variation in the decision-making about the reimbursement of the medicine.

Based on the interviews, there are reasons to doubt this would often be the case:

- Agencies considering the same data within a country can come to different conclusions; for example, the GBA and IQWiG sometimes come to a different conclusion about the added therapeutic value (ATV) (a study found that in 23% of the cases the GBA decisions were overall more positive than the IQWiG recommendations).[80]
- Even if use of EU REA is mandatory, there will be some opportunity to allow for national differences; this provides an opportunity to appraise medicines differently (although less so than before).
- The appraisal, according to the industry interviews, takes into account broader issues associated to the healthcare system, and this influences the appraisal. A more scientific assessment may reduce but not entirely mitigate this.

Considering countries that have a process which results in an ATV. A single European assessment could also lead to an increase or decrease in average ATV. It was reported in the interviews that this will depend on the evidence requirements in EU REA and is impossible to predict. Based on previous EU Joint Actions, there is no evidence it will improve or reduce the average assessment of value. Alternatively, it could change the distribution of the ATV for particular types of product we observe across countries. It could lead to a more uniform appraisal of any given product (even if the average appraisal of therapeutic value across products stayed the same). In other words, we could see more uniformity in whether a product is judged to be highly value or less highly valuable (this could occur, for example, if EU REA is more flexible in accepting different forms of evidence or agreeing particular methodologies for comparison or types of outcome).

Drawing on the experience of JA 2, there is an argument that it favours more differentiated products over less differentiated products:

- The experience of JA2 was that the assessment allowed indirect comparisons, took into account different types of evidence, and was receptive to different types of

79 Osipenko L (2013), "Early engagement between manufacturers, HTA assessors, and regulators: learning from the past to guide the future". London, UK. Delivered at ISPOR 16th Annual European Congress, 2-6 November 2013.

80 Ruof J, Schwartz FW, Schulenburg JM, Dintsios CM (2014), "Early benefit assessment (EBA) in Germany: analysing decisions 18 months after introducing the new AMNOG legislation", *European Journal of Health Economics* 15(6): 577-589.

outcomes (surrogate endpoints).[81] This might be more valuable for more differentiated products.

- Where products were in competing classes, the number of comparisons and the requirements on evidence generation were seen as problematic.

If we extrapolate from this experience, EU REA could provide a favourable outcome for the assessment of differentiated products but less favourable outcome to the assessments of less differentiated products.[82] This would not have an industry-wide impact but affect individual companies depending on the product portfolio. From a societal perspective, this could be beneficial, focusing resources where they can be best used and increasing rewards for innovation. However, it should be noted that while some companies considered that strengthened cooperation could impact the appraisals, others see EU REA as only an input into the appraisal with limited impact.

We conclude that given the link between the HTA and the reimbursement decision is complex and the reimbursement decision takes into account the value for money of the medicine and the budget impact, it is very unlikely that adoption of EU REA in itself would increase the number of products being reimbursed or have a significant impact on prices. It is ultimately the reimbursement decision that affects the investment decisions. This will not be affected by strengthened cooperation on REA. However, it seems reasonable to conclude that although this will not remove variation in subsequent appraisal (and the impact on reimbursement decision) across countries it could reduce it, and this could lead to greater convergence for particular products (both in terms of added value and in terms of those assessed as offering less significant benefit).

EU REA could also help to increase transparency and, consequently, predictability of national timelines. As it has been reported, the timeline for national assessment is not formally defined in some countries; participation of these countries to EU REAs (and adoption of the EU REA timeline) would therefore contribute to increasing predictability.

Cooperation on full HTA

Turning to cooperation on full HTA, the same argument applies as for consistency. The inclusion of economic considerations would negate the benefits resulting from cooperation on REA as Member States may prefer to preserve autonomy in the assessment of economic domains and may find ways to conduct an additional full HTA at national level, potentially decreasing the predictability of the outcomes (as, in this case, the process to overcome the joint full HTA may be less transparent).

Summary

In terms of predictability, although common tools and templates can lead to some greater consistency in the evidence reviewed and in terms of the methodology applied, the outcome of the assessment depends critically on the process of evidence assessment and the methodological choices. Therefore, the impact of common tools on the predictability of the resulting assessment is small. Turning to the value of early dialogue, based on our interviews, the process represents an opportunity for companies to receive a clear 'red light'

81 Although there were concerns about the applicability of some of these approaches to safety comparisons.

82 The experience of JA3 with many more planned assessment will provide a greater insight into this issue.

message on certain aspects of medicine development. Therefore, this exercise can increase predictability and guide applicants to invest resources in viable developments from both a regulatory and a reimbursement perspective, to provide the required evidence to support regulatory and reimbursement decision-making, and to have a timely access to the market in the interest of patients, so there is a modest benefit from early dialogue. In terms of strengthened cooperation on REA, we need to take into account that the assessment is only an input into the appraisal and any resulting decision on reimbursement, this would only improve predictability to a degree but would still be valued by industry and by patients. We do find that cooperation on full HTA is unlikely to improve predictability, for the same reasons that it is unlikely to improve consistency.

Table 10: Summary of degree to which different outputs of cooperation would deliver a societal benefit – predictability

EU Output	Predictability
Common tools and templates	+
Early dialogue	++
Joint REA	++
Joint full HTA	-

Source: CRA analysis. Key: + positive societal impact, - negative societal impact, O no impact

3.3. Improved governance and processes improving quality of assessment

The third area where increased HTA cooperation could lead to significant benefits is the governance of the process, specifically the transparency of the process and the role of different stakeholders. The question is whether the increased cooperation will (1) increase transparency, (2) increase the role and the contribution of stakeholders (e.g. patients), and (3) lead to better decisions from a societal perspective.

As evidenced in the literature,[83] patient involvement is an opportunity to provide HTA agencies with information on the experience of living with a condition or receiving existing treatments and the treatment under assessment. The patients can provide information on the value and impact of the treatment from a patient perspective, to help agencies understand unmet needs. In some cases, patient input has made a difference to the HTA process.

83 Scott AM and Wale JL (2017), "Patient advocate perspectives on involvement in HTA: an international snapshot", *Research Involvement and Engagement* 3:2

Stakeholders' involvement also brings more transparency and coherence to the process and introduces the possibility of having consultation on strategic issues, implying better decisions reflecting the perspective of all the stakeholders.[84]

Common tools and templates

Common tools and templates can help improve governance and the quality of the assessment if they stipulate the role of different stakeholders. For instance, the EUnetHTA "evidence submission templates to support production of core HTA information and rapid assessments" consider the consequences of the disease or health condition for the patients and for the society.[85] The templates also set out the requirement to capture health-related quality of life of patients and consider (i.e. it is not mandatory) the collection of evidence on patient satisfaction. If use of common templates implies that these elements of value for patients are also adopted in countries where they are not currently captured, increased cooperation on common tools and templates will result in greater consideration of the patient perspective, more transparency regarding the value of this information, and consequently improved quality of the assessment.

Early dialogue

It is possible that strengthened cooperation in early dialogue improves the overall governance of HTA by improving the involvement of different stakeholders. Although the form of early dialogue under the EC's proposal is not defined, we can draw on the experience of the parallel regulator–HTA advice process. Presentations by patient groups suggest that the experience of patients has been positive in terms of their involvement:[86]

- Patients gain experience of EMA scientific committees, scientific advice, parallel scientific advice and national HTA
- The possibility of attending the meeting as eye witnesses of the process is important in itself
- Engaging patients at all steps of regulatory and HTA processes can only help build trust in the system as patients can see from inside how new technologies are evaluated and how important decisions are being prepared.

In terms of EMA parallel advice, overall patient representatives participated in 40% of the finalised procedures (25 out of 63). Patient representatives were routinely invited from December 2014. There was indeed a steep increase over two years: patient participation rose from 18% in 2014 (2 out of 11 finalised procedures) to almost 60% in 2015 (17 out of

84 BEUC (2012), "BEUC response to the public consultation on stakeholders involvement in HTA". Available at [last access 3 July 2017]: http://www.beuc.eu/publications/2012-00519-01-e.pdf

85 EUnetHTA (2015), "Evidence submission templates to support production of core HTA information and rapid assessments: adaptation notes". Available at [last access 3 July 2017]: http://eunethta.eu/sites/default/files/sites/5026.fedimbo.belgium.be/files/EUnetHTA%20evidence%20submission%20template_adaptation%20notes%20FINAL2.pdf

86 Eurordis (2016), "Feedback from patient organizations". Contribution from François Houÿez. Available at [last access 3 July 2017]: http://www.eurordis.org/sites/default/files/patients-chmp3-francois-houyez.pdf

29 finalised procedures).[87] This was substantiated by interviews with patients groups who encouraged the involvement of patients from the earliest dialogue. (In contrast, early dialogue in some countries such as Germany does not integrate the role of patients.)

Therefore it seems reasonable to conclude that early dialogue improves the representation of patient groups and improves the governance process.

Cooperation on EU REA

EU REA could lead to improving the governance of the EU REA process, specifically the role of different stakeholders, such as patients being involved in the REA process and the industry being able to appeal HTA decisions.

We first look at the question of whether the EU REA process will (1) increase the role of patients, (2) increase the influence of patients in the EU REA process, and (3) lead to better decisions from a societal perspective.

To consider the first issue, there are some countries where patients are not involved in the process. Even where they are involved, there is considerable variation in the extent of involvement. In many markets, patients are involved in the HTA process but argue that they still have little impact in the decision-making process. Therefore EU REA could improve patient involvement in 16 markets which do not have patient involvement today.[88] This would also result in patients being involved earlier in the process. It is clear from the results of a survey conducted by Scott and Wale[89] that HTA agencies reach out to patients either actively or passively, and that their involvement is often at the appraisal stage of HTA (Table 11).

Table 11: The role of patient groups

Country	How does the agency reach out to patient groups?	Stage of HTA at which the patient representative or patient groups are involved?	How are the patient representative or patient groups involved in the HTA?
Scotland (SMC)	• Patient group is registered with the HTA agency	• Appraisal stage	• Provide submission to the agency. Participate in meetings of

87 EMA (2016), "Report of the pilot on parallel regulatory–health technology assessment scientific advice". Available at [last access 3 July 2017]: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/03/WC500203945.pdf

88 According to a survey conducted by the European Federation of Patients in 2012, 18 EU HTA agencies (out of 40 respondents) declared some form of patient involvement. This implies that 22 agencies (55% of the sample) do not involve patients. If we apply this percentage to the number of Member States, it results that about 16 markets do not consider patient involvement in HTA. Source: IPPOSI website [last access 3 July 2017]: http://ipposi.ie/old/index.php/docman/presentations/101-nicola-bedlington-presentation-ipposi-information-day-hta/file

89 Scott AM and Wale JL (2017), "Patient advocate perspectives on involvement in HTA: an international snapshot" *Research Involvement and Engagement* 3:2.

	and notified by the HTA agency		patient groups, clinicians, agency
England and Wales (NICE, AWMSG)	• Patient group is registered with the HTA agency and notified by the HTA agency • At the scoping stage, stakeholders are asked to recommend patients for patients groups. Through disease registry, newsletter or social media	• Scoping stage workshop. Appraisal stage • Appeals of recommendation • Scientific advice stage	• Provide patient experts who participate in workshops or committee meetings • Provide submission to the agency
The Netherlands (ZIN)	• Patient group is registered with the HTA agency. HTA agency reaches out to umbrella groups	• Appraisal stage	• Provide submission to the agency • Provide a statement at public meetings

Source: Scott et al.

According to the interviews with patient associations and industry, patient involvement in scoping of the EU REA would be valuable as this ensures that the assessment of relative efficacy includes evidence to appropriately reflect the value of the product.

Regarding the impact on decision-making (beyond the EU REA process itself), there is relatively little quantitative evidence and no evidence that relates directly the Europe. However, qualitative evidence from patient representatives who participate on HTA committees is supportive of the conclusion that patients have an impact. It is reported that they were able to "discuss specific funding decisions; for example, a decision to fund a medicine due to information on improvement in quality of life, and identification of subgroups that were particularly negatively impacted by the disease". In addition, patient involvement can help "contextualising the quality of life data from trials, illustrating unmet need, clarifying the impact on daily life of the disease or health technology, helping to educate HTA personnel about the disease or its treatment, and helping to create a fuller evidentiary picture by adding to industry and clinician evidence".[90]

Hence, if EU REA allowed for consistent patient representation (which it did not do in JA2), this would deliver benefits in patients' involvement providing greater clarity on the choice of

90 Scott AM and Wale JL (2017), "Patient advocate perspectives on involvement in HTA: an international snapshot" *Research Involvement and Engagement* 3:2.

outcomes and the role of Patient Reported Outcomes (PROs) and in terms of the consistent interpretation of this evidence.

Cooperation on full HTA

Cooperation on full HTA would have a mixed impact on governance. In terms of the full HTA this could increase transparency and the role of different stakeholders. However, in particular, Member States may prefer to preserve autonomy in the assessment of economic domains and may find ways to conduct additional analysis at national level (if this occurs in an informal negotiation this could be without the input from different stakeholders), undermining the potential benefits delivered by common tools, early dialogue and joint REA.

Summary

The use of common templates implies that elements of value for patients are also adopted in countries where they are not currently captured. Early dialogue would bring benefits in countries without an early dialogue process (21 countries) and in the seven countries with a process but with little patient involvement today. In terms of cooperation on REA, this again would increase patient involvement in the assessment, and the limited evidence that exists suggests that incorporating patient views is helping to deliver evidence that satisfies HTA processes, to the benefit of patients and society, in about 16 markets. In terms of cooperation on full HTA, our findings are that it would, on the face of it, increase transparency regarding the process, but in reality the countries will still want to undertake their own economic assessment, potentially by introducing this assessment into an informal negotiating process, reducing transparency overall.

Table 12: Summary of degree to which different outputs of cooperation would deliver a societal benefit – governance

EU Output	Governance
Common tools and templates	+
Early dialogue	+
Joint REA	++
Joint full HTA	-

Source: CRA analysis. Key: + positive societal impact, - negative societal impact, O no impact

3.4. Faster decision-making process at national level

As shown in the literature, time to access is very variable across EU countries. The difference in the delay is composed of a number of components (the application process, the REA, the appraisal and decision to reimburse) and we can observe significant differences between European countries as illustrated by the EFPIA Patient W.A.I.T. indicator.

Table 13: Market access delays from marketing authorisation across the EU[91]

Country	Average delay in days (2016)
Bulgaria	686
Czech Republic	503
England*	138
France	467
Germany	110
Italy	370
Latvia	558
Netherlands	207
Norway	172
Poland	338
Romania	n/a
Slovakia	366
Spain	390
Sweden	292
***Note: data for the UK**	

Source: EFPIA Patient W.A.I.T. 2016

Each of the different outputs could accelerate market access.

Common tools and templates

The adoption of common tools and templates is likely to have a limited impact on the speed of market access. Although this output can increase consistency and predictability and improve governance, Member States would still be fully responsible for national HTA timelines.

Early dialogue

In principle, early dialogue between companies and HTABs could lead to a better understanding of the evidence requirements, making the assessment and appraisal simpler with fewer requests for additional information and additional evidence resulting in faster

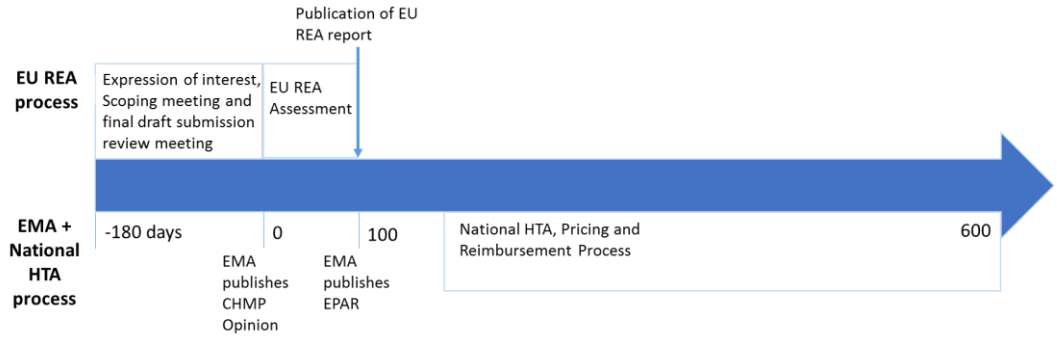
91 EFPIA (2016), Patient W.A.I.T. 2016, Internal document

decision-making and faster market access. We have found no evidence for this being the case nor support for this in the interview programme. We therefore conclude that early dialogue would not lead to a substantially faster decision-making process.

Cooperation on REA

The REA process, as part of the full HTA process, is clearly a component of the delay between the marketing authorisation and the price and reimbursement decision. If strengthened cooperation on REA were to be implemented, this would establish a clear time duration for the REA process (Figure 8).

Figure 8: EU REA, pricing and reimbursement process timeline



Source: CRA analysis

As already noted in another report for EFPIA,[92] it is possible to distinguish three different situations across countries regarding the potential for adoption of EU REAs:

1. Countries where the national HTA process ends before the EU REA report is expected. Waiting for the publication of the final EU REA report would delay the national process for the majority of products, even though some specific product sub-categories follow different, compatible, timelines (for instance, England, Italy and the Netherlands belong to this category). There are not time savings for this category but it is possible that this could deliver benefits if national submissions and submission to the EU process could be aligned.
2. Countries where the EU REA report is published before the completion of the national HTA process.
    - For national HTA processes where only REA is undertaken, or REA and CEA are sequential, EU REAs can clearly substitute for the national REA process and any localisation can occur following EU REA (France, Germany,[93] Spain)
    - For processes where REA and CEA are undertaken simultaneously, the timelines are more of a problem (as waiting for the EU REA could delay the

92 CRA (2016), "EU REA – A discussion of barriers for adoption and possible actions to overcome them". Available at [last access 3 July 2017]: http://www.efpia.eu/uploads/Modules/Documents/cra-efpia---eu-rea-adoption-at-national-level.pdf

93 Given the market access process in Germany (access is possible from marketing authorisation, and REA is conducted while the product is already on the market), EU REA would not accelerate market access. However, it would still accelerate the final price and reimbursement decision.

CEA). In this case, it is possible for the data to be consistent with the EU REA (which brings benefits to the companies, as it would increase internal consistency and reduce internal duplication) but it is less clear how this substitutes for the assessment process (Norway and Sweden are in this category).

3. Countries where the HTA process starts considerably after the publication of EU REA (one year or more) according to the schedule (this is the case for Poland). As noted in the interviews with national trade associations, CEE countries (Bulgaria, Czech Republic, Slovakia) typically belong to this category.

It was noted in the interviews, that independent of the theoretical timelines, EU REAs can be particularly helpful in countries where there are not enough resources / expertise to conduct national HTA (for instance in Croatia or the Czech Republic).

At this stage (i.e. before EU REA has been implemented) it is difficult to estimate to what extent EU REA can accelerate the HTA process in these countries. Therefore we have based our analysis on the current EUnetHTA timelines and views expressed in the interviews and an analysis of the current timelines:

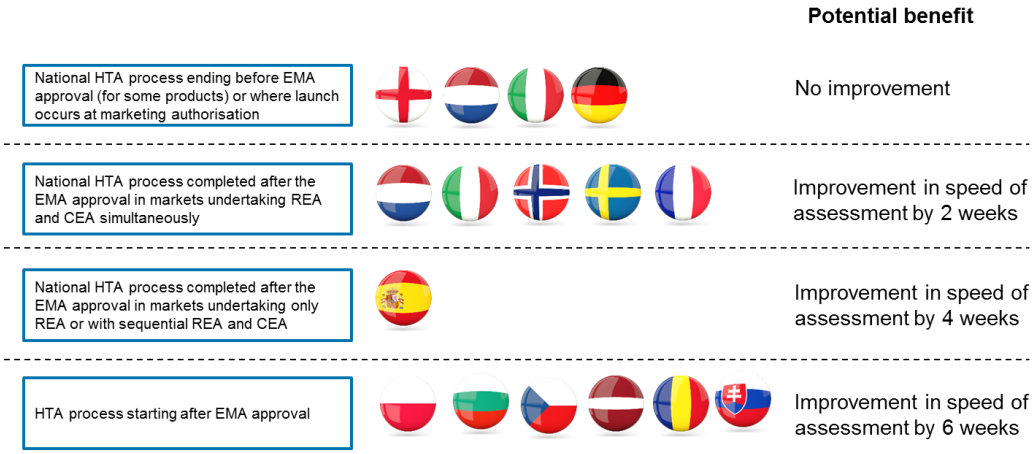
- For countries in the first category, the potential benefits in terms of speed of access is very limited[94]
- For countries in the second category, according to interviewees and comparing existing timelines, it would be reasonable to assume that the national process could be accelerated by two weeks in markets conducting REA and CEA simultaneously, and by four weeks in markets conducting REA and CEA sequentially (or conducting only REA)[95]
- For countries in the third category, it has proven particularly difficult to assess the potential gain but we have assumed six weeks is a reasonable estimate (according to interviewees).

Therefore, countries and the potential benefits can be grouped as in Figure 9.

94 Although the HTA process in Germany starts after the marketing authorisation, Germany would fall into this category because it is possible to launch a medicine before the HTA process is conducted.

95 Where the REA and CEA are sequential (or if a market only undertakes REA), the total time saved because of the implementation of EU REA is independent of the CEA process. The faster EU REA process will mean the CEA process can start earlier and we can assume it will also finish earlier. We assume this would accelerate the process by 4 weeks. When REA and CEA are simultaneous, the potential time savings resulting from a faster EU REA might not lead to the same direct time savings. This depends on how a faster REA process helps to accelerate the CEA timeline. We assume this would accelerate the process by 2 weeks.

Figure 9: Potential reduction in HTA length by country[96]



Source: CRA analysis

There are two main caveats to these assumptions. First, even if EU REA can accelerate the HTA process, countries might delay the reimbursement decision for financial reasons. Second, manufacturers might also consider delaying launch in some countries for commercial reasons (e.g. to avoid negative consequences of international reference pricing, IRP). However, there was consensus across stakeholders (including industry and patient groups) that *some* of the potential benefits in terms of faster access can also be passed to patients.

Patient associations also believe that the adoption of EU REA has the potential to accelerate access to medicines in Europe, especially in CEE countries. Patients' associations agree that EU REA can both replace part of the national process and also imply an earlier start of the HTA process in markets where HTA begins later than the marketing approval (although patient groups found it difficult to estimate this impact). Clinical groups also agree on this, in addition, they report that EU REA may have the potential to accelerate the production of national clinical guidelines (which ultimately affect the uptake of medicines) for some therapy areas and to bring more equality in access across Europe (i.e. implying some convergence in the speed of access to innovative medicines).

Therefore there are benefits in terms of faster patient access. It should be noted that this analysis is based on the timeline as currently envisaged; if it were possible to accelerate the publication of the EU REA to CHMP, these benefits would be larger.

Cooperation on full HTA

Cooperation on full HTA would have no impact on speed of market access. In particular, joint full HTA would require a longer timeline for production of the final output than the current timeline in most Member States. In this case, we have assumed that Member States would not use full HTA as it would slow down access. Even when the timeline of joint full

96 Italy and the Netherlands have reported two different timelines for different types of products (and therefore appear twice on the table).

HTA is compatible with the national one, Member States are likely to prefer preserving autonomy in the assessment of economic domains and may find ways to conduct an additional full HTA at national level. This, again, would imply that joint full HTA would have no positive impact in terms of speed of access.

Summary

We do not find any evidence that common tools or templates or early dialogue lead to a faster decision-making process. Based on our interviews we conclude that EU REA could lead to faster patient access. We do not find that full HTA would bring any benefits because the process will delay the communication on the REA with the result this will have a significantly diminished impact and the national process will adapt to ensure a national value assessment is undertaken.

Table 14: Summary of degree to which different outputs of cooperation would deliver a societal benefit – speed of market access

EU Output	Speed of market access
Common tools and templates	0
Early dialogue	0
Joint REA	0/+
Joint full HTA	0

Source: CRA analysis. Key: + positive societal impact, - negative societal impact, O no impact

3.5. Summary

The benefits delivered by the four types of EU output are summarised in Table 15. It is clear that benefits progressively increase from 1 to 3, Joint REA delivers the largest societal benefits and joint full HTA offers few benefits.

Table 15: Summary on degree to which different outputs of cooperation would deliver societal benefits

EU Output	Consistency	Predictability	Governance	Market access
Common tools and templates	+	+	+	0
Early dialogue	++	++	+	0
Joint REA	++	++	++	0/+

Joint full HTA	-	-	-	0

Source: CRA analysis. Key: + positive societal impact, - negative societal impact

4. Implications for the EC proposals

In the previous chapter we set out the potential benefits for strengthened cooperation of different forms. In this chapter we consider the implications for the five options set out by the European Commission. We first briefly discuss these different options.

4.1. The options in the roadmap and the survey instruments

The EC set out in the Inception Impact Assessment five possible options. These options, illustrated in Table 16: cover four elements: common tools and procedures (including: common submission templates, an IT system with planned and ongoing assessments, common methodologies,[97] a joint prioritisation process, and cooperation on data requirements, including Horizon Scanning); joint early dialogue for HTA, joint REA; and joint full HTA (including cost-effectiveness).

Table 16: The five options in the EC Inception Impact Assessment

Key characteristics	Option 1 The status quo – voluntary cooperation on HTA (until 2020)	Option 2 Long term voluntary cooperation on HTA (beyond 2020)	Option 3 Cooperation on collection, sharing and use of common tools and data	Option 4 Cooperation on the production of joint REA reports	Option 5 Cooperation on the production of joint full HTA reports
Regulatory	Non-legislative	Non-legislative	Legislative	Legislative	Legislative
Participation of HTA bodies and industry	Voluntary	Voluntary	Compulsory (tools) Voluntary (HTA)	Compulsory (tools) Voluntary / compulsory (HTA)	Compulsory (tools) Voluntary / compulsory (HTA)
Uptake joint output	Voluntary	Voluntary	Compulsory for tools	Compulsory for tools and REA	Compulsory
Financing	Largely depending on EU budget Ending 2020	Largely depending on EU budget Long-term	Mixed funding model (EU budget + MS + Industry contribution) Long-term	Mixed funding model (EU budget + MS + Industry contribution) Long-term	Mixed funding model (EU budget + MS + Industry contribution) Long-term
Main joint output					
A. Common tools/templates	(✓)	(✓)	✓	✓	✓
B. Joint REA	(✓)	(✓)	(✓)	✓	✓
C. Joint full HTA	(✓)	(✓)	(✓)	(✓)	✓
D. Early dialogue	(✓)	(✓)	✓	✓	✓

Source: European Commission (2016), "Study on impact analysis of policy options for strengthened EU cooperation on HTA" where a tick means complete delivery and tick in brackets means partial delivery

In addition, the options set out whether the application would be voluntary or mandatory and whether it would be implemented through a legislative mechanism and which of the following organisational mechanism it includes different organisational mechanisms: project-based cooperation (the secretariat is set up by the Member States that participate); EU/MS secretariat (a permanent secretariat is established); existing EU agency (a permanent secretariat is integrated in an already existing EU agency); new EU agency (a

97 In addition to developing methodologies and tools, joint work would also include literature reviews, structured information for HTA and scientific advice on R&D planning and study design.

permanent secretariat is integrated in a new EU agency). For financing the joint cooperation, several funding mechanisms are conceivable: EU funding; funding by Member States joining the collaboration; funding through industry fees or a mix.

This was subsequently updated in the survey instrument used by the Austrian Public Health Institute, reported in Table 17: below.

Table 17: The five European Commission proposals as presented in the survey[98]

		Baseline	Non-legislative	Legislative			
		PO1	PO2	PO3	PO4		PO5
		No EU action after 2020	Voluntary cooperation through Public Health Programme	Legislation covering common tools and early dialogues	Legislation covering Joint work on REA Plus common tools and early dialogues		Legislation covering Joint work on Full HTA (incl. REA) Plus common tools and early dialogues
					4.1 REA V/M	4.2 REA M/M	
Outputs	Common tools, incl. templates, methodology	V/V	V/M	M/M	M/M	M/M	M/M
	Early dialogue	V/V	V/M	V/M	V/M	M/M	M/M
	Joint REA	V/V	V/M	V/V	V/M	M/M	M/M
	Joint Full HTA	V/V	V/V	V/V	V/V	V/V	V/M

Key:
V/V: Voluntary participation/voluntary uptake
V/M: Voluntary participation/mandatory uptake
M/M: Mandatory participation/mandatory uptake
Legislative framework required

Source: Questionnaire provided by Gesundheit Österreich Forschungs- und Planungs GmbH (GÖ FP), London School of Economics (LSE Health) and SOGETI

In terms of the outputs considered in this report, there is some mapping between the options and the outputs: we could associate early dialogue to option 3, cooperation on joint REA to option 4 and cooperation on joint full HTA to option 5.

However, there are some significant differences between the options in the Inception Impact Assessment and the survey:

- In option 2 of the survey instrument, the use of common tools, early dialogue and EU REA are voluntary in terms of participation but mandatory in terms of uptake (different to JA2). So as part of the contract it would be required that participating HTABs use the assessments. However, in practice there are significant doubts as whether this would be effective, in particular, it is unclear how participation would be enforced in such a contract. This was voluntary under the EC Impact Assessment (similar to JA2, which was also found to have limited impact on participation).

98 The EC's Inception Impact Assessment summarises the five options in a different graphical way, with fewer details (the EC's version is available at [last access 3 July 2017]: http://ec.europa.eu/smart-regulation/roadmaps/docs/2016_sante_144_health_technology_assessments_en.pdf). This table, from the questionnaire, is the most recent update to the version in the Inception Impact Assessment; it is consistent with the earlier version and articulates more detail on some of the concepts.

- In option 3 of the survey, early dialogue is defined as voluntary/mandatory, this means if a country participates it is mandatory to use them in the survey but not specified in the Inception Impact Assessment.
- In option 5 of the survey, EU REA is mandatory for all countries, but this is unclear in the Inception Impact Assessment.

The uptake of tools is clearly vitally important in terms of the benefits they will deliver. The experience of JA2 shows the difficulty with a voluntary based contractual system. Therefore, the application of our results to the options clearly depends on which assumptions we are making and whether we are using the original options or the updated ones set out in the survey or a combination of both.

However, it is possible to combine the assumptions in the two table as suggested in Table 18. If we do this it is easier to map our analysis to the revised options. Our analysis suggests the societal impact will be greatest where participation in early dialogue and EU REA will be delivered (revised option 3 and revised option 4 but will be lowest in revised option 5).

Table 18: Combining the options in the Inception Impact Assessment and the Survey Instrument

	Revised Option 1	Revised Option 2	Revised Option 3	Revised Option 4.1	Revised Option 4.2	Revised Option 5
Output	Any possible	Any possible, probably focus on Tools	Tools + ED	REA (based on Tools+ED)	REA (based on Tools+ED)	HTA (based on Tools+ED+REA)
Participation / Uptake	V / V	V / V	V / M	V / M	M / M	M / M
Form of collaboration	Contract between MS	EU Contract	Legislative	Legislative	Legislative	Legislative
Funding	MS funding (EU funding ends 2020)	EU funding	Mixed	Mixed	Mixed	Mixed
Secretariat	MS	Project based / MS	EU / MS Secretariat	Existing EU agency	Existing EU agency	New EU agency

Source: EFPIA

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