Attitudes, perceived impacts and motivational factors for European Member State collaboration for pricing and reimbursement of medicines: a review of the evidence

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Abstract

Initiatives for European Member State collaboration in the area of pricing and reimbursement of medicines started in recent years. In view of the perceived benefits from collaboration and the challenges being experienced with current initiatives, it was necessary to study the attitudes, perceived impacts and the motivational factors concerned. The researcher is a practitioner in this area.

The methodology for evidence–based management set by Barends and Rousseau (2018), was found to be systematic, enabled balance of the evidence, filled gaps and addressed biases.

Voluntary co-operation was generally favoured for all activities of pricing and reimbursement except for relative effectiveness assessment (REA), where Member State authorities had divergent attitudes while industry adamantly favoured mandatory cooperation. While Member State authorities prioritised impacts related to sustainability of healthcare systems and access to medicines, industry supported economic impacts. Member States' motivation for collaboration was highly dependent on purpose, political will, implementation climate and cultural factors.

The findings of the study were applied to the two decisions already taken. The Proposal for a Regulation on HTA was based on evidence which did not reflect the evidence obtained from this study. The vote at Council is still to be taken. Hopefully Member States realise the risks from this legislation. Regional collaborations are encountering difficulties and need to take bold steps such as transparency of prices and forcing industry participation in joint negotiation.

The evidence can be used for future decisions on collaboration. This case study can inform the use of evidence-based management methodology for health policy and regulation.

Key words: evidence-based management; Europe; Member State collaboration; pricing and reimbursement of medicines; attitudes, perceived impacts, motivational factors.

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I appreciate the support from colleagues from the various entities and national authorities who are contributing towards European Member State collaboration and who gave me moral support as well as helped me to access the grey literature. I hope that my work will be of use to them in their efforts to achieve maximum effectiveness from their initiatives.

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1. Introduction

1.1 Introduction

In the last twenty years there were a number of initiatives for European Member State (MS) collaboration in the area of pricing and reimbursement. Up to now these were driven by the MSs and were voluntary. Unfortunately, these initiatives were sporadic and there was lack of coordination between them. In 2018 the European Commission came up with a legislative proposal which introduced the concepts of mandatory participation and mandatory uptake of the products of collaboration in the area of health technology assessment. This introduced a paradigm shift from the voluntary approach.

The developments and progress of collaboration depend first and foremost on the MSs, which are the main actors. MSs have different attitudes regarding collaboration and these may vary for the various activities concerned. MSs perceive the impacts (benefits and risks) from collaboration differently. There are various positive and negative motivators (barriers and facilitators) for collaboration and these challenge / facilitate progress. Although this project focused on collaboration between MSs, this could not be isolated from the various stakeholders participant in the system, who are very influential. The stakeholders also have different perspectives and interests in MS collaboration.

MS collaboration in the area of pricing and reimbursement is a paradigm shift in the pharmaceutical framework and is expected by MSs to support improved sustainability of healthcare systems and access to medicines for their citizens. The aim of this research was to provide evidence to inform decision making for current and future initiatives for MS collaboration for pricing and reimbursement of medicines.

1.2 Member State collaboration for pricing and reimbursement – current state and challenges

The system of pricing and reimbursement involves various activities, such as horizon scanning, coordination of patient registers, health technology assessment (HTA), economic evaluation, national pricing of medicines, reimbursement decisions, pricing decisions, negotiation of prices and of conditions, procurement and medicines use. There were some initiatives to increase collaboration between MS pricing and reimbursement authorities; these were voluntary and were not systematic (World Health Organisation [WHO] 2015).

One of the main motivators for governments to pursue initiatives for MS collaboration within the system for pricing and reimbursement is their need to address challenges with the sustainability of their healthcare systems, and their motivation to address the problem of lack of access and affordability to new medicines to cater for the medical needs of their population. Access to affordable medicines is one of the objectives of universal health coverage and of the WHO sustainable development goals. All governments within the European Union, including those of high-income countries, are experiencing increasing difficulty to provide sustainable access to medicines. Specific circumstances such as the differences in price and in availability of treatment for hepatitis C across Europe and the introduction of new advanced therapies at very high and unaffordable prices have increased governments' concerns on universal coverage and have instigated a number of initiatives by governments and by public authorities for pharmaceutical pricing and reimbursement. These initiatives have included innovative models for the management of entry of new medicines, horizon scanning, financing of innovative medicines, strategies to improve prescribing and medicines use, and initiatives for regional collaboration between MSs (WHO 2015; Godman et al. 2018; Vogler et al. 2018).

Council Conclusions of different 'Presidencies of the Council of the European Union' supported exclusively MS driven voluntary cooperation on health technology assessment (HTA). The

Conclusions advocate for collaboration between groups of MSs and encourage the sharing of HTA methodologies and outcomes of assessments. They stress on voluntary collaboration for improvement of access to medicines (Council of the European Union 2016; Council of the European Union 2017).

The European Commission has been trying to achieve coordination, and there were several initiatives to this effect such as the 'Competitiveness Round Table', the G10 Group and the Pharmaceutical Forum. In 2002 the G10 Group set seven recommendations, with the main objective of having governments coordinate together by means of intervention through 'soft law' mechanisms such as guidelines and benchmarks which enable assessment of the effectiveness of national systems with respect to market access. Each national health system needs to achieve a balance between industrial and health policy objectives (Hancher 2004). Pricing and reimbursement authorities of most MSs have collaborated on a voluntary basis within the 'European Network for Health Technology Assessment' (EUnetHTA). This is a network of governmental organisations, a number of regional agencies and non-profit organisations which collaborate on HTA. EUnetHTA has achieved a number of joint outputs particularly tools, guidelines and methodologies for HTA and has formed a number of Joint Actions (JA) to support research, communication and work between the collaborators (EUnetHTA 2018). However, EUnetHTA experienced difficulties including: a number of MSs did not use the joint assessments for national decision making, MSs implemented different national HTA models, technical expertise and capacity for HTA differed between MSs, MSs wanted to retain their national method for HTA and the model of EUnetHTA was considered to be economically unsustainable (European Commission 2016). The funding for EUnetHTA has been provided by the European Commission, mainly through Joint Actions. The current Joint Action (the third) finishes in 2020.

In 2016 the European Commission started studying alternative long-term solutions for MS collaboration for HTA and an impact analysis was commissioned: 'Study on impact analysis of

Policy Options for strengthened EU cooperation on health technology assessment (HTA). Final Report' (European Union 2017), henceforth referred to as 'the Study'. This considered five Policy Options (PO), which were set by the European Commission, at three levels of governance: base-line (no EU action); voluntary cooperation without legislation and cooperation covered by EU legislation (mandatory) (refer to Table 1.1).

Table 1.1 The five Policy Options (PO) and respective level of governance considered in the 'Study on impact analysis of Policy Options for strengthened EU cooperation on health technology assessment (HTA). Final Report'

Level of governance	Policy Options	Description
Baseline	PO1	After 2020 (when the JA finishes) there will be no action by the EU
Non-legislative	PO2	Voluntary collaboration (funded by the public health programme)
Legislative	PO3	Legislation for common tools, early dialogues.
	PO4	Legislation for joint REA, common tools, early dialogues
	PO5	Legislation for full HTA (including REA), common tools, early dialogues

REA: Relative Effectiveness Assessment

Following the publication of 'the Study', the European Commission chose the option of legislation for joint relative effectiveness analysis (REA) through a Regulation, which mainly adopted PO4. A 'Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU' (European Commission 2018a), henceforth referred to as the Proposal for a Regulation on HTA, was published by the EC on 31st of January 2018, together with a 'Commission Staff Working Document Impact Assessment' (European Commission 2018b). To enter into force, the Proposal for a Regulation

on HTA will need to be adopted by the Council of the European Union and the European Parliament. In October 2018 the European Parliament adopted amendments to the Proposal and was ready to start inter-institutional negotiations with the Council (Council of the European Union 2018). The Proposal only covers REA and does not regulate any other activities for pricing and reimbursement (Ampelas & Schmitz 2019). The Proposal is currently (end August 2019) still being discussed at Council. If approved through Council and Parliament, this legislative proposal will set a regulatory framework (a Regulation with no room for manoeuvre) for MS collaboration for REA.

More recently initiatives for the development of 'regional co-operations' within groups of MSs have started (e.g. Valletta Declaration, BeNeLuxAIr, FINOSE and Fair Pricing Initiative). These are voluntary and collaborate on different activities according to priorities (Espin et al. 2016).

Although there is a concerted motivation for MS cooperation (the Council Conclusions were approved by all MSs) and there are a number of ongoing and proposed initiatives for collaboration between MSs within the system for pricing and reimbursement, experience has shown that in practice collaboration for activities of pricing and reimbursement is difficult, challenging and slow. There is lack of evidence on positive outcomes from collaboration and tangible impact on access to medicines has not been proven yet.

To date initiatives for collaboration between MSs have not been coordinated and were ad hoc. In spite of all the motivation and support, there are various interests and conflicts of interest between stakeholders, and progress has been slow. Other stakeholders of the pharmaceutical framework will be affected by MS collaboration directly or indirectly, and these support or hurdle the initiatives according to their perspectives and priorities. The collaborations exist in the context of a real-life European environment which is continuously in flux and is currently in turmoil and this can have significant and sudden impact on the initiatives for collaboration.

Internal and external stakeholders have different attitudes, perceptions of impacts (benefits and challenges) and motivators (positive or negative) for MS collaboration for pricing and reimbursement of medicines. Knowledge of these will shed an insight into the feasibility and effectiveness of collaboration and will support inferences to make recommendations for collaborative initiatives.

1.3 Significance of this research

The area of new medicines is very significant for MSs because it highly affects the sustainability of healthcare systems. Access and affordability of new medicines are a challenge for all MSs, to different levels. A number of MSs consider that by collaborating together they can benefit from increasing access to new medicines: by a stronger stakeholder position within the pharmaceutical policy framework and through augmented negotiation power, particularly with the industry.

The topic of collaboration is complex and there are many interests from different stakeholders. In practice collaboration is not easy and the balance between benefits and risks fluctuates for different activities and for different stakeholder perspectives. Collaboration involves a lot of effort and resources. The national authorities for pricing and reimbursement already have limited resources to do their routine work and this will be over and above that. It is important to maximise the efficiency and effectiveness of systems.

1.4 The PICOC for the study

The PICOC (Population, Intervention, Comparison, Outcome and Context) is a tool which supports the conceptualisation and the scope of a project (Barends & Rousseau 2018). The

PICOC for this project is presented in Table 1.2. The main population of the study are the MS governments and the authorities for pricing and reimbursement. There are other populations affected directly such as the industry, patients and health care professionals. The intervention under study is the introduction of formal collaborative initiatives between MS authorities.

Table 1.2 The PICOC for this study

P	Population	MS governments, National MS authorities for pricing and reimbursement, payers and health insurances, patients who require new medicines, health care professionals and the pharmaceutical industry.
I	Intervention	Different initiatives for collaboration between MS authorities for pricing and reimbursement and between other national bodies/players involved in activities for pricing and reimbursement.
C	Comparison	Comparison between the scenario where national authorities and bodies for pricing and reimbursement function separately, each in its own jurisdiction, and the other scenario where they collaborate together. Also comparison of attitudes for different models for collaboration.
O	Outcome	To get evidence on the attitudes, perceived benefits and motivators for MS collaboration for pricing and reimbursement of medicines using different sources of evidence. To make inferences for collaboration between MSs to improve effectiveness of collaboration. Sustainability of healthcare systems and challenges with access to medicines are a problem for all MSs, to different extents.
C	Context	National competent authorities for pricing and reimbursement and other bodies are involved in these activities in the different MSs. MSs have national systems which are at various levels of development and have different resources, expertise and processes. MSs have conflicting views on collaboration. There are a number of external stakeholders, such as the pharmaceutical industry, which can be impacted by MS collaboration; these are powerful and may exert influence. The European system is in flux and will change continuously, and possibly dramatically throughout the period of this study (e.g. a new European Commission, a new European Parliament).

The comparison is between the situation where MS authorities act separately on a national level (mainly the current situation) and the alternative scenario with the introduction of established formal collaborative initiatives. The outcome of this study is to get evidence on the attitudes, the perceived impacts (benefits and risks) and motivators (barriers and facilitators) for MS collaboration in order to be able to guide the way forward and have the best available evidence for decision making on collaboration. The context is important because the interventions will be introduced and implemented in a real-world setting which is political and is continuously changing.

1.5 Scope of the study

The researcher did her PhD in the area of pricing and reimbursement of medicines and is a practitioner and a researcher in the field of pharmaceutical policy and management, both nationally as well as on a wider EU level. Since 2017 she was appointed as a member as well as secretary of the Valletta Technical Committee, which is a 'regional cooperation' between ten EU MSs, mainly from the South of Europe. Hence the topic of MS collaboration for pricing and reimbursement activities is significantly relevant to her practice. The researcher has an insight into what is going on with regards to MS collaboration in the area of pricing and reimbursement, and she has mixed opinions and feelings about it.

The researcher is aware that a significant number of management decisions are based on practitioners' expertise and experience and not on the best available evidence. The researcher understands that her direct involvement may increase the risk of bias in her perspective and that her personal judgement may be susceptible to systematic errors such as cognitive biases and information-processing limits (Barends, Rousseau & Briner 2014).

The evidence from this work is useful to inform decisions about ongoing and future initiatives for collaboration. These decisions will need to be taken by politicians, policy makers and practitioners in the MSs and by key stakeholders such as the European Commission, industry, patient organisations etc. These decisions will be affected by external factors such as political and stakeholder pressures and powers. The Proposal for a Regulation on HTA which was proposed by the European Commission will need to be voted upon by the MSs at Council. The activities and outputs from the regional co-operations are dependent on the attitudes and perceptions of key players involved. EUnetHTA Joint Action will finish by 2020 and hopefully the work done to-date will not be lost. The evidence from this work will be useful to inform decisions on these initiatives.

On a much smaller scale, as a practitioner the researcher is in a position and role to guide, support and influence the way that cooperation between MSs will move forward, particularly on a national level and within the Valletta Technical Committee where she is directly involved. On an academic level the researcher often participates and coordinates collaborative research with other professionals mainly in presentation of joint professional opinions. This type of activity can influence practice and decisions at a higher level.

1.6 Summary

Conscious of the fact that her involvement as a practitioner may increase her level of bias and aware of her limited access to evidence; the researcher set to adopt an evidence-based approach to review the evidence available on attitudes, perceived impacts and motivators of the different players and stakeholders with respect to MS collaboration. It was considered that this evidence would strengthen the basis for decision making with respect to MS collaboration, with the objective of supporting current initiatives and future developments.

The study needed to bridge practice with a valid academic approach. The research required the building of a theoretical framework and review of the literature: as a basis for the building of the research questions, to adopt the correct methodology for evidence-based management and to be academically sound. While the researcher was knowledgeable and experienced with evidence-based practice in health through her practice, she had no first-hand experience with evidence-based practice in management. The theoretical framework and the review of the literature were presented in Chapter 2.

2. Theoretical Framework and Supportive Literature

2.1 Introduction

As seen in Chapter 1, the researcher, who was also a practitioner, realised the risk of bias from taking decisions based on limited evidence, personal considerations and experience. In line with the scope of this project a review of the evidence regarding attitudes, perceived impacts and motivators for Member State (MS) collaboration between authorities involved in the pricing and reimbursement of medicines was started, using an evidence-based approach. This project is an academic dissertation and a sound academic approach was adopted with the compilation of a theoretical framework and review of the literature for the areas relevant to the research.

This chapter was presented in the same sequence as the steps of the project. The chapter started with a description of the system of pricing and reimbursement within the pharmaceutical policy framework (Section 2.2) which gave the basis for building of the logic model for the system of pricing and reimbursement. This Section was considered particularly useful for readers who are not conversant with this technical pharmaceutical area. The next step of the research was the planning and implementation of the methodology for evidence-based management for this research. Literature on evidence-based management and the relevant methodology (Section 2.3) was presented. This literature supported the planning and conduct of the method of the research, which was presented in detail in Chapter 3.

It is imperative to highlight that the methodology for evidence-based management involves acquiring evidence about the specific subject under study from different sources, including the scientific literature and empirical studies. This contrasts with conventional study design for academic studies. Thus the scientific literature and the grey literature regarding MS collaboration for pricing and reimbursement were presented as part of the results of this study,

and not in this Chapter. The knowledge on application of evidence for decision making (Section 2.4) was mainly used in the compilation of Chapter 6 on the Application of the Evidence.

Collaboration is a complex and challenging task and there is a vast theoretical framework on collaboration. The concept of collaboration is of particular interest and challenge to the researcher in her current role as a practitioner and this theoretical framework was of significant insight for the researcher. Pricing and reimbursement are mainly regulatory functions. A review of the theoretical framework relevant to collaboration was carried out (Section 2.5) with a focus on organisational theories relevant to the regulatory function and cooperation between MS Regulatory organisations. Models for international cooperation between regulatory organisations were presented (Section 2.5).

The theoretical knowledge on evaluation of attitudes, measurement of perceived impacts and study of motivational factors (Section 2.7) supported the drawing up of the 'Framework' which was used for the collection, appraisal and aggregation of the evidence for the study. This extensive theoretical framework and literature review led to the setting up of the Research Questions to address the scope of the study.

2.2 The System for Pricing and Reimbursement as part of the Pharmaceutical Policy Framework

Hood, Rothstein & Baldwin (2001) use the term 'regime' to picture the framework for the structure, practice and principles for a system which involves a particular risk or hazard, and consider the risk regulation regimes as 'systems' with interacting parts. For the purpose of this project the system for pricing and reimbursement will be considered holistically to include all activities for the pricing and reimbursement of medicines, such as horizon scanning, coordination of patient registers, health technology assessment, price setting and

reimbursement decisions, negotiation and procurement, and monitoring of effectiveness. The system is evolving and new activities may be developed. The process is also developing. Although the basic description of the activities is applicable to all MSs, the national structures, the details of the activities and the processes are different (WHO 2015).

A key objective of the pharmaceutical policy framework is a high level of protection of human health and the improvement of public health through the use of medicines. The framework is a complex system, which can be systematically represented by a logic model (refer to Figure 2.1). The elements of a logic model (resources, activities, stakeholders [customers reached], outputs and outcomes) and the logical linkages among them support the description and evaluation of the pharmaceutical framework, which is a complex framework of systems (Vella Bonanno 2010; Vella Bonanno & Flores 2011).

The pharmaceutical framework covers five main systems: research and development, medicines regulation, pricing and reimbursement of medicines, manufacture and supply chain and medicines use. The systems consist of groups of activities: research and development, including clinical trials; medicines regulation, including marketing authorisation and pharmacovigilance; reimbursement and pricing are of national competence and include activities such as horizon scanning, health technology assessment and price setting, negotiation and procurement; manufacture and supply, including activities of pharmacies and wholesale dealing; and the use of medicines, including prescribing, dispensing, administration and monitoring of medicines in clinical care.

<table>
<tr><th colspan="2">Resources</th><th rowspan="2">Activities</th><th rowspan="2">Stakeholders (customers reached)</th><th rowspan="2">Outputs</th><th colspan="5">Outcomes</th></tr>
<tr><th>Legislation & policy</th><th>Structural & human</th><th>Unmet medical needs</th><th>Quality, safety, efficacy</th><th>Affordability</th><th>Access & availability</th><th>Rational use</th></tr>
<tr><td rowspan="8">European legislation

European policy

National Legislation

National policy</td><td>Academia

Investigators

Pharma industry</td><td>Research &Development, clinical trials

Application for Marketing Authorisation</td><td rowspan="8">Regulators

Policy makers

Pricing and reimbursement authorities

Pharma industry

Healthcare professionals

Patients

Health Service providers

Payers</td><td rowspan="8">Risk governance

Free movement of goods

Innovation

Intellectual Property Protection

Public health

Allocation of resources

Equity

Sustainability of healthcare systems</td><td rowspan="8"></td><td rowspan="8"></td><td rowspan="8"></td><td rowspan="8"></td><td rowspan="8"></td></tr>
<tr><td>Regulatory agencies:
EMA
National agencies</td><td>Scientific advice to industry pre-authorisation
Evaluation for marketing authorisation
Post-authorisation monitoring</td></tr>
<tr><td>National pricing bodies</td><td>Setting of national price (where a price is set prior to placing on the market)</td></tr>
<tr><td>Reimbursement and pricing authorities

Health Technology Assessment (HTA) bodies</td><td>Early dialogue (HTA) to industry pre-authorisation
Horizon scanning
Health technology assessment
Reimbursement decisions
Setting of maximum price and financing models
Monitoring of outcomes</td></tr>
<tr><td>Payers
D&T Committees
Procurement agencies</td><td>Procurement, negotiation, managed entry agreements, monitoring of outcomes of treatment</td></tr>
<tr><td>Operators of the supply chain</td><td>Manufacture, distribution, storage, supply</td></tr>
<tr><td>Health care professionals</td><td>Prescribing, dispensing, administration, monitoring of treatment</td></tr>
<tr><td>Patients and carers</td><td>Access to medicines, Administration, Monitoring of treatment</td></tr>
<tr><td colspan="9">External Influences</td></tr>
<tr><td colspan="9">The Treaties; The European Commission, the Council and the European Parliament; Regulatory governance framework set by the pharmaceutical legislation; Associations/groupings for stakeholders; Pricing and Reimbursement bodies; Pressures by/on different stakeholders; Research and funding initiatives</td></tr>
</table>

Source: Updated / adapted from Vella Bonanno (2003, 2010); Vella Bonanno and Flores (2011).

Figure 2.1 General Logic Model representing the EU Pharmaceutical Policy Framework as in March 2018

These systems involve different activities and processes and require decision making. The systems involve the relevant resources (structural, legislative, policy and institutions); activities and processes; the outputs (with the main challenge being the balance between public health and competitiveness) and the different stakeholders (policy makers, health care professionals, patients and the industry). The process for each system represents a conceptual series of activities.

Public health and social security remain within MS jurisdiction both from the political as well as from the legal perspective. Article 152 of the EC Treaty, as amended by the Treaty of Amsterdam, specifies that the European Commission has limited competence in the area of health, and this relates only to certain areas of health policy (Hancher 2004). The systems of medicines research and development, medicines regulation and manufacture and supply are highly governed by legislation. The other systems, pricing and reimbursement and medicines use, are within MS jurisdiction. MS activities regarding HTA, reimbursement and pricing are governed through the Transparency Directive (Directive 89/105/EEC 1988), but this legislation only regulates the transparency of procedures. As discussed above, the European Commission presented a Proposal for a Regulation on HTA and this is still being discussed through the co-legislative process.

Different stakeholders play an important role in the system of reimbursement and pricing. Most stakeholders (e.g. regulatory agencies, patient organisations, healthcare professionals and industry) are represented through networks, groupings and associations which serve to protect the interests of the relevant stakeholder group and to coordinate joint positions.

MSs are a major stakeholder of the pharmaceutical framework. There are different models and levels of collaboration between MS authorities for different systems of the pharmaceutical policy framework. MS activities and collaboration in the areas of clinical research, medicines

regulation and pharmaceutical activities are highly regulated and standardised through legislation. This activity is coordinated by the European Medicines Agency, which offers the secretariat and support for the regulatory processes, while the MSs give the technical expertise (European Medicines Agency n.d.). There is also coordination and collaboration between the national competent authorities responsible for medicines regulation through the Network of Heads of Medicines Agencies (Heads of Medicines Agencies n.d.). Collaboration is also exercised between MSs on joint scientific advice to the pharmaceutical industry on medicines in the pipeline. This advice relates to marketing authorisation of medicines and to HTA.

To date, activities related to reimbursement and pricing of medicines are within MS jurisdiction and MSs take national decisions. The area of medicines use is not regulated and practice varies from one MS to another. Recently, European Reference Networks, for the treatment of orphan disease conditions, have been set up in centres of clinical excellence across Europe through the Cross Border Directive (Directive 2011/24/EU 2011) and these are aimed at improving treatment of rare diseases.

The pharmaceutical framework has different outcomes. Outcomes could be short-, medium- and long-term. The main outcomes relate either to medicinal products (quality, efficacy and safety) or to public health (access, availability, affordability and effectiveness of medicines). The outcomes of the separate systems and of the processes and the logical flow from one system to another affect the final collective outcome of the pharmaceutical framework.

The pharmaceutical framework also highlights the contextual factors external to the programme and not under its control ('external influences‘) that could influence its success either positively or negatively.

2.3 Evidence-Based Management and the relevant methodology for review of evidence

Most practitioners involved in the system for pricing and reimbursement are experienced with evidence-based practice as applicable to the medical field and may find difficulty with certain principles of this practice as applied to management.

The 'hierarchy of evidence' ranks different designs of studies in the order of their internal validity (Petticrew & Roberts 2002). The concept of hierarchy of evidence is highly applied in medicine but is considered less relevant for some other areas. Experts in management and in organisational studies advocate for the identification of "the best available evidence from a variety of sources to answer research questions" and recommend that the decision on the design should ensure that the review is "fit for purpose" (Briner & Denyer 2012, p. 328). In fields where there is concern over the quality of evidence, the "a matrix based approach, which emphasises the need to match research questions to specific types of research may prove more useful" (Petticrew & Roberts 2003, p. 527).

In their definitions of evidence-based management leaders in the field stress that this is about making decisions through the "conscientious, explicit and judicious use of the four sources of information" and emphasise on the use of the "best available evidence" (Briner, Denyer & Rousseau 2009, p. 19; Barends, Rousseau & Briner 2014, p. 2; Rynes & Bartunek 2017, p. 239). Conscientious refers to the fact that there is significant effort to gather and use the best available evidence in spite of obstacles, such as time constraints, the need for resources and commitment. The need to be explicit entails that the evidence is "spelt out in detail" to enable scrutiny of the evidence. Judicious use of evidence entails cutting through distracting noise and making judgements which allow critical appraisal of the quality of the evidence. The evidence used should be trustworthy, relevant and applicable to the specific context. The evidence

obtained needs to be the best available evidence which addresses the particular circumstances, and needs to be reliable and relevant (Briner 2019, pp. 1-7).

Barends, Rousseau and Briner (2014, p. 3) describe evidence as “information”. The authors consider that the evidence can be presented in a variety of forms and comes from four sources (refer to Figure 2.2). The first source of evidence is the “scientific literature and empirical studies”. The evidence could originate from the field of management and also from other disciplines. The second source of evidence is from the organisation, “organisation internal data”. Such data can be financial or business data; it can come from customers and it can also come from employees. The evidence can be quantitative or can consist of soft elements such as perceptions. Evidence from the organisation is necessary to “identify problems as well as to determine the likely causes, plausible solutions and what is needed to implement these solutions”. The third source of evidence is “practitioners’ professional expertise”. Professional experience is accumulated over time and is different from intuition. It reflects the specialised knowledge acquired by repeated experience and practice of specialised activities. The fourth source of evidence is “stakeholder values and concerns”. Stakeholders can be internal to the organisation as well as external. Stakeholders are “any individuals who may be affected by an organisation’s decisions and their consequences” and their values and concerns will affect how they tend to react to the organisation’s decisions (Barends, Rousseau & Briner 2014, pp. 5-9; Barends & Rousseau 2018, pp. 5-10).

Evidence-based decision making involves the intersection of the evidence from the four sources. The “strength of the influence of the evidence from each source” varies for different decisions. In decision making the highest emphasis from the evidence should be made in a “mindful and conscious fashion”. The evidence should be “combined with the application of factors which are necessary for evidence-based decision making (e.g. critical thinking, values and concerns)”. The researcher needs to follow the steps for evidence-based management: “asking answerable questions, acquiring research evidence, appraising the quality of the

evidence, aggregating the evidence, applying the evidence in decision-making and assessing the outcomes of the previous steps to make more informed decisions" (Refer to Figure 2.2) (Briner, Denyer & Rousseau 2009, pp. 21-22; Barends, Rousseau & Briner 2014, pp. 5-9; Rynes & Bartunek 2017, p. 241).

In reality there is limited practice of evidence-based management because managers lack knowledge of the evidence and consultants who advise management are limited in their knowledge of the evidence too. Challenges with evidence-based practice include lack of time, the evidence is not always clear or well understood and it can be difficult to interpret research findings (Rousseau 2006; Barends et al. 2017). Moreover managers may consider that evidence-based management can limit them from taking decisions freely (Rousseau 2006).

As seen in Figure 2.2 and explained above, in evidence-based management scientific literature and grey literature are main sources of evidence and form part of the methods for the collection of the evidence. This contrasts with the traditional academic dissertations. In this study, which is an evidence-based management research, scientific literature and grey literature were used as a source of evidence (Refer to Chapters 3, 4 and 5).

Leaders in the field of management and organisational research, Denyer and Tranfield (2009); Briner and Denyer (2012), endorse systematic reviews, however they consider that this methodology is not directly transferable for management research. In the field of management, "research findings are inevitably presented in an over-simplified way in order to present a clear and coherent narrative about how research has developed and what has been found emphasising the linear development and progress of knowledge" (Briner & Denyer 2012, p. 335). In this study, narrative synthesis was used to present the evidence and the method was carried out in a step-wise manner.

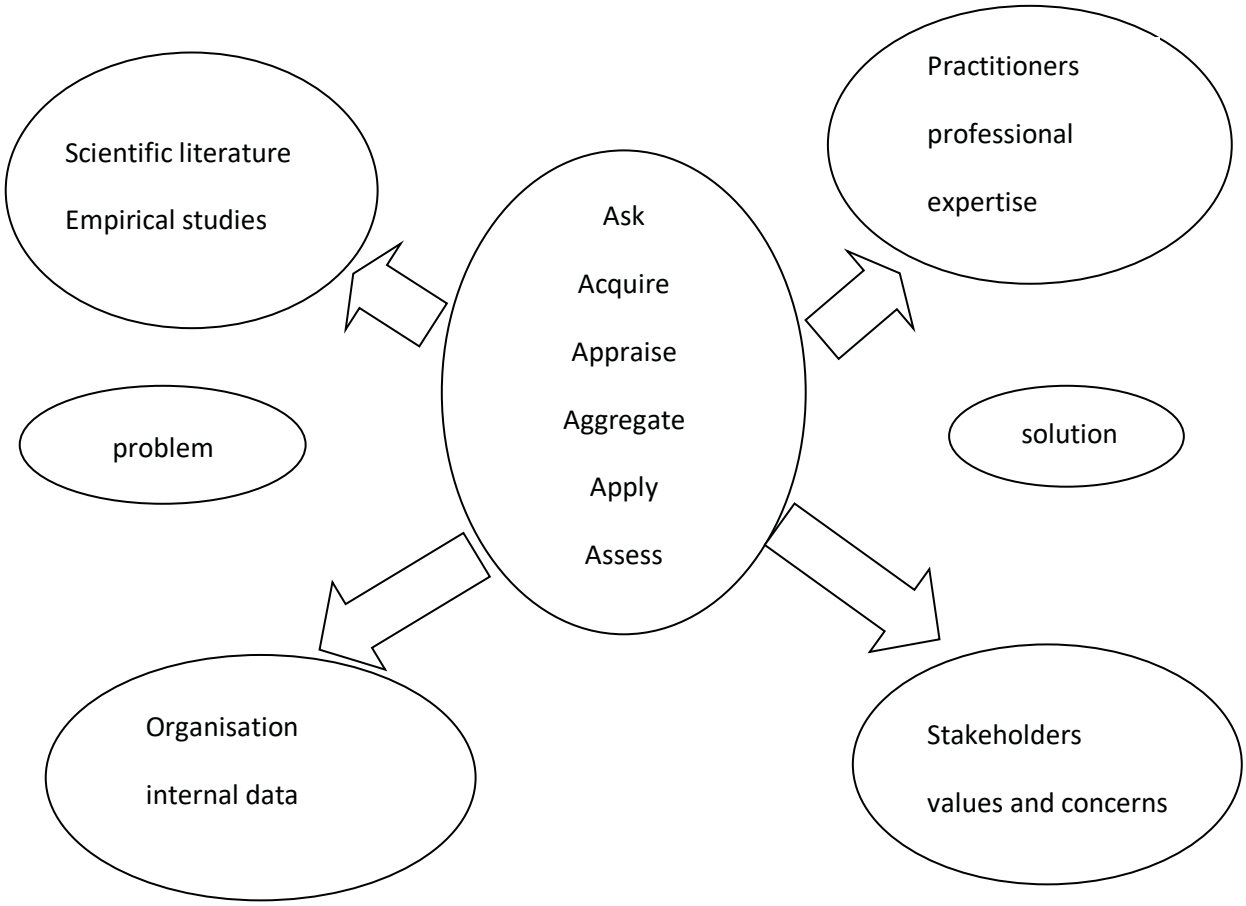


Figure 2.2 Model for the sources of evidence and for the steps for collection of evidence for evidence-based management decisions adopted from Barends and Rousseau (2018, p. 5)

2.4 Evidence-based decision making in management

As stated in the scope of this research, the evidence was collated to make inferences regarding MS collaboration in the area of pricing and reimbursement and to support future decision making. The aim of evidence-based management is to make good decisions in practice. Evidence-based management considers that "good quality decisions should be based on a combination of critical thinking and best available evidence" (Barends, Rousseau & Briner 2014,

p. 2). In addition to the use of evidence, “the perspectives of those people who might be affected by the decision” need to be considered. Evidence-based management “is something done by practitioners not scholars”, although scholars and consultants can support (Briner, Denyer & Rousseau 2009, p. 19). Evidence-based management is “informed by practitioner judgement regarding experience, contextual circumstances and ethical concerns” (Briner, Denyer & Rousseau 2009, p. 21).

Many decisions require organisational change to be realised in practice. Professionals in the field and the different stakeholders have different opinions and attitudes on what is needed and what should be achieved, and attempts to change practice without considering these factors are likely to fail. Key stakeholders should be involved from an early stage of the initiative, and barriers to change need to be identified. There are various approaches to support the implementation of change and this awareness led to the study of understanding of “social, behavioural and organisational factors which may act as barriers to change” through cognitive theories, management theories, learning theories and “reminder systems and social influence theories” (Haines & Donald 2002, p. 3).

Management professionals are frequently conversant with research on cognitive biases which affect individual judgement, described by Kahneman (2011) in his book ‘Thinking Fast and Slow’. Rousseau (2018) considers that because organisational decisions occur in a social setting where information is held in different places, in the right environment this can help mitigate bias in organisational decisions. Failure in decision making can be attributed to factors such rushing in decision making, managers who force their opinion, failure to question what lies behind decisions taken, lack of good quality evidence, ignoring the seriousness of risks, and not considering available options. Rousseau (2018) recommends the “use of de-biasing practices and appropriate decision processes” for improved decision making. Rousseau (2018, p. 2) describes six qualities by which organisations, “by virtue of their structuring and the environments in which they operate tend to introduce their own peculiar decision challenges”:

the type of work, influencers, accountability, types of decisions to be made, the levels of uncertainty and decision supports (Rousseau 2018, p. 2).

A systematic review on "the effectiveness of research implementation strategies for promoting evidence-informed policy and management decisions in healthcare" identified the following "inter-relating factors" perceived to be associated with the effective implementation of research (in hierchical order): *establishment of a need for change in practice, building trust among the stakeholders involved in implementation, development of a shared vision, actioning mechanisms for change, strategies for communication and giving resources for change* (Sarkies et al. 2017, p. 132).

Hodgkinson (2012), who claimed to be a supporter of the principle of evidence-based practice, presented some possible risks if evidence-based management is not used transparently. The author argued that evidence-based decision-making is as political as other decision making. He criticised the advocates for evidence-based management for creating an illusion of rationality and clarity. Hodgkinson considered that abuse of evidence-based management may be a way for practitioners to embelish their decisions in the language of evidence-based managemet to increase the legitimacy of their political decisions.

2.5 Theoretical framework and organisational theories

Pricing and reimbursement are regulatory functions and for this reason it was pertinent to focus on the theoretical framework applicable to regulatory organisations.

Baldwin, Cave and Lodge (2012, pp. 74-77) described four main considerations for successful regulation and attributed these to the inherent limitations and failures of regulation. The first consideration was that regulators should prioritise public interest, "interest centred approaches".

There may be different and competing opinions of what public interest is and how it can be achieved. The second consideration was competition between concerns and interests of different stakeholders involved, which can lead to regulatory failure. Capture theories show that organised stakeholder groups influence regulation to meet their interests. The economic theory of regulation shows that economically powerful and concentrated interests have the ability to manipulate regulation. Politicians' behaviour shows that governments change their minds over time ('the time inconsistency problem'). Some regulatory agencies adopt blame- and risk-avoiding behaviour and focus on achieving popular outcomes, rather than those that are significant and often difficult and unpopular. It is important that there is alignment between the organisational self-interest and regulatory alignment (Baldwin, Cave and Lodge 2012). The third consideration by Baldwin, Cave and Lodge (2012) was the 'ideas-based approaches', which show how beliefs and ideas and world views impact regulation. A strand of such theories stresses the "inherent plurality of rationalities or world views that characterise any debate regarding regulatory instruments". The fourth consideration concerned 'institutional theories', which agree that regulatory developments are driven by institutional structures and arrangements and by social processes. Failure of recognising this will result in inter- and intra-institutional pressures. It is important that regulatory systems do not "drift" and lose focus and direction. Regulatory authorities could undergo different types of 'drifts' including 'coalition drifts' (governments changing preferences over time), 'agency drift' (agencies not following their statutory objectives) and 'industry drifts' (industry not following regulatory requirements). Information asymmetry may lead to drift (Baldwin, Cave & Lodge 2012, pp. 74-77).

The regulatory function of organisations is highly linked to the process of decision making of the organisation. The 'principle of bounded rationality' by Simon (1990) shows how the decision-making process impacts the decisions made and considers the cognitive limitations of the decision maker. It considers shortcomings in evidence as well as in computational capacity (Simon 1990 p.15). As described by Baldwin, Cave and Lodge (2012, p. 74) bounded rationality

“affects individual and organisational decision making. Information is costly and the capacity of any one individual, organisation or system to process all available information within time and other constraints is inherently limited. As a result our decision-making is inherently bounded”. It is considered that uncertainty and ambiguity of knowledge can result in limitations of regulation. There needs to be consideration that there are differences in context, legal systems, political systems and constituencies. This limitation in knowledge results in reduced prediction that the regulatory strategies will achieve their intended effect. The authors recommended that due to this limitation of knowledge regulatory strategies for change should not rely on “grand schemes” but rather on incremental “trial and error” approaches (Baldwin, Cave & Lodge 2012, p. 74). Simon (1991, pp. 125-126) explained the relationship between bounded rationality and organisational learning. He explained that learning within an organisation takes place through the learning of the members of the organisation and by enrolling new participants who have new knowledge. Simon stressed that internal learning is an important component of organisational learning and that this is a social phenomenon. Simon pictured organisations as “systems of interrelated roles” whereby “a role is a system of prescribed decision premises”. Roles tell the members of the organisation how to reason about the problems and decisions they need to take, where they find the official information needed and evaluative norms, and what techniques to use to process them. Each of the roles in an organisation presumes the correct enactment of the other roles that surround it and interact with it. Thus the organisation is a “role system” (Simon 1991, p. 127).

As explained in the introductory chapter of this research, the change from national authorities acting independently to structured cooperation between national authorities is challenging and perplexing in practice. It was clear that there needed to be strong motivators and benefits to be gained for national authorities to agree to collaborate voluntarily. For collaboration to take place these motivators need to overcome the perceived risks and de-motivators. The research required a theoretical framework on different aspects of organisational collaboration to provide

an intelligent and plausible conceptual framework for the study, particularly to draw up a framework for studying attitudes, perceptions on impacts of intervention and motivational factors for collaboration. One of the major challenges with the introduction of cooperation between national authorities was that the national organisations were structured and oriented to work independently and working together involved a major change and a paradigm shift in the way they operated and in the perception of their autonomy and power. Moreover most of these organisations were well-established institutions with a long history and stated power. The introduction of collaboration would change the power balance because the dynamics change. One basic organisational concept relevant to the regulatory function of organisations is organisational politics which relates to the use of personal or aggregate power to influence others and to achieve one's goals in the workplace and secure personal or collective interests. Professionals and workers within an organisation are unwilling to bring to the open the political secrets and networks that support their progression and their personal egendas (Vigoda-Gadot & Drory 2004). Another challenge from cooperation would be that globalisation would make the environment more complex and would introduce a degree of uncertainty. Simon (1990) stressed that in complicated environments people do not adapt easily or at least to the required level. Kezar (2006) made an important observation that a number of organisations are designed to operate individually and adaptation is required for collaboration. Organisational change is thus required. Kezar noted that collaboration depends on the members of the organisations their interests and their willingness to achieve common objectives and rules. For collaboration to succeed there needs to be communication and networking over time. Kezar (2006) considered theories which explain perceived benefits for external (inter) collaboration. The author explained that the 'resource dependency theory' shows that people tend to collaborate if they have limitations of resources and the strategic choice theory shows that collaboration is motivated by the perception of increased power and output. Mohrman et al. (1995, cited by Kezar 2006, p. 809) claimed that "one of the main reasons collaboration fails is that one cannot impose collaboration within a context designed to support individualistic work". To make collaboration

successful, there needs to be “redesign for collaborative work based both on external challenges and pressure and on the documented benefits of working in this manner” (Kezar 2006, p. 804). Kezar (2006, p. 810) stressed on the need for development of skills for collaboration and also for the “unlearning of non-collaborative skills”. Redesign of organisations requires the support of management. Kezar (2006, pp. 809–811) utilised the model by Mohrman et al. 1995 which identified areas that needed to be redesigned to empower an organisation to support collaboration: *strategy, the tasks of the organisation, organisational structure, general processes, developing rewards to incentivise and introduce accountability, and training and empowerment of people to learn collaboration*. Kezar identified other elements which are necessary to foster collaboration including culture, values and relationships; interplay of human dynamics; shared values between the groups or a set of values that draw people together. Kezar noted that a “sense of priority from senior executives” was also a critical element for successful collaboration (Kezar 2006, p. 822).

Cooperation needs to be implemented within a global environment, which impacts the progress and the shape of the cooperation. The global environment can affect public policies through cooperation whereby countries pledge to abide with certain regulatory obligations agreed between governments. Views on international organisations range from organisations which are totally devoid of autonomous power to the “rationalist institutionalist approach” which explains how “states succeed in cooperating for mutual advantages despite international anarchy”. Institutionalists support coordination by “providing a favourable context for bargaining and, crucially, by presenting focal points to negotiators”. Joint initiatives which have problems with collaboration must be designed to build trust between countries, in order to minimise their motivation to abandon agreements. Once international organisations are created, they set the perception of appropriately normative behaviour among their members and this is likely to direct cooperation among the players. One reason for international delegation among countries is

blame-management and as a blame-shifting incentive by governments (Koenig-Archibugi 2010, pp. 416-418).

2.6 Models for international collaboration among regulatory authorities

One of the main issues contended by the different stake holders during 'the Study' was the level of governance for the cooperation as offered by the different policy options (refer to Table 1.1). Understanding of attitudes and perceptions of key players towards collaboration required knowledge of the different alternative models which were possible for collaboration, particularly for organisations with a regulatory function.

Baldwin, Cave and Lodge (2012, pp. 159-164) described various models for international collaboration. The models have different levels of complexity and may involve different types of regulatory frameworks: regulators from different countries that set standards, application of instruments for regulation, legislative set ups, smart regulation, professional self-regulators and certification bodies. Coordination in such networks is a major challenge. The regulators involved will have different perception of norm and of what is good or not. The capacity, skills and resources of the organisations will be different and this will affect the way they work and regulate as well as their approach and responsiveness. Some regulators will be able to manage change while others will not. Regulatory cultures differ across countries and this affects the way in which regulation in implemented. Certain regulatory organisations will be considered to have good reputation and status at the international level. The national structure for regulation differs between countries in terms of power between institutions, sources of funding and governance (Baldwin, Cave and Lodge 2012, pp. 159-164).

Baldwin, Cave and Lodge (2012, pp. 160-161) described five “modes of coordination” or “regulatory cohabitations”: “hierarchy” within government networks involves a body at the top which imposes rules and policies on the inferior organisations below it; “community” coordination of a network of peers that have common interests and recognise each other’s membership by “mutual recognition”; “network management” has a lead party or “manager” body that takes action to coordinate behaviour through building levels of consensus to enable actions to be taken; networking bases on “rituals” which can be adopted voluntarily or imposed; and coordination which is left to “markets” and all exchange is based on the interests of the participants and their mutual gains (Baldwin, Cave and Lodge (2012, pp. 160-161).

MS authorities involved in the pharmaceutical framework have adopted different models of collaboration and networking for the different systems of the pharmaceutical framework. The systems of research and development, medicines regulation and manufacture and supply are covered by European legislation. The collaboration within EUnetHTA is operated in the form of a ‘manager’ body which coordinates the different members. The regional collaborations are mainly adopting the ‘community’ collaboration model. Overall the participation or otherwise in collaborative initiatives has been fully voluntary and is governed by markets. The ‘Proposal for a Regulation on HTA’ as set by the European Commission incorporated a hierarchical structure governed by legislation, with the Commission placing itself at the top of the hierarchy.

2.7 Evaluating attitudes, perceptions on impacts and motivational factors for collaboration

As explained in Chapter 1, the scope of this study is to review the evidence on attitudes to collaboration, the perceived impacts (benefits / risks) and the positive and negative motivators for collaboration. This requires a study of these three concepts. The information on the concepts

was used to build a 'Framework' to support the collection and review of the evidence (refer to Chapter 3).

2.7.1 Measuring attitudes for collaboration

Attitudes are a way of describing differing likes and dislikes of people. In contrast to transient moods or feelings, attitudes are consistent and enduring thoughts, beliefs and feelings that people have about particular issues, people or events. Attitudes are generally evaluated in relation to the beliefs people have about a specific issue and the actions they take about it.

Edelmann (2000, pp. 277-278) considered that attitudes consist of three aspects: "an emotional or evaluative component; a belief or cognitive component; and an action or behavioural component". Beliefs are thoughts which show whether one feels or evaluates positively or negatively about an idea or a thing. Generally if someone holds negative attitudes about a thing, then he has predominantly negative thoughts about this thing, and vice versa for positive attitude. The behavioural component shows that the relationship between evaluations and behaviour is less clear and direct, as attitudes are not the only factor which predicts behaviour. Behaviour is also affected by factors such as expectations of significant others, concerns about time and commitment involved, anxiety about an action, and these may prevent a favourable attitude being turned into direct action. Cognitive, evaluative and behavioural components of attitude can be assessed and may provide different results from each other. Assessment of beliefs provides a clearer link with evaluative judgements (Edelmann 2000).

2.7.2 Perceived impacts (benefits and risks) from collaboration

A systematic review by De Freitas, De Oliviera and Alcantara (2018) considered the benefits of collaboration between companies. Collaborative initiatives were considered to lead to improvement, primarily in the supply chain. The benefits were classified as primary and secondary. Primary benefits included: better planning, more production, stronger relationships, diversification of product, shorter cycles and smoother launch of products. Secondary benefits included: reduced costs, improved customer service, increased sales, competitiveness, better financial performance and more accommodation of the needs of the customer. The study showed that the secondary benefits were only achievable subject to the realisation of the primary benefits. The concepts of this systematic review were considered usable for different scenarios (De Freitas, De Oliviera & Alcantara 2018).

The European Commission measures impacts as part of the process for getting feedback about a new proposed legislation in line with the 'EU Better Regulation Guidelines'. These include a 'toolbox' to have timely information on which the Commission bases its decisions. The Better Regulation methodology is aimed to increase the transparency, the evidence-base and the perspectives of stakeholders for the setting of EU policies. The guidelines include measurement of impacts or effects of an initiative or an intervention such as a proposed new legislation. The final results of an impact assessment are presented in an 'impact assessment report', which should cover three categories of impacts: environmental, social and economic impacts. The impacts prioritise the perspectives of small and medium enterprises, competitiveness and the stakeholders that will be affected by the initiative (European Commission 2017).

The European Commission commissioned an impact analysis to study the policy options for the future of HTA: 'Study on impact analysis of Policy Options for strengthened EU cooperation on Health Technology Assessment Final Report'. This was written by Gesundheit Ostrerreich Forschungs-ind Plannungs GmbH and The London School of Economics and Political Science,

supported by Sogeti in August 2017 (European Union 2017). This study on impact analysis henceforth referred to as 'the Study', considered that for the purpose of the topic of HTA two types of impacts were relevant: social health impacts and economic impacts (European Union 2017).

2.7.3 Motivational factors (facilitators and barriers) for collaboration

The systematic review by De Freitas, De Oliveira and Alcatraz (2018) classified different types of barriers and motivators for initiatives for collaboration between companies in a supply chain. This systematic review explained 'motivators' as factors external to the company that contribute to the adoption of the initiative; and 'barriers' as all elements that hinder the process of implementing an initiative. Although this systematic review did not study national organisations, the characterisation of the concepts identified in the systematic review was considered relevant for this study. The analyses of the motivators for adopting collaborative initiatives were divided into economic and organisational. Communication and information technologies were considered as facilitators for companies seeking to collaborate. Human resources were considered another important factor. Barriers were grouped into cultural, physical and behavioural. Cultural barriers identified in the systematic review included: *deficiency in training to achieve new skills and preparedness, variation in aims and objectives, disassociation, lack of integration of new processes, stringent organisations and resistance, lack of accountability and measure of output, lack of support from senior management, incongruence of function, conflicting organisational culture, lack of comprehensive documentation, lack of joint planning*, *lack of prioritisation of customer service focus and goals, separated problem solving and decision making*. Behavioural barriers identified in the systematic review included*: lack of trust, resistance to information sharing, problems in information and communication flow, resistance to change and lack of commitment.* Physical barriers included: *low investments in IT / IS and*

telecommunications, insufficient financial resources and lack of other investments (De Freitas, De Oliveira and Alcatraz 2018).

The publication by Kezar (2006), which focused on collaboration between educational institutions, identified barriers and facilitators for collaboration which were also considered applicable to this project. It identified that campuses realised the need for collaborative work on the basis of impact by external factors and on the available evidence supporting the collaboration. External challenges which acted as motivators for collaboration, included: *difficult financial times, changing demographics, globalisation, increased complexity and the possibility of combining expertise and enhancing the resources and ability of the institution to meet the needs of the changed environment*. Barriers for collaboration within educational institutions included the fact that higher educational institutions often acted as independent entities and adopted highly administrative and hierarchical frameworks (Kezar 2006).

Comprehensive literature regarding influencers of successful cooperation in forestry was identified. Gorriz-Mifsud et al. (2019) identified a number of challenges for coordination of joint management between forest owners. These included: *procedures for decision-making, geographical cohesion, building of trust and legitimacy, internal communication and transparency, trade-offs in efficiency and equity, local idiosyncrasy, dynamics of the management committee, flexibility as compared to risk aversion, legal considerations, long-term vision and joint motivation.* These can be relevant to collaboration between MS entities.

Haines and Donald (2002) listed potential barriers to change in clinical practice settings. Those most relevant to the topic of MS collaboration included: practice and healthcare environment (e.g. limitation of time, financial resources), educational environment and social environment (e.g. influence of media).

As motivational factors can be positive or negative and the same factor can be considered through different perspectives by different stakeholders, in this project the term ‘motivational

factors' was considered generically. The framework of the main motivational factors which can act as barriers or facilitators for collaboration, as collated from the different literature sources was summarised in Table 2.1.

Table 2.1 **Motivational factors for collaboration**

Social Access to social protection and health systems, sustainable health systems, access to medicines
Economic External factors arising from an economic factor or by a market event e.g. more intense competition, globalisation, market reaction, competitive advantage
Behavioural Trust, ability or willingness to share information, resistance to change, mutual respect, ability to compromise, communication, personal interests
Organisational Internal factors related to the form of organisation: the willingness of the organisation to collaborate; the need for the organisation to change to be able to collaborate; external motivators and pressures towards collaboration such as supply chain problems, pressure from trading partners and availabilty of expertise; adaptability; development of appropriate policies and guidelines within the organisation.
Contextual / environmental History of collaboration, local context, meeting the demands of the new environment
Factors related to purpose Objective reachable goals, common vision, specific and well-defined purpose, membership characteristics, common and agreed procees and outcomes
Implementation climate Political and social climate
Cultural Differences /similarities in goals and objectives, relationships, capacity to share risks, integration of key processes, flexibility of organisational system, compatibility of organisational culture
Resources / physical Investments, financial resources, funds, staff, expertise, skilled leadership

For the purpose of this project barriers / challenges were considered as negative motivational factors and facilitators / drivers were considered as positive motivational factors and the generic term ‘motivational factors‘ was used.

2.8 The research questions

The literature presented in Chapter 2 supported the formulation of the scope of the study as described in Chapter 1 into structured research questions.

The theoretical framework on organisational theories, the knowledge on models for international collaboration and the information for evaluation of attitudes, perceptions of impacts and motivational factors presented in this Chapter were used to formulate the framework for the collection and presentation of the evidence.

The Research Questions

1. What is the evidence from various sources regarding attitudes, perceived impacts and motivational factors for MS collaboration for pricing and reimbursement of medicines?

2. Does the evidence from the different sources corroborate?

3. What inferences can be made for collaboration between MSs for activities related to pricing and reimbursement of medicines?

Objectives

The objectives were set in order to answer the Research Questions.

The logic model for the pharmaceutical framework (Figure 2.1) showed that the system for pricing and reimbursement is part of the pharmaceutical policy framework. The first objective for this study was to map out the system for pricing and reimbursement using a Logic Model. The study considered the different activities in the system for pricing and reimbursement holistically. During the course of the study the context of the system continued to evolve and there were major events which influenced the system. The Logic Model was updated during the course of the study.

As seen in Section 2.3, evidence-based management methodology involves acquiring evidence from different sources of evidence, appraisal of the evidence and aggregation of the evidence. Thus the objectives of the study were to follow evidence-based management methodology for a review of the evidence:

- To map out and the system for pricing and reimbursement including its different activities, resources, stakeholders, outputs and outcomes

- To review different sources of the evidence and collect, appraise and aggregate the evidence

- To consolidate the evidence and consider the perspectives of different stakeholders

2.9 Summary

The building of the content of this chapter started at the inception of the project, and continued throughout the project. The final chapter as presented was consolidated at the end.

There is an extensive theoretical framework for organisational cooperation. Cooperation between international organisations involves specific considerations. The literature specific to regulatory organisations is more specialised and the literature provided insights specific to this area.

The researcher had experience of evidence-based practice in the clinical field particularly in relation to pharmaceuticals. This adopts strict methodological rules and requires strong study designs such as randomised clinical trials. There are significant differences and challenges for the applicability and use of the evidence–based approach for policy and management. The evaluation of management interventions in real life settings, as is the system for collaboration between MS authorities, needed an approach which addresses this challenge. A methodological design and framework specific to management interventions in the real life setting was warranted for this study and was presented in Chapter 3.

3. Method

3.1 Introduction

In this Chapter, the model for evidence-based management from Barends and Rousseau (2018) described in Section 2.3 and Figure 2.2 was used for setting the design and process of this study.

A 'Framework' was built to collect the evidence used for this study. This consisted of a Logic Model of the process for pricing and reimbursement and tools with themes for the three concepts covered in the Research Question: attitudes, perceived impacts and motivational factors for MS collaboration for pricing and reimbursement.

As explained in Chapter 2, an evidence-based practitioner should obtain evidence from the four sources of evidence: scientific literature and empirical studies, organisation internal data, practitioners' professional expertise and stakeholder values and concerns (refer to Figure 2.2). The researcher identified four methods to get the best available evidence to cover these four sources: collection of evidence from published scientific literature, collection of evidence from grey literature, evaluation of the 'Study on impact analysis for policy options for strengthened EU cooperation on Health Technology Assessment, Final Report' ('the Study') and a focus group with practitioners in the field. Some of the methods produced evidence from more than one of the four sources of evidence. The 'Framework' was used to collect and present the evidence from each method. This analysis was done as systematically as possible.

At this point it is pertinent to remind the reader that in the case of this project the theoretical framework and supportive literature as presented in Chapter 2 related the methodology to organisational theory and to the concepts relevant to the study. The literature regarding MS

collaboration for pricing and reimbursement (the scientific literature and the grey literature) were used as sources of evidence for the study.

3.2 The process / design of the study

The process / design of the study were based on the model from Barends and Rousseau (2018) and the methodology for evidence-based management described in the same source (Refer to Figure 2.2). The collection of evidence and its presentation involved six definite steps: ask, acquire, appraise, aggregate, apply and assess (as represented in the middle of the model in the same Figure). These steps are described below. The Steps were formulated into the process for this study and were presented in Table 3.1. Table 3.1 also includes a summary of each Step and the relevant Chapter in this study where the step is presented.

Table 3.1 **The process of the study**

Step Refer to Figure 2.2	**Description**	**Chapter in this study**
Step 1 Ask	• Description of the situation and challenges with Member State collaboration (the problem) • Defining the scope of the study	Chapter 1 Introduction
	• Presentation of the theoretical framework and relevant literature • Setting the research questions and the objectives of the study	Chapter 2 Theoretical framework and literature
Step 2 Acquire	• Setting the process for the study (presented in this Table) • Building a logic model of the process for pricing and reimbursement • Building a 'Framework' for collection of the evidence for the concepts being studied: attitudes, perceived impacts (benefits and risks) and motivational factors (barriers and facilitators). • Using different methods to collect and present the evidence: scientific literature, grey literature, evaluation of 'the Study', focus group discussion	Chapter 3 Method
Step 3 Appraise	• Appraising of the evidence - critical appraisal of the evidence from each method for its trustworthiness and relevance • Evaluation of the balance and coverage of the evidence	Chapter 4 Appraisal of the evidence
Step 4 Aggregate	• Aggregation and presentation of the evidence from the different sources within the themes of the 'Framework' • Corroboration and evaluation of the evidence from the different sources to see if there were gaps or paradoxes in the evidence.	Chapter 5 Aggregation of the evidence
Step 5 Apply and Step 6 Assess	• Inferences for the use of evidence-based management in practice • Application of the evidence for collaboration between Member State authorities for pricing and reimbursement • Use of the evidence to assess ongoing initiatives for Member State collaboration for pricing and reimbursement • Implications of the evidence for future initiatives for MS collaboration for pricing and reimbursement	Chapter 6 Application of evidence-based management and of the evidence from the study

3.3 Building a 'Framework' for the collection and presentation of the evidence

The system of collaboration for the pricing and reimbursement between Member States (MSs) is a natural interaction within the complex system of the pharmaceutical framework. The evidence collected for this research was qualitative. The research question of this study required a tradition of naturalism, whereby the researcher tries to understand the environment of the research and describes the setting and the interactions and networks involved as they are. Thematic analysis entails presenting the evidence as it is "telling it like it is" (Bryman & Bell 2011, p. 572). The evidence for each method used was collated and analysed by thematic analysis. A 'Framework' was built to support the collation and presentation of the evidence in relation to the research questions of the project and to support the thematic analysis of the evidence.

As shown by the Logic Model depicting the Pharmaceutical Framework, which includes also the system for pricing and reimbursement (Figure 2.1), the Pharmaceutical Framework is complex. As described in Barends and Rousseau (2018, pp. 195-196), a logic model ("also referred to as causal model or theory of change") pictures the processes and is a "graphical representation" of the links between inputs (resources), activities and processes (what is done to inputs), outputs and outcomes (immediate results and long-term consequences). The Logic Model of the Pharmaceutical Framework and the description on logic models from Barends and Rousseau (2018) were used to build a Logic Model for the System of Pricing and Reimbursement as at the beginning of the project (Model 1). Logic Model 1 was included as Part 1 of the 'Framework'.

The other parts of the 'Framework' (Parts 2, 3 and 4) were drawn to collect and present the evidence related to each of the concepts covered in the research question: attitudes, perceived impact and motivational factors for MS collaboration for pricing and reimbursement of medicines. The different parts of the 'Framework' were presented in Table 3.2.

Table 3.2 **The parts of the 'Framework' used as a tool for the collection of evidence**

Part of the 'Framework'	**Description**
Part 1: Baseline logic model for the system of pricing and reimbursement (Model 1)	This consisted of the draft logic model for the system of pricing and reimbursement, which was one of the objectives of the project. A draft logic model (Model 1) was drawn to depict the system and describe the processes involved in the system for pricing and reimbursement. This was compiled using the literature presented in Chapter 1 as well as from the knowledge and experience of the researcher. This logic model was presented in Part 1 of the 'Framework' in Figure 3.1 below.
Part 2: Attitudes	'Framework' for presentation of attitudes on collaboration among national health authorities for pricing and reimbursement. The literature in Section 2.7.1 was used to support the compilation of this part of the 'Framework'.
Part 3: Perceived impacts	'Framework' for presentation of perceived impacts (benefits and losses) for collaboration between national health authorities for pricing and reimbursement. The literature in Section 2.7.2 was used to support the compilation of this part of the 'Framework'.
Part 4: Motivational factors	'Framework' for the presentation of motivational factors which act as barriers (challenges) and factors which act as facilitators (motivators, drivers) for collaboration between national health authorities for pricing and reimbursement. The literature in Section 2.7.3 was used to support the compilation of this part of the 'Framework'.

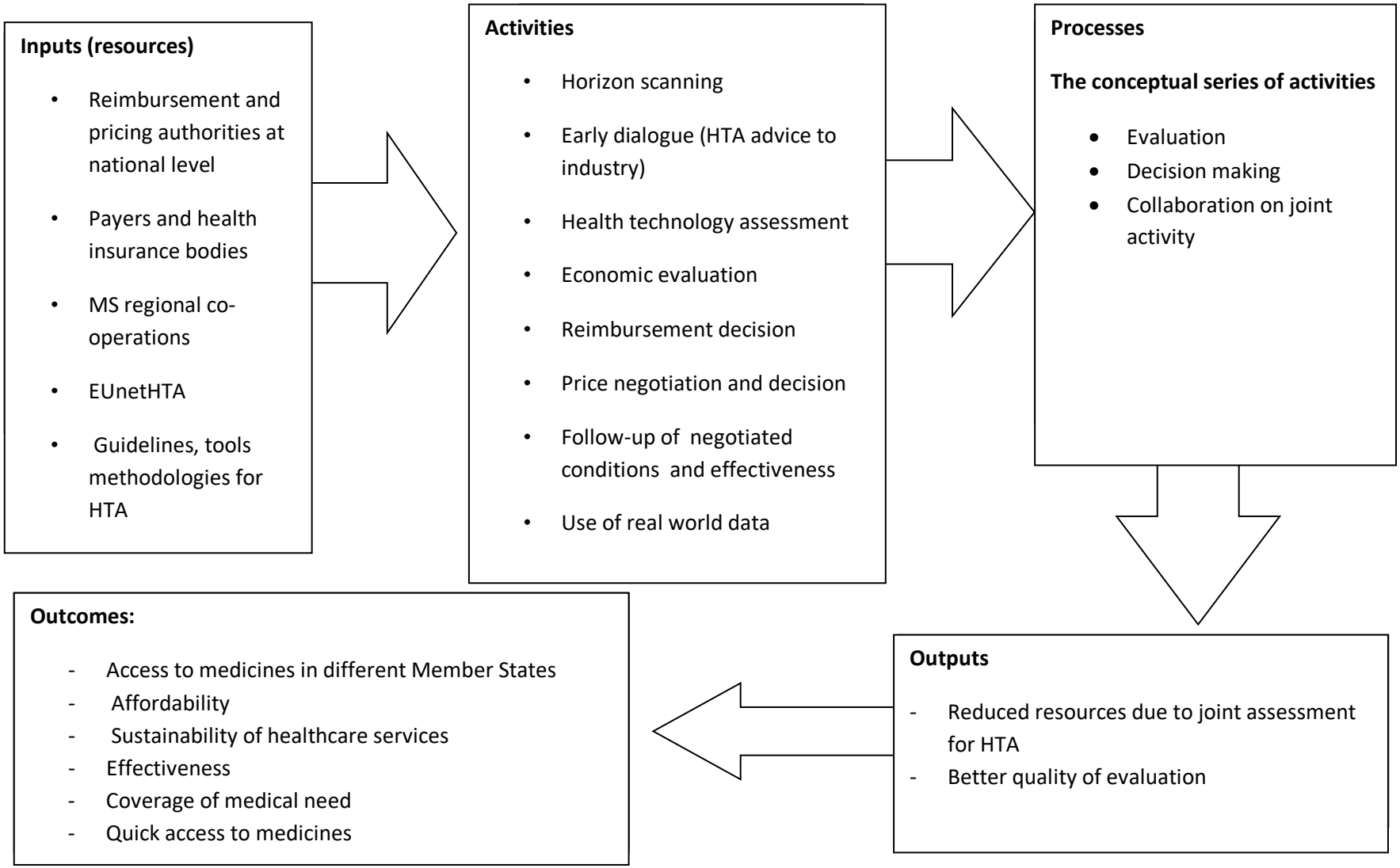
The collated 'Framework' for the project covering Parts 1 to 4 was presented in Figure 3.1 below.

The ‘Framework’ was used as a tool to collect evidence from the different methodologies. For certain themes of the ‘Framework’, additional indicators were included. These supported having information specific to the theme.

During the course of this project the different sources of information as well as additional literature, were used to update the Logic Model (Model 1). A final updated Logic Model (Model 3) was presented in Chapter 4. The ‘Framework’ was adapted according to the method used: for collection of information from scientific literature, and from grey literature, to collect information from ‘the Study’ and as a focus group guide. The ‘Framework’ served as a tool to support the evaluation of the collated evidence (Chapter 4) and to enable aggregation of the evidence from the different methods (presented in Chapter 5).

Having a ‘Framework’ to build the tools for the collection of evidence and for the evaluation of the evidence helped to ensure consistency and standardisation and enabled aggregation and comparison of the evidence from the different methodologies. The themes used in the ‘Framework’ and the indicators for the themes, supported standardisation during the stratification of the evidence.

Part 1: Draft Logic Model for the system of pricing and reimbursement as at the beginning of the project (Model 1)



Part 2: Attitudes on collaboration between national health authorities for pricing and reimbursement

Attitudes are a way of describing differences between people with reference to their different opinions (likes and dislikes). Attitudes are not transient feelings or moods but consistent thoughts that people have about a particular object or intervention (in this case collaboration between national health authorities) and the action they take towards it. Attitudes consist of three aspects: (1) an emotional or evaluative component, (2) a belief or cognitive component, (3) an action or behavioural component.

a. Should collaboration between national health authorities for pricing and reimbursement be:

i. voluntary participation and voluntary adoption
ii. mandatory participation and voluntary adoption
iii. mandatory participation and mandatory adoption

b. Should collaboration between national health authorities for pricing and reimbursement be regulated through:

i. soft regulation (e.g. guidelines set by the collaborating countries)
ii. EU legislation set by the European Commission
iii. legislation set by the collaborating countries
iv. other

c. What is the role of the European Commission with regards to collaboration between national health authorities for pricing and reimbursement?

i. to set legislation to regulate the collaboration
ii. to support a structure for governance

d. Attitudes on collaboration between national health authorities for pricing and reimbursement for specific activities

Activity	
Horizon scanning	
Early dialogues with industry	
Sharing of information	
Relative effectiveness evaluation (REA)	
Full HTA (with economic evaluation)	
Price negotiation	
Reimbursement agreements	
Post-marketing authorisation studies	
Generation of real-world data	

Part 3: Perceived impacts (benefits and losses) from collaboration between national health authorities for pricing and reimbursement

Social health impacts: Governance, robust administration; access to health systems and social protection; sustainability of health systems; public health

Economic impacts: Costs related to processes; administrative burden; competitiveness; innovation and research; functioning of internal market

Themes for Social health impacts	Indicators	Benefits / losses
Employment		
Governance, participation and good administration	Indicators: i. Impact of collaboration on involvement of different stakeholders in processes ii. the responsibilities of public administrations and other organisations at MS level iii. the uptake of joint outputs (e.g. HTA reports, early dialogues, tools) iv. resource efficiency of processes v. the sustainability of European cooperation (sustainability of processes)	
Access to social protection and health systems	Indicator: The potential effect of collaboration on the access to treatments that could be considered as “innovative”	
Sustainability of health systems	Indicators: i. the effect of collaboration on the financing of expensive treatments with little or no added value ii. the negotiating power of MSs in setting prices	
Public health	Overall public health i. Availability of health technologies on the market ii. Access to medicines	

Themes for Economic impacts	Indicators	Benefits / losses
Costs The costs related to the processes	Variability in methods and processes currently employed by national health authorities across the EU; possible duplication of efforts; areas for improvement in consistency and transparency in the criteria used for decision making; what clinical and economic evidence is used in processes.	
Administrative burden	Administrative burden derived from processes: Overall administrative burden; repeated processes / products across European countries; time needed for process; complexity of processes e.g. HTA assessment processes	
Competitiveness of EU health technology sector	Competitiveness of SMEs; revenues for industry; predictability of national systems in Europe	
Innovation and research	Effect of the intervention on: research climate; innovation in the European market; predictability of the market; reduction in fragmentation	
International trade innovation and research		
Functioning of the internal market and competition	Fragmentation of the system in Europe; convergence of methodologies; attractiveness of the European market for industry	
Consumers	The availability of medical technologies for patients	
Macroeconomic environment	Overall economic growth; labour market	

Part 4: Motivational factors which act as barriers (negative motivators, challenges) and factors which act as facilitators (positive motivators, drivers) for collaboration between national health authorities for pricing and reimbursement

Themes (Category of motivational factors)	Factors which act as barriers (challenges)	Factors which act as facilitators (drivers)
Social Access to social protection and health systems, sustainable health systems, access to medicines		
Economic External factors arising from an economic factor or by a market event e.g. more intense competition, globalisation, market reaction, competitive advantage		
Behavioural Trust, ability or willingness to share information, resistance to change, mutual respect, ability to compromise, communication, personal interests		
Organisational Internal factors related to the form of organisation: supply chain problems, pressure from trading partners, flexibility, development of clear policy and guidelines		
Contextual History of collaboration		
Factors related to purpose Concrete attainable goals, shared vision, unique purpose, membership characteristics, sharing a stake in process and outcome		
Implementation climate Political and social climate		
Cultural Difference/similarities in goals and objectives, relationship, capacity to share risks, integration of key processes, flexibility of organisational system, compatibility of organisational culture		
Resources / physical Investments, financial resources, funds, staff, expertise, skilled leadership		

Figure 3.1 **The collated 'Framework' for the project covering Parts 1 to 4**

3.4 Identification of methods for acquiring the evidence on Member State collaboration for pricing and reimbursement from different sources of evidence

As seen in Chapter 2, evidence-based management entails the collection of evidence from the four different sources of evidence: scientific literature and empirical studies, organisation internal data, practitioners' professional expertise and stakeholders' values and concerns.

The researcher identified different methods for obtaining evidence for each of the four sources of evidence. The first step was to collate the evidence from documents which were already available. Three methods involved analysis of available documentation: analysis of published scientific literature from academic journals identified through searches in data bases; analysis of grey literature such as reports, websites, conference presentations etc. and the analysis of the 'Study on impact analysis for Policy Options for strengthened EU cooperation on Health Technology Assessment Final Report' (European Union 2017), 'the Study'.

The evidence from these methods was mapped across the different sources of evidence as shown in Table 3.3 below. This mapping and also the knowledge of the challenges being faced by ongoing initiatives for collaboration showed that the main gap in evidence which needed to be filled by a different method was obtaining primary evidence of a deep insight of the perspectives of practitioners from different Member States, who are the main players in the system for collaboration. It was thus decided that the researcher would get primary data to strengthen the evidence and a focus group discussion with practitioners involved in Member State collaboration was added as a fourth method for getting evidence for this research.

Table 3.3 **Mapping of the evidence collected through different methods with the four sources of evidence**

		Sources of evidence			
Methods		**Scientific literature & studies**	**Organisation internal data**	**Practitioner professional expertise**	**Stakeholder values and concerns**
1. Analysis of published scientific literature		X		X	
2. Analysis of grey literature	Various documents and reports	X	X	X	
	Websites and documents of collaborations		X		
	Conference proceedings		X	X	X
	Results of WHO interviews with members of the regional cooperations		X	X	
	Reports from stakeholder groups / organisations: patient organisation, industry				X
	Media reports		X		X
3. Analysis of Study on impact analysis for Policy Options for strengthened EU cooperation on Health Technology Assessment Final Report					X
4. Focus group with practitioners (primary data)			**X**	**X**	

3.5 Faculty Research Ethics Committee (FREC) Approval

Once the design of the project was planned and the methods for the collection of evidence were determined, the researcher submitted an application to FREC (Unique Form ID:682:29.012019-Patricia Vella Bonanno) in January 2019. 'Substantial issues' were identified during the filling of the self-assessment form and an application for FREC Review was subsequently submitted which included a detailed assessment. A copy of the Consent Form to be used during the focus group discussion was also sent.

The main issue identified during the detailed assessment related to the category 'other issues' included:

21b Conflict of interest: the student works as an Advanced Pharmacist Practitioner within the Ministry for Health in Malta and is involved in activity related to collaboration between Member State authorities for pricing and reimbursement of medicines. The student is also a Member and Secretary of the Valletta Technical Committee which is a regional cooperation involving ten Member States. The student has a PhD in the field of pharmaceutical policy, regulation and pricing and reimbursement and is a member of the PIPERSKA group and is involved as main or as co-author in a number of publications. The student will be using evidence obtained through research commissioned by the European Commission and by the WHO. The researcher may have contributed to some of these studies as an interviewee. The researcher will use mainly secondary date. The researcher is a participant in the system and it will be difficult to get primary data from some of the other participants from other countries. The participant may have access to certain organisational information which is confidential and will not be able to use organisational data which is confidential. The project may need to be embargoed. The field of study is quite sensitive because it involves communication and coordination between different Member States. Moreover there are also involvement and the interest of different stakeholders including the European Commission, the pharmaceutical industry etc. The politics of the

situation evolve and at times may be sensitive e.g. the vote on the Proposal for a Regulation on HTA at Council is very sensitive.

21c Dual role: The student has direct involvement in the system.

21h Other considerations: There are a number of meetings which were held under Chatham House rules. If the researcher needs to use information from these meetings this will be consolidated together in a manner where its source will not be identifiable. If needed, parts of the project will be embargoed.

The ethical approval for the project proposal was received from FREC on the 29th May 2019 (copy of the e-mail is attached at Appendix 1).

3.6 Methods for collection of evidence from different sources

3.6.1 Method for collection of evidence from published scientific literature

The first method was an analysis of published scientific literature. The researcher was guided by the methodology for systematic reviews, as much as possible.

Search terms were identified using the PICOC (Refer to section 1.4) as well as from the literature described in Chapter 2.

The following search terms were used:

Area	Search terms
Collaboration	Collaboration, cooperation, inter*, network; cross border; European;
Activities for pricing and reimbursement	Early dialogue; scientific advice; Health technology assessment; pric*; reimbursement; horizon scan*; procurement; real world data; pharm*; medicine
Attitudes	Attitude; belie*; perspective; critical success factors
Impacts	- benefit, - risk, loss,
Motivational factors Barriers and facilitators	- influencers - barrier, challenge, obstacle - facilitat*, motivat*, driver, bridge;

The search terms were run through different databases (MEDLINE COMPLETE (EBSCO); Pro Quest ABI/INFORM Global; Cochrane database of systematic reviews; EBSCO host; SCOPUS; PLOS ONE; Psychology and Behavioural Science Collection). A number of search strategies were conducted. Details of the search words and the search strategies in different databases were presented in Appendix 2. The PRISMA methodology for reporting of reviews (Moher et al. 2009) was used as a guide to present the literature review.

The inclusion criteria used for title and abstract screening included articles directly relevant to the subject of collaboration (or related terms); articles related to the different activities for pricing and reimbursement as presented in Model 1 (Figure 3.1 Part 1) and articles making recommendations for Member State (inter) collaboration in their recommendations.

The exclusion criteria for title and abstract screening were: articles which covered cooperative partnership and networking between different stakeholders within the supply chain; articles

focusing on techniques for evaluation, methodology, procedures for pharmaceutical activities; papers describing cases for a specific medicine or medicinal product; activities such as manufacturing and the supply chain; articles which covered technologies other than human medicines; papers covering activities outside the scope of this dissertation such as pharmacy practice, prescribing, guidelines, supply chain, integrated healthcare networks, community care; and articles before 1st January 2000.

The number of articles for each search strategy was identified. The articles were screened through title and abstract. Those abstracts which possibly fitted the criteria and were directly relevant to the subject of collaboration and the abstracts which were possibly relevant for the building of the general logic model and for the description of the problem in the introduction were identified. Further screening was done of the abstracts and further stratification was done.

Records were consolidated for the different search strategies, and finally all together for all the strategies. Duplicates were removed. Papers were sorted as follows:

a. Papers directly relevant to the subject of collaboration
b. Papers not relevant to collaboration but possibly relevant for the update of the Logic Model
c. Papers not relevant to the dissertation

For the abstracts which were considered directly relevant to the subject of collaboration the full papers were found as in the scheme below:

<table>
<tr><td>No. of abstracts directly relevant to collaboration identified through database searching (duplicates removed)
78</td><td></td><td colspan="2">Additional records identified through other sources
Other sources:
- References as part of reports
- Articles identified during search for full-text articles
7</td></tr>
<tr><td colspan="4">Total no. of records: 85</td></tr>
<tr><td colspan="2">No. of full text articles found: 84</td><td colspan="2">Abstracts without full text article
1 (abstract in English, article in German)</td></tr>
<tr><td colspan="2">Articles considered relevant during synthesis and included in the evaluation
45 full text articles and one abstract</td><td colspan="2">Full text articles excluded: 39</td></tr>
</table>

The selected articles were analysed and the information was presented using the ‘Framework’.

3.6.2 Method for analysis of grey literature

The term ‘documents’ will be considered to cover a very wide range of grey literature such as public documents, organisational documents, mass media outputs. Organisational internal data was mainly obtained through hand searches, searching in websites and from reports of the Member State entities for pricing and reimbursement activities and of the different regional collaborations. The researcher is a practitioner in the field and follows different activities and initiatives in this area and collects relevant documentation.

The researcher used only data which was intended for public use. There were many documents and the researcher tried to get as holistic and updated a picture as possible. The cut-off date for collection of documents was end of May 2019. The list of documents included in the analysis of grey literature is in Appendix 5.1.

3.6.3 Method for analysis of the 'Study on impact analysis for Policy Options for strengthened EU cooperation on Health Technology Assessment Final Report', 'the Study'

The researcher did an analysis of a report of the stakeholder consultation which had been conducted by the European Commission as part of the Better Regulation Exercise in preparation for the Proposal for a Regulation for Health Technology Assessment. This report was the final report of this stakeholder consultation: 'Study on impact analysis of Policy Options for strengthened EU cooperation on Health Technology Assessment (HTA), Final Report' (European Union, 2017). The report was published in August 2017 on behalf of the European Commission by Gesundheit Ostrerreich Forschungs-ind Plannungs GmbH, The London School of Economics and Political Science, and Sogeti. It was prepared for the European Commission through a contract with the Consumers, Health, Agriculture and Food Executive Agency.

The researcher did the analysis of this report by presenting the information in the report using the 'Framework' for this study (Refer to Section 3.3). As the evidence presented in the study was collected from different stakeholders, the specific stakeholder who submitted the information was also specified. While the scope of 'the Study' covered pharmaceuticals, medical technologies and other technologies; for this research only pharmaceuticals were considered.

3.6.4 Method for focus group with practitioners in the field

A focus group discussion was conducted. The researcher considered that practitioners in the field had an important role in the process and success of MS collaboration. It was considered important to obtain an insightful understanding of the different views of practitioners.

The main possible options for methods to obtain primary data for practitioner evidence were interviews, self-completion questionnaires or a focus group. The researcher was aware that the attitudes for collaboration for certain activities, particularly in relation to the Proposal for Regulation on HTA, were considered sensitive, political and were very diverse.

Different sources were consulted to decide on the choice of method for evaluation, for example Bryman and Bell (2011), Kitzinger (2001) and Woodford Guegan and Cook (2014). In their evaluation of success factors for international HTA projects, Woodford Guegan and Cook (2014) considered the strengths of different methods for obtaining information from stakeholders for their study. They considered that interviews could probe a subject to obtain rich qualitative data, but were expensive and could present difficulty to present the information. Focus groups also allow probing and the collection of qualitative data; however, they were considered expensive and it could be difficult to gather all participants in one location. Self-completion questionnaires were considered to eliminate the possibility of interviewer bias but they were considered impersonal and inflexible.

For this research, the focus group method was chosen because it was considered that a focus group would be more powerful to probe into the practitioners' views and the reasons for such views, particularly for sensitive topics. The focus group was considered to be able to use group interaction to elicit a wide variety of views, qualify positions with respect to particular issues and reveal dimensions of understanding which are not achieved by other techniques (such as interviewing where the respondents may choose to keep answers superficial). The focus group was considered to be appropriate to bring to the fore important and significant issues around a

topic and facilitate expression of ideas and experiences. Moreover, the focus group would give the researcher the opportunity to study how the practitioners involved collectively tackle and discuss a phenomenon and construct meaning around it, in the same way as would be required if there was collaboration between the practitioners.

The main difficulty which was envisaged was to get the participants from different countries to meet in one place. This was overcome by forming the focus group from participants from different Member States from within the same European organisation, and by making the focus group meeting coincide with a scheduled meeting of the organisation. The researcher was aware of the possible limitations if the participants of the focus group did not achieve a dynamic for discussion, or if the participants decided not to collaborate and was also aware of the difficulty if the interactions were overlapping, thus not allowing for clear recording.

The researcher convened a focus group discussion with practitioners from the field. A professional organisation which consisted of representatives from authorities and entities involved in pricing and reimbursement activities from different Member States was approached. For reasons of confidentiality the organisation is not named. The President and the Secretary of the organisation accepted to include this focus group discussion on the agenda of a scheduled meeting which took place in Brussels in April 2019, as a last item on the agenda.

A letter to participants and a focus group guide were prepared. The letter and focus group guide were circulated two weeks before the meeting through the Secretariat of the group where the focus group was held (Refer to Appendix 3).

The focus group meeting took place in the premises of the European organisation in Brussels. Five of the participants at the meeting left just before the focus group started. Thirteen of the participants of the meeting stayed for the focus group discussion. At the beginning of the focus group discussion the participants were quite concerned with the fact that they represent their organisations and with the anonymity of their replies. It was agreed that the researcher was to

record the discussion, prepare a transcript and circulate it to participants, and then participants were to send any feedback and their consent. During the discussion some participants contributed actively, while others kept a low profile. There was good response and there was open discussion. The participants had diverse opinions on a number of aspects, and there were topics where there were clear opposing attitudes and critical views of certain activities.

A transcript of the focus group was prepared and circulated to the participants to give feedback and to give their consent. Only four of the participants gave feedback following the circulation of the transcript. Three participants agreed with the transcript and consented to the use of the reply of the focus group for the project. The fourth respondent did not consent to the use of the transcript because the respondent did not have the approval of the organisation he worked for to participate in the focus group. The researcher did not publish the transcript of the focus group discussion in this dissertation. Some general inferences and observations were made.

3.7 Presentation of the evidence generated from the different methods using the 'Framework' built in Section 3.3

The 'Framework' built in Section 3.3 was used to present the evidence generated from the different methods. The data collected from the analysis of published scientific literature was presented in Appendix 4, the data collected from the analysis of grey literature was presented in Appendix 5.2 and the data collected from the 'Study on impact analysis of policy options for strengthened EU cooperation on health technology assessment, final report' was presented in Appendix 6. As the transcript from the focus group could not be published the evidence from this method was not presented using the 'Framework'. The evidence from each of the methods was thematically placed in the 'Framework' according to the themes. The information was placed "telling it like it is" as described by Bryman and Bell (2011, p. 572), refer to Section 3.3. Care was taken to include the context and the stakeholder perspective involved so as not to

introduce bias due to interpretation. For certain themes specific indicators were included to give more detail and specificity. The 'Framework' was found to be comprehensive to represent the evidence collected from the different methods. The evidence collected for each method was appraised (refer to Chapter 4) and aggregated all together (refer to Chapter 5).

3.8 Limitations of the methodology

The focus group discussion entailed a lot of work and required that the researcher had to go to Brussels for the session. Due to political sensitivity of the topic discussed, the results of the transcript could not be published in the project due to lack of consent by all the participants. However, the exercise in itself and the outcome from it were still highly informative and gave great insight. There were still a number of conclusions which could be made. In view of the fact that the transcript was not included, this dissertation does not need to be embargoed.

Due to time constraints and the amount of work involved in the compilation and aggregation of the evidence, it was not possible to enrol an independent expert to validate Step 4 Aggregation in order to reduce researcher bias. It is recommended that this step is done as a next step, as a follow-up to this study. All the raw data was placed in the Appendices and can be used.

The fact that the researcher is also a practitioner could introduce researcher bias. Care was taken to keep as objective as possible and to clearly state what was from the evidence and what was the opinion of the researcher.

3.9 Plan of the project over time

The Gantt-chart in Figure 3.2 presented the activities of the study over the time period October 2018 to end August 2019.

Action	Oct 18	Nov 18	Dec18	Jan 19	Feb 19	Mar 19	Apr 19	May 19	Jun 19	Jul 19	Aug 19
Project proposal - **Asking**											
Literature review											
Submission of Faculty Research Ethics Committee (FREC) application											
Acquiring Building of 'Framework' for formulation of tools for collection of evidence and collection of evidence using different methods											
Focus group with practitioners											
Appraising the evidence											
Aggregating the evidence											
Applying and Assessing											
Write up and corrections											

Figure 3.2 **The Gantt-chart for the study**

3.10 Summary

The design for the project based on the model by Barends and Rousseau (2018) was considered to be systematic and logical. The 'Framework' was found to be a good tool for the collection and presentation of the evidence from the different methods and was comprehensive. The collection of the evidence was very time consuming and laborious. It would not be feasible to go through such an intensive process for routine management issues in practice.

Chapter 4 presented the appraisal of the evidence and Chapter 5 presented the aggregation of the evidence.

4. Appraisal of the Evidence

4.1 Introduction

Barends and Rousseau (2018, pp. 2-5) described 'evidence' as "information, facts or data supporting (or contradicting) a claim, assumption or hypothesis". The authors explained that a fundamental principle of evidence-based practice is to appraise the evidence to focus on the best available evidence which is judged to be trustworthy and relevant. The authors considered that the evidence can be "presented in a variety of forms and come from different sources including: scientific research, people including professional experiences, organisational practices and organisational metrics and stakeholders".

As explained in Chapter 3, four methods were adopted in this study to acquire evidence: appraisal of scientific literature, appraisal of grey literature, evaluation of the 'Study on impact analysis for Policy Options for strengthened EU cooperation on Health Technology Assessment Final Report', 'the Study' and a focus group with practitioners in the field. As described in Chapter 3 these four methods were used to 'Acquire' the evidence (Step 2 in the process of the study as detailed in Table 3.1).

Chapter 4 described the next step of the study: Step 3, 'Appraisal of the evidence'. The evidence acquired from each of the four methods was appraised. For each of the methods the sourcing, trustworthiness and relevance of the evidence was presented and discussed.

4.2 Appraisal of the evidence from published scientific literature

As described in Chapter 3, the evidence gathered from the published scientific literature and the full list of articles used for the purpose were presented in Appendix 4.

The process for stratification of the information from published scientific literature into the themes of the set 'Framework' was lengthy and very laborious. One additional title was included: 'Behavioural' with the list of impacts.

The classification of concepts was subjective and care was taken to keep it as standardised as possible. At times the same concept could be fitted under different alternative themes depending on the perspective, the specific aspect and point of view considered e.g. IT infrastructure can be a challenge and can be a benefit, depending of the perspective. At times it was difficult to determine where to classify certain concepts which could be considered as a benefit or as a motivator. If the intervention of collaboration had already started it was generally classified as a benefit while if the activity had not yet started it was presented as a motivator. It was also difficult to classify 'critical success factors' and the classification adopted depended on the perspectives taken by the author of the source of the evidence. In general, critical success factors were not quantified or qualified and the impact of collaboration on the critical success factors was not stated. Critical success factors were listed according to the perspective taken, as motivators (e.g. building trust between countries) or as recommendations.

For this review of the scientific literature, articles were collected as from the year 2000. Generally the articles up to 2014 gave more of a historical background and considered international collaboration as a wishful recommendation, with the exception of the EUnetHTA exercise which was considered primarily for the generation of guidelines and tools to be used by the MSs.

The papers were chosen on the basis that they fit the inclusion criteria. There were different types and quality of papers. No systematic reviews were identified in the literature review. In some papers collaboration was the main, or one of the main, objectives of the paper and these papers were considered very valuable. Some papers were specific to the measurement of opinions about collaboration, used clear and specific methodology for measurement of opinions and reported the results through structured titles/themes. Different methodologies were used for the purpose of getting opinions. Some papers gave results from questionnaires or other methods within the paper either as the raw data or else in a collated manner. The presentation of raw data within a paper enabled direct evaluation of the results by the reader, rather than just having access to the reporting and the interpretations given by the authors of papers. The interpretation between the authors of the paper and the reader could be different. In other papers the opinion or recommendation for collaboration was made in an indirect manner.

The Critical Appraisal Skills Programme (CASP) checklist for qualitative research was used to evaluate the quality of the papers (Critical Appraisal Skills Programme 2018). Five papers had clear methodology (usually involving both quantitative and qualitative information) and results were presented in a comprehensive manner. These papers classified well using the CASP tool. Woodford Guegan and Cook (2014) used questionnaires for project participants and for external stakeholders to evaluate the experience of EUnetHTA first Joint Action and gave the results in a global manner. Kleijnen et al. (2015) gave detailed results from semi-structured interviews for the evaluation of opinions on collaboration for REA with representatives from eight HTA organisations. The results from this paper, which were published in 2015, were very congruent with the responses of the Member State (MS) Representatives in the 'the Study'. Rajan et al. (2011) evaluated motives, enablers and barriers to the promotion of health technology assessment mainly through a two-phase study using a questionnaire and compared responses on enablers and the prioritisation of enablers across context and cultures. Henshall et al. (2012) summarised the main points from presentations, discussions among attendees at

conferences and produced an advanced background paper at an international meeting. Panteli et al. (2015) extracted information from online sources.

Three papers, Ferrario et al. (2017); Vogler et al. (2017) and Vella Bonanno et al. (2019), were 'perspectives' papers. These papers did not adopt a standard method but involved a presentation of ideas and alternative opinions. It was difficult to classify such papers using the CASP tool – e.g. it was not possible to comment on the validity of the results given that these were mainly opinions. On the other hand, these types of papers were very enlightening in terms of giving insight and bringing out perspectives which went beyond just facts and direct questions. Thus for the purpose of this study these three papers were considered as the most useful for the generation of evidence. Two of these perspectives papers were written jointly with staff from WHO and showed perspectives about contemporary issues which were impacting outcomes related to medicines: Vogler et al. (2017) dealt with policies for pricing and reimbursement and Ferrario et al. (2017) gave perspectives on strategic procurement. Vella Bonanno et al. (2019) gave perspectives on the 'Proposal for a regulation on health technology assessment' from thirty-six policy makers, payers and academics from the field of HTA. It is pertinent to declare that the researcher was the main author in this paper.

Eight papers reported actual experiences of collaboration and gave a description of personal or third-party experiences of practitioners who worked in organisations. Some papers went to the level of reporting the achievement or progress of the collaboration. These papers were of high quality in relation to the CASP tool and had clear objectives related to the collaboration through existing projects, mainly the EUnetHTA project. These papers were presented in a structured way with clear methodology and five of these papers were published in the same journal: 'International Journal of Technology Assessment in Health Care'. The biggest experience in collaboration was in activities of the EUnetHTA JA projects. A number of papers were published between 2010 and 2014 coinciding with the first EUnetHTA Joint Action (JA 1), which dealt with the development of tools and the EUnetHTA Core Model: Quentin et al. (2009); Lo Scalzo et al.

(2014); Woodford Guegan and Cook, (2015). The highest volume of papers with experience on collaboration concerned relative effectiveness assessment (REA) and these papers were mainly published between 2014 and 2016 at the same time as the second EUnetHTA JA: Huic et al. (2013); Woodford Guegan, Huic and Teljeur (2014); Kleijnen et al. (2014); Panteli et al. (2015); Mayer, Ettinger and Nachtnebel (2017). The paper by Nachtnebel et al. (2015) gave a deeper insight and brought out points about the challenges with the adoption of the HTA assessments at the national level. The paper by Erdos et al. (2018) gave a more recent update and was highly insightful.

A number of papers focused on specific activities related to pricing and reimbursement (refer to Table 4.1). These papers often made no specific recommendations for collaboration as a means for the improvement of the activity. In these papers it was difficult to apply the criteria of the CASP tool directly. The objectives of these papers were the activities and not collaboration. There was a pattern of activities over time. There were activities with good build up of experience (e.g. REA), while some activities such as real-world evidence gathering and disinvestment were still being developed, defined and described.

Four papers described initiatives for national HTA in different countries, mainly at the time where the specific country was taking up initiatives for improvement / development of their national system e.g. Belgium, Cleemput and Van Wilder (2009); Hungary, Kalo et al. (2013); Greece, Souliotis et al. (2016) and Slovakia, Tesar et al. (2017). These papers were mainly descriptive and made recommendations for collaboration in the future.

Four papers compared differences and similarities in considerations and recommendations by HTA agencies in different countries during HTA evaluations: Kleijnen et al. (2012); Oyebode et al. (2015); Panteli et al. (2015); Allen et al. (2017); and for the use of real-world data in HTA Makady et al. (2017) as a case to make justification for recommendations for collaboration. One

paper described the benefit of the use of the HTA Core Model by a pharmaceutical company (Ducournau et al. 2018).

Table 4.1 Activities of pricing and reimbursement covered in the published literature

Activity for pricing and reimbursement	Papers specifically covering this activity
generation of evidence and sharing of information for HTA	Quentin et al. (2009); Rajan et al. (2011)
orphan diseases	Denis et al. (2010); Mincarone et al. (2017)
disinvestment	Henshall and Schuller (2012)
external reference pricing	Leopold et al. (2012); Vogler et al. (2017)
joint procurement	Huff-Rousselle (2012)
the experiences of WHO countries in joint procurement	Ferrario et al. (2017)
the evidence-based approach to decision making	Panteli et al. (2015)
horizon scanning	Douw and Vondeling (2006); Wild and Langer (2008); Nachtnebel et al. (2016); Oortwijn et al. (2018)
managed entry agreements	Bouvy et al. (2018)
real-world data	Garrison et al. (2007); Chatzidionysiou et al. (2018); Eichler et al. (2018); Geldof et al. (2019); McAuslane et al. (2019)
use of data to create a 'learning healthcare system'	Eichler et al. (2018)
prices for orphan medicines	Luzzatto et al. (2018)

Some papers included in this review were used to update the Logic Model, for example: horizon scanning systems Douw and Vondeling (2006); Wild and Langer (2008); reference pricing Leopold et al. (2012); horizon scanning Packer et al. (2015), experience of HTA agencies Loblova et al. 2016). Few papers specified outcomes, for example Zaprutko et al. (2017) measured affordability.

Some authors were involved as main authors and / or co-authors in more than one paper. This led to a level of standardisation in the presentation of the papers e.g. the papers on the outcome of EUnetHTA Joint Actions.

The inclusion and exclusion criteria for publications were listed in Section 3.6.1. Reference price systems were considered as initiatives for MS collaboration because there were organised systems for exchange of information on prices and on policies. The highest reason for exclusion of papers was in cases where papers dealt with or recommended collaboration between different stakeholders (interdisciplinary collaboration) e.g. payers, life-sciences companies, industry, stakeholders within the supply chain; and did not cover international cooperation between MSs. One paper was excluded because it considered collaboration across healthcare services in councils within the same country. Another reason for exclusion of papers was where papers only considered countries outside the European Union. The EuroScan network was not considered as a MS collaboration for pricing and reimbursement because it consisted of an international network of publicly funded agencies doing horizon scanning which were not necessarily national agencies for pricing and reimbursement but included different types of agencies, such as public health agencies. Members of EuroScan were often service providers for Pricing and Reimbursement agencies (Packer et al. 2015). EuroScan was included in the Logic Model.

A number of papers considered technical aspects of pricing and reimbursement but did not consider collaboration between Member States. Examples of aspects considered included

medicines adaptive pathways, pricing frameworks, aspects of decision making for HTA (e.g. multiple criteria decision analysis, sequence of activities for reimbursement decisions), personalised medicines, medicines availability and affordability and big data.

A number of papers covered comparison of the requirements, similarities and differences between reimbursement evaluations in different countries. These papers were included if they linked these aspects to recommendations regarding collaboration. There was increased literature about experiences of disinvestment in different countries.

Documents which were not published in peer-reviewed journals (e.g. the Policy Briefs published by the European Observatory on Health Systems and Policies) were not included with the published scientific literature but were included as grey literature (Refer to Section 4.3).

4.3 Appraisal of the evidence from grey literature

Details about different types of documents used as grey literature and examples of the specific documents for each document type were presented in Appendix 5.1. The evidence gathered from the grey literature was collected and presented within the 'Framework' (refer to Appendix 5.2). In addition to the information which was compiled in the 'Framework', more general information on two specific topics was presented: ongoing cross-country regional co-operations and an update on the Proposal for a Regulation on HTA (refer to Appendix 5.2).

The grey literature was constituted of different types of documents. Table 4.2 presented a collation of different types of documents used as grey literature and the main sources of evidence served by the different types of documents. Details about each type of document and examples of each type of documents were presented in Appendix 5.1. As the researcher was a practitioner and also an academic researcher in the area, she had access to sources of grey literature, particularly to documents which were published, but not widely distributed.

It was important to note the time when the information was published because issues evolved continuously. The stakeholder concerned was also of relevance because different stakeholders had varied perspectives. The documents from the grey literature were very useful to study different perspectives and in particular in-depth insights from different stakeholders; although in some cases the evidence could not be directly linked to a specific stakeholder.

As shown in Table 4.2, a number of documents from the grey literature represented the perspectives and priorities of organisations: individual member states or collective opinions. The Policy Briefs gave a comprehensive and balanced overview of the relevant topic. Policy briefs mainly adopted the Member States' perspective/s. The Council of the European Union represents the Member States and thus Council documents gave the position of Member States. Council Conclusions gave joint positions from Member States. Conferences and conference proceedings were particularly relevant because they gave an overview of a topic and also provided an insight about evidence from sources of information (such as organisational information or stakeholder perspectives) which was not published in scientific literature (unless the conference proceedings were published as a Supplement to a Journal). The evidence from the international conference organised by INFARMED and WHO (INFARMED 2018) was of particular good level and covered the topic very comprehensively. The involvement of WHO helped to get the best contemporary presenters on board. The proceedings of this conference were available online but were not openly accessible.

Table 4.2 **Different types of documents used as grey literature and the sources of evidence served**

Type of document Refer to Appendix 5.1 for details and examples of this type of document	Scientific Literature & studies	Organisation internal data	Practitioners' professional expertise	Stakeholder values and concerns
Policy Briefs	X	X	X	
Council of the European Union e.g. Council Conclusions		X		
Research study on impact and benefits of cross border collaboration in WHO European region, Vogler and Suleman (2018)		X	X	
International Conference 'Facing the Challenges: Equity, sustainability and access' (INFARMED 2018)		X		
Information from the Regional cross-country collaborations (websites, press-releases)		X		
Interdisciplinary Platform on Benefit Assessment				X
Innovative Medicines Initiative				X
On-line magazines		X		X
Patient Associations				X
Industry opinion on cross-country collaborations				X

The media gave information and insights of happenings which would otherwise have remained hidden. Often journals used the tactic that they reported what they got to know from someone (e.g. an insider of the organisation) who was not allowed to divulge information.

A few of the documents included in the grey literature were prepared and organised according to systematic methodology; these included studies contracted out through bodies such as WHO, for example the 'Research study on impact and benefits of cross border collaboration in WHO Europe region' by Vogler & Suleman (2018) and the Policy Briefs. Vogler and Suleman (2018) presented 'facilitating factors'. In the template for this dissertation this theme was not included and facilitating factors were included with the motivators. The classification depended on whether the initiative for collaboration started, and there was experience with it, or whether it was still being considered. The same issue was also experienced during the analysis of the published scientific literature.

From the evidence it was difficult to clearly qualify and quantify the achievements and outcomes from the activities of the MS collaboration. In actual fact there were few significant achievements beyond sharing of information.

4.4 Appraisal of the evidence from the 'Study on impact analysis for Policy Options for strengthened EU cooperation on Health Technology Assessment, Final Report', 'the Study'

The 'Study on impact analysis for policy options for strengthened EU cooperation on health technology assessment, Final report' (European Union 2017), referred to as the 'Study', was contracted out to a consortium composed of practitioners and academic institutions thereafter collectively referred to as the 'authors'. This was the most robust study identified which measured the perceptions on impact of MS collaboration. It contained feedback from different

stakeholders. One main limitation with regards to 'the Study' was that it was limited to only one activity: health technology assessment.

In terms of methodological criteria, 'the Study' used robust methodology and the methods used to collect evidence were well documented. The main objective of 'the Study' was to evaluate sustainable cooperation for HTA beyond 2020. 'The Study' was sponsored by the European Commission and the authors had a specific contract with CHAFEA; thus there could be a conflict related to the opinion of the sponsor. The authors were 'experts' within their organisations or in academia and took up contractual work on behalf of their organisations. 'The Study' included a constant peer review by an expert panel in the field as a method for validation. 'The Study' used the Policy Options (PO) set by the Commission (refer to Table 1.1). The authors used the European Commission's Better Regulation Guidelines and methodology (refer to Section 2.7.2). The main method for collection of data in 'the Study' was through collection of information by use of structured questionnaires which were filled by the stakeholders. A number of additional methodologies e.g. focus groups, interviews, follow-up discussions and literature were included to gain an in-depth insight, to supplement the responses of the questionnaires and to validate the information. Kappa score agreement levels were established to quantify the level of agreement. Multiple criteria analysis was used for evaluation of the data. A data plausibility check was carried out by the authors, which included test for elimination of duplicated responses, comparison of usage mode, comparison of standard deviation and calculation of inter-correlation coefficients. A quantitative measure of the impact was done. For the cost prognosis the authors did sensitivity analyses to investigate uncertainties; assumptions of the future number of joint outputs were made by the authors. The methodology and analytical approach of 'the Study' were well described by the authors.

Detailed analysis of 'the Study' revealed some limitations with 'the Study' and its methodology. 'The Study' was commissioned by the Commission and the policy options (PO) for the Proposal on HTA (Table 1.1) were actually set by the European Commission prior to 'the Study'. Thus the

Commission pre-conditioned the options with its criteria and did not present a blank drawing sheet. The authors of 'the Study' adopted the POs and conditions set by the Commission. 'The Study' did not consider an implementation mechanism without EC funding because the Commission considered that intergovernmental collaboration without input from the EU was strictly the responsibility of the Member States.

The authors of 'the Study' expressed their collective opinion about specific issues in quite a definitive and specific manner; and this could bias the output of 'the Study'. In the presentation of the results some raw data was given including collective results from the questionnaires and a summary of the information gathered through the focus group. When the information on the results was presented in 'the Study' as a write-up there was a lot of input by the authors but not all of the raw data was represented. Some of this input by the authors was considered to introduce bias in the report of 'the Study'.

The presentation of the results was based on the Better Regulation framework of impacts and the impact analysis focused on impacts. The information was presented in a way which placed much more emphasis on the economic impacts rather than the social impacts. This reflected the priorities of perspectives of stakeholders, where the industry was much more concerned with economic rather than social impacts.

The response on impacts was presented according to different stakeholder groups. Not all stakeholder groups responded. The pharmaceutical industry and public administrations provided most of the feedback. The point of view of these stakeholders (particularly of the industry, where there were most respondents) overpowered the results and also the recommendations. The recommendations of these two major stakeholders were not fully in congruence. The recommendations of the industry won and were most reflected in the final legislative proposal. Not all countries responded to this study and thus the opinion of the MSs

as reported in ‘the Study’ did not reflect certain opposing views which were later expressed during the discussion of the Proposal for a Regulation on HTA at the European Council.

The participation in the survey by patient organisations was far too low and the authors decided that they could not analyse the feedback from the patient response. Nothing was included on the patient response in the summary of the results. The detailed report had some information on the perspectives of patient associations, where concern was expressed about uncertainty due to conditional approval. This response was very significant and very contrasting to the feedback by the industry.

The different stakeholder groups had conflicting perspectives. The information was presented in a way where there was much more emphasis on the economic impacts rather than the public health impact. This reflected the volume and power of the response by the industry.

This contrast in responses of the stakeholders was most visible through analysis of the detailed responses in the results. This analysis was very laborious and it is quite unlikely to be done in routine practice. When ‘the Study’ was published and the researcher had gone through it as a practitioner, she had mainly read the summary and the conclusions (probably as most busy practitioners do) and following this analysis she realised that as a practitioner she had missed out on important details.

4.5 Appraisal of the evidence from the focus group with practitioners in the field

The method for the focus group with practitioners was reported in Section 3.6.4. The organisation identified for the focus group was an umbrella organisation for practitioners from the field of pricing and reimbursement from different Member States. It was one of the biggest organisations of its type and represented large and small countries from all over the EU. It was

decided to conduct a focus group with the practitioners in order to achieve in-depth insight into certain issues related to Member State collaboration (refer to the mapping of the evidence and methods in Section 3.4).. The focus group was conducted at the periphery of a general meeting of the organisation in order to ensure participation from different members. There were 18 participants at the meeting of the organisation; of these 13 stayed on for the focus group discussion.

Some participants asked for postponement of giving of consent to after approval of the transcript of the focus group. Only four the participants gave consent after the circulation of the transcript and thus the transcript was not published in this dissertation.

The researcher made some observations on this method. The practitioners worked in national organisations and found difficulty in separating their personal perceptions from those of the organisation which they worked for; in fact they considered that they represented their organisation and could only give the perspective of their organisation. At first the participants were hesitant to speak about the topic of collaboration on HTA because they considered that this topic was sensitive and political, particularly in view of the discussions on the Proposal on a Regulation on HTA which at that time was being discussed at Council. Although the focus group guide was circulated well before the interview, some participants felt that they did not have a mandate to discuss the themes openly. Some participants wanted to discuss the content (themes) of the focus group guide during the meeting. The moderator made it clear that she would not force any participant to discuss any theme and would not conduct a *tour de table; the* participants were free to discuss at will.

The interaction between the moderator and the participants of the focus group required communication skill. The researcher had previous experiences of chairing or participating in meetings between practitioners from different countries and was therefore conscious of the defensive and ‘aggressive’ reactions adopted when practitioners felt uncomfortable or

threatened. The participants agreed to proceed with the discussion. The discussion was quite tense in the beginning. The moderator tried not to interfere in the discussion so as not to bias the content and the flow. Once the participants realised that they were not going to be forced to speak when they were uncomfortable to speak, they adopted a more relaxed approach and there was a good sequence and flow of interventions.

The interaction between the participants of the focus group was at times complementary and at times more argumentative and challenging. Certain moments were tense and sensitive. The participants were recruited from a naturally occurring group; they formed part of an organisation and they were experienced with collaborating, mainly on the sharing of information about different policy aspects. The participants knew each other well through their meetings and had experience of discussion and debate between themselves.

The topic of the Proposal for a Regulation on HTA was not discussed. Everybody knew that there were divergent positions among the organisations of the participants on the Proposal on HTA and the group avoided getting into conflict on this theme. It was evident that on the political level there were divergences of opinion in the same way as were expressed during discussions at Council. There was a divide mainly with respect to the attitude towards collaboration, particularly whether this should be voluntary or mandatory. During the focus group discussion views supporting voluntary collaboration were vociferous; the mandatory attitude was not openly expressed.

There was a general positive consideration on collaboration for the other activities for pricing and reimbursement such as horizon scanning and collection of real-world data, although this discussion was kept at a technical level. There was a divergence of opinion on the experience and success of regional collaborations. Some participants came from countries which were involved in a regional collaboration while some participants were from countries that were sceptical of such collaboration. The discussion about the regional collaborations was quite

challenging. There were times where the moderator gave examples from her experience within the Valletta Technical Committee to reaffirm the similarity of the experiences between the different collaborations, particularly with regards to the challenges being faced by the regional collaborations. There was very in-depth insight regarding the politics and the challenges being faced in the interaction between the industry and the Member States within the regional co-operations. Participants were open about the different approaches and perspectives on collaboration between MSs. There was also a clear demarcation between the approach adopted depending on the size and resources of the country. Critical views on the achievement of progress and the outcomes of the regional collaborations were expressed.

The issue of sharing of sensitive information was highlighted and this mainly related to information about products and conditions of managed entry agreements when different countries have discussions with the industry on a national level. The participants of the focus group did not consider changing the current situation of lack of transparency of prices.

The interaction between the participants enabled insight into the respondents' attitudes, priorities, language and framework of understanding of collaboration. Different respondents gave their view point depending on the perspective and priorities of their countries. Countries that had established systems for pricing and reimbursement considered limited benefits from collaboration, while smaller countries considered specific benefits from collaboration to overcome the limitations of their size, market volume and low level of resources and expertise.

The participants of the focus group recognised and appreciated the fact that this exercise was a one-off opportunity to discuss such a sensitive and political topic. In fact they specifically mentioned that they had never discussed this topic. However, the participants were concerned with the release the transcript of the discussion.

4.6 The balance and coverage of the evidence

The mapping of the evidence available through the different methods for the different sources of evidence as shown in Table 3.2 was generally achieved. The presentation of the information from the focus group was limited, as publication of the transcript and of quotes was not conceded to by the participants, the fact that there were these reservations showed that the focus group discussion brought up information beyond what was usually placed in the public domain.

There was an imbalance in the publication of evidence. A lot was published about the Proposal for a Regulation on HTA, but less was published regarding certain new activities. The grey literature gave the widest range and deepest insight of different activities. The scientific literature concentrated on certain topics such as the work of EUnetHTA and real-world data but other activities, particularly from the organisational perspective, were not covered in this source. The generation of evidence came in waves, for example the concept of real-world data in response to conditional marketing authorisation was still evolving and the evidence followed the same patterns.

Certain seminars and meetings, particularly those organised at the organisational level, were considered as confidential or were carried out under Chatham House rules. Confidential data, such as minutes of meetings, was not used in this dissertation. Because of the sensitivity of the focus group discussion, the organisation concerned was not named.

The field of study was very sensitive because it involved attitudes and perceptions on collaboration between Member States, which was a political topic. Moreover there were different interests, perspectives and powers of different stakeholders including the Member States, the European Commission, the pharmaceutical industry, patients, healthcare professionals etc.

The study covered real-life situations and organisations which were continuously in flux. The study was carried out through an iterative process. The politics of the situation in relation to Member State collaboration and the external environment evolved during the course of the project. By the date of submission of this research, end August 2019, the vote on the Proposal for a Regulation on HTA, was not taken by Council.

From the aggregation of the evidence from different sources it was evident that some individuals and / or organisations participated in more than one initiative, publication and/ or study, on an individual basis and/or as part of consortia. Some individuals or organisations were considered as 'opinion leaders' and were very influential in the generation of evidence and in the driving of actions and initiatives. Certain activities such as projects of the Innovative Medicines Initiative or co-operations between different stakeholders could involve collaborations which served to change the balance in relationships and possibly reorganised the power between stakeholders.

4.7 Summary

Having evidence generated from different sources resulted in a much wider coverage of evidence and of perspectives of stakeholders. The amount of evidence about different topics differed depending on the interest and perceived impacts of the topic and the power of the stakeholders involved / affected. There was a lot of evidence on the activity of HTA and minimal evidence on other activities such as horizon scanning and joint negotiation. The scientific literature was limited in the extent of coverage and depended mainly on the interests of the people who took the initiative to publish, what they achieved or what they intended to do, according to their priorities. Although grey literature is generally considered as lower quality of evidence in terms of the hierarchy of evidence, for the purpose of this project it proved to cover a more holistic picture and was particularly useful to cover organisational insights and

professional opinions. The media was specifically useful to uncover the sore points and to bring them to light. The media was like a balance check for the evidence, although it was still biased. While 'the Study' was robust and comprehensive in terms of methodology, the final message did not present the holistic picture and reflected mainly the opinion of the stakeholder group where there were the most responses. The focus group discussion was probably 'too good' a method to bring out the issues, so much so that the participants decided to block it. This gave an indication of what may actually happen in reality, and with the exception of the media (where there is still an element of lobby and alliances); the evidence which gives too much insight of reality may tend to get blocked.

Generation and processing of the evidence was very time consuming and needed a lot of dedication. It would be difficult to generate such a lot of evidence to address decision making in routine practice. This methodology would probably be limited to very important decisions, as were the decisions on initiatives for Member State collaboration for pricing and reimbursement.

This appraisal of the different sources of evidence was used to set the calibration and importance of the evidence for decision making. The aggregation of the evidence was presented in Chapter 5.

5. Aggregation of the Evidence

5.1 Introduction

The evidence was gathered through different methods: analysis of the scientific literature, analysis of grey literature, evaluation of the 'Study on impact analysis of Policy Options for strengthened EU cooperation on Health Technology Assessment' 'the Study', and the focus group discussion. The raw data from the methods was presented in Appendices 4, 5.2 and 6. This chapter presented Step 4 in the process for evidence-based management: 'the aggregation of the evidence' to represent a final consolidated picture (Refer to Table 3.1). This step of aggregation of the evidence in evidence based management methodology was equivalent to what in a conventional dissertation would be presented in results and discussion of results.

5.2 Method for aggregation and presentation of the evidence

Aggregation involves the weighing and pulling together of the evidence (Barends & Rousseau 2018). The process sought to cover the different sources of evidence as comprehensively as possible. The level of corroboration of the evidence was evaluated and some gaps in evidence were identified. The level of robustness of the evidence was considered to give weight in prioritisation and in the determination of the impact of the different evidence. Perspectives by different stakeholders were noted and power mapping of stakeholders was done. The aggregation of the evidence was presented as a structured narrative. The 'Framework' presented in Figure 3.3, with its themes and indicators, was used to give a structure to the aggregation and to ensure address of the Research Questions as set in Section 2.7.

This aggregation exercise was carried out by the researcher. The researcher prioritised the information which was directly related to Member State (MS) collaboration between pricing and reimbursement authorities. Care was taken to minimise subjective interpretation and selection of evidence. As this aggregation was based on the raw data collected in the Appendices, this was the second round of classification of the evidence under the relevant themes by the researcher, and some repositioning of the evidence was made. The method from which the evidence was obtained was noted to support cross reference to the relevant Appendix. The methods were referenced as follows: SL – scientific literature; GL – grey literature; SIA – Study on Impact Analysis; FG – focus group.

Validation by a person other than the researcher was recommended but this was not possible due to time constraints. This validation should include verification that the relevant evidence from the Appendices was transferred to this Chapter and that there were no changes in the interpretation. It is recommended that validation will take place at another phase of the project either by another researcher or by co-authors if the evidence is used for publication of a paper.

5.3 Summary of the evidence for the updated Logic Model for the system of pricing and reimbursement (Model 3)

The evidence on the different processes for pricing and reimbursement from the different methods was used to update the original Logic Model (Model 1) which was presented in Figure 3.1. The final updated Logic Model (Model 3), included the updates with the new evidence, and was presented in Figure 5.1. The updates to Model 1 which were derived from scientific literature were highlighted in yellow while the updates derived from grey literature were highlighted in grey.

There were a number of changes in the process for pricing and reimbursement, including collaboration between pricing and reimbursement authorities, which was a relatively new concept. More recently there was a high level of initiative for 'coordinated collaboration alongside the life-cycle' (Eichler et al. 2018; Vogler, Paris and Panteli 2018) and this required collaboration between different stakeholders both at national level as well as across countries. The major updates to the Logic Model for Pricing and Reimbursement were listed in Table 5.1 and presented in Model 3 in Figure 5.1.

Table 5.1 Major updates to the Logic Model for the system of pricing and reimbursement

Section of the Logic Model	Main updates of evidence
Inputs	Health technology assessment agencies in Europe were in three streams: forerunners, which were well-established agencies, mainstreamers and non-adopters (SL). Some agencies contracted out horizon scanning from horizon scanning systems, while others set up their own systems (SL). There were regional collaborations between pricing and reimbursement authorities and other collaborations such as EUnetHTA, which functioned together to different extents (SL).
Activities	The term 'joint scientific consultation' was being used in recent literature instead of early dialogues; horizon scanning was associated with needs assessment (GL). There was increased emphasis on coordinated generation of real-world data and optimisation and disinvestment (SL). Needs assessment involved data collection at country level to inform prioritisation and research and development (GL). New flexible access and reimbursement pathways were being considered to decrease uncertainty due to accelerated marketing authorisations and address return on investment (SL). External reference pricing was applied in most European Countries.

	The PPRI network was a network where P&R authorities exchanged pricing information (SL). Financial managed entry agreements (MEAs) were commonly used in Europe, but outcomes-based MEAs were not frequently used for products with conditional marketing authorisations (SL). A new term "managed exit" was connotated and involved optimisation i.e. assessment and re-assessment of a technology and disinvestment (SL). In 2018 and 2019 there was a surge of literature on the motivation for collection of real-world data through the medicinal product life-cycle due to the increased use of adaptive pathways (SL).
Processes	Distinction was made between assessment of scientific evidence and appraisal. Assessment of scientific evidence is done by scientists and includes relative effectiveness assessment (REA) of a medicine as compared to other treatment. Appraisal for reimbursement is done by committees (SL, SIA). There was also distinction between REA and joint full HTA with economic evaluation (SIA).
Outputs	EUnetHTA generated tools, methodologies and the HTA Core Model (SL). There was heterogeneity in HTA roles, methods and processes across countries (SIA).
Outcomes	There were significant differences in access, affordability and availability to medicines across Europe (SL). There was lack of collaboration on the prices of medicines (SL, FG). While availability of medicinal products was always considered as a major public health outcome, there was increased experience with lack of availability due to shortages of medicinal products and market failure (GL).

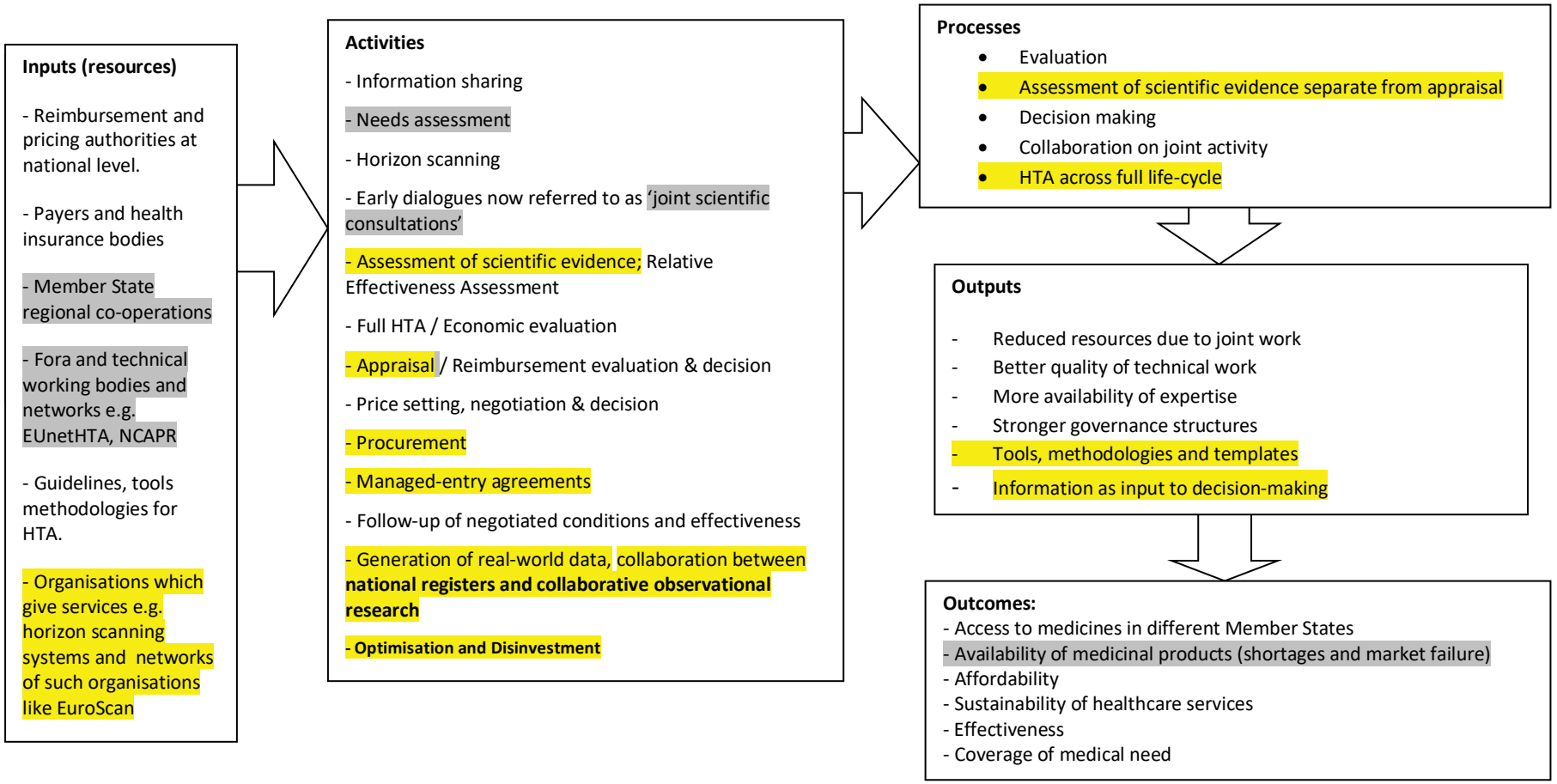


Figure 5.1 Logic Model for the system of Pricing and Reimbursement cumulatively updated with evidence from the scientific literature (yellow) (Model 2) and from grey literature (grey) (Model 3)

5.4 Evidence from different methods on attitudes on collaboration between national health authorities for pricing and reimbursement

The evidence on attitudes on collaboration between national health authorities for pricing and reimbursement from the different methods was aggregated.

A main theme concerning attitude on collaboration was whether collaboration should be voluntary or mandatory. The policy options for the Proposal for a Regulation on HTA presented different options for the type of participation and for the uptake of joint outputs (SL; SIA). In 2016 The Council of the European Union recognised that a number of MSs expressed interest in pursuing voluntary cooperation and stressed that these activities should remain voluntary and be focused on added values (GL). The European Commission proposed that collaboration would be voluntary for all activities except for HTA (GL). During the focus group discussion a number of practitioners were vociferously supportive of voluntary collaboration and against mandatory collaboration. The opinion towards mandatory collaboration was overshadowed (FG). 'Strong' countries which have well established systems for pricing and reimbursement considered that they did not gain from collaboration; in fact they stood to lose (FG; GL).

The stakeholders had differing opinions on collaboration on HTA. The authors of 'the Study' considered that economic impacts were particularly relevant to the industry; sustainability of healthcare systems was mainly relevant to public administration authorities and social impacts were relevant to citizens, patients and healthcare professionals (SIA). The industry considered that collaboration on HTA would be positive for mandatory participation and uptake of REA but would be negative for full HTA, i.e. the economic part of the assessment was not to be considered, because of the high level of agreement that would be needed. Industry graded PO5 negatively for all themes (SIA). In 'the Study' public administrations were reported to favour policy option PO5 i.e. full HTA including the economic part with a legislative framework and mandatory participation and uptake (SIA). Patients also favoured POs with mandatory

participation and uptake as these were considered to increase availability of medicines and to ensure standardised monitoring of health technologies prior to market access (SIA).

Collaboration could take place at different levels, ranging from loose collaboration such as exchange of information and development of common methodologies, to joint collaboration on cross-border assessments (SIA). Traditionally (up to 2015) the MSs collaborated by setting joint tools, guidelines and methodologies which were then to be used at a national level, bringing a level of standardisation but allowing for differences between MSs. The experience of the project-based cooperation of EUnetHTA experienced challenges: the joint work was used to a limited extent by the MSs; there was low uptake of joint work by national HTA authorities mainly due to legal and administrative hurdles; there were concerns on quality assurance; the joint timelines needed to be aligned with national timelines, and there was lack of sustainability of the work produced at the project setting (GL). More recently it is preferred to do work together as one output (SL; SIA; GL). While practitioners seemed to generally agree on the technical aspects related to tools, guidelines and methodologies for HTA, at the political level there was divergence of positions on joint work, which were more at the level of national politics than the perspectives of individual practitioners (FG).

'The Study' showed that the European Commission and the authors of 'the Study' considered that intergovernmental cooperation without input from the European Commission was not to receive EU funding and was strictly the responsibility of the MSs (SIA). Practitioners considered that the Proposal for a Regulation on HTA, as published, was much more supportive of the economic rather than the public health perspective. They felt that with the introduction of a Regulation for HTA, the position of the MSs within the power balance will decrease as compared to industry. Practitioners had mixed opinions on the power position: those who felt less influential and powerful in the MS hierarchy (the 'weaker' MSs) preferred to have legislation which brought all MSs at par, rather than them being bullied by 'stronger' MSs. MSs which had well-established HTA systems and had negotiating power (the 'stronger' MSs) strongly resisted

mandatory collaboration. Practitioners felt that there were advantages from collaboration including production of evaluations of high quality. They considered that the European Commission proposed collaboration which was 'coercive'. Practitioners believed that power within HTA collaborations would be restricted. If the methodology for HTA including the criteria for REA were to be set through legislation, as set in the original Proposal, this was considered to restrict the collaborators from evolving and adapting the methods. MSs were concerned with transferring the authority for REA outside national jurisdiction and the Proposal was considered to take over national legislation (SL).

During the focus group discussion there were divergent opinions with respect to regional collaborations, particularly with regards to their outcomes and success. Practitioners involved with regional collaborations (directly or indirectly) saw these collaborations positively and considered that there was potential for benefit. There was a divergent, critical opinion from participants from countries which were not participating in regional collaboration. There was consensus that the industry was not willing to participate in joint negotiation (FG). The regional collaborations were considered as the reaction of the MSs to the industry's game of divide and rule (GL).

In 2019 the main innovative industry association (EFPIA) considered that some initiatives for collaboration could support increased access to medicines and sustainability of healthcare systems, while in some cases national procedures were preferred. EFPIA considered that collaboration was in its infancy and there was little successful experience of enhanced access to medicines through collaborative initiatives. EFPIA suggested that until there was evidence of benefit from collaboration, national access processes were to remain the preferred way for timely access (GL). In 2018 the media criticised the BENELUXA cooperation because of lack of concrete negotiation deals (GL). The BENELUXA stated that at times industry did not want it publicly known that negotiations were underway (GL).

MSs had a general positive attitude for voluntary collaboration for different activities, with the exception of a clear divergent position on voluntary/mandatory REA. The scientific literature was the main source of information to inform of or promote new activities such as the generation of real-world data. MSs tended to keep the information on their actions and initiatives for collaboration internal e.g. the building of the horizon scanning initiative within BENELUXA and the regional collaborations kept the information within their organisations. There was consensus from the different sources that sharing of information on HTA was the first step towards collaboration, and the one which is most likely to be successful. The attitudes on other activities are not so clearly stated, probably because there was uncertainty on the possible level of achievement of outcomes. The MSs participating in regional collaborations were more interested in activities which they considered to increase access to medicines, particularly joint negotiation. The industry was supportive of mandatory REA and early dialogues but not of the other activities. Patients were mainly focused on the attitude that there should be patient involvement in activities and in decision making.

Table 5.2 Consolidation of information on attitudes on collaboration between national health authorities for pricing and reimbursement for specific activities

Activity	Attitude
Horizon scanning	There was positive consideration for voluntary collaboration on horizon scanning, at technical level (FG; GL). Some regional cooperations such as the BENELUXA and the Nordic Pharmaceutical Forum aimed to work together on horizon scanning (SL). BENELUXA was starting a horizon scanning initiative; it was questioned whether another initiative was needed (GL).
Early dialogues with industry (joint scientific advice)	The experience of joint scientific advice for HTA was considered positively (SL; GL). It was considered that participation in early dialogues takes up a lot of national resources (FG). The industry welcomed the opportunity for parallel EMA and HTA scientific advice (GL).
Sharing of information	EUnetHTA partners considered three levels of collaboration for HTA, with increasing level of commitment: at the lowest level of commitment there could be sharing of information on the generation of evidence, next

	level would be coordinated action based on an agreed commom core protocol and the highest level involved cross-border joint studies (SL). WHO believed that the priority for MS collaboration was to share information on HTA (SL). Espin et al (2016) considered that collaboration on information sharing and knowledge exchange should be the first step for collaboration as it was envisaged that there would be challenges for joint procurement (GL).
Health technology assessment (REA)	Smaller countries or countries with less expertise and well-developed systems for HTA were motivated for cooperation, particularly for low volume products such as orphan medicines (FG; SL). It was considered that in the shorter term smaller countries were to collaborate on REA, and with time there will be more exprience and success, and larger countries would be motivated to join in collaboration on REA (SL). As countries had significant differences in their health systems, various priorities and differences in willingness to collaborate, the level and extent of collaboration would be different (SL). It was considered that collaboration on the evaluation of clinical aspects and essessment in terms of scientific evidence were feasible and were recommendable prior to moving to activities which required more trust and commitment (GL). EUnetHTA was considered to be able to deliver tangible outputs in terms of tools and methodologies (SL). EFPIA (2019) considered that national assessments created duplication and conflicting outcomes (GL).
Full HTA (with economic evaluation)	There was a general consensus that reimbursement decisions were to remain at national level and at the competence of MSs (SL; SIA). Harmonisation of the context-specific elements such as economic and organisational elements was considered difficult (GL)
Price negotiation	Confidential discounts and MEA were increasingly used particularly for newly patented medicines. The industry argued that confidentiality of prices was essential becasue of the extensive use of reference pricing (SL). The participants of the focus group did not consider changing the position on introducing transparency of prices and of confidential information (FG). A joint publication by policy makers and practitioners (Vogler et al. 2017) recommended increased cooperation on pricing between countries by sharing information on discounted prices.

	EFPIA (2019) believed that joint price negotiations should not aim for short-term financial cost containment but should be based on solid legal grounds and offer legal predictability e.g. confidentiality of prices (GL). While there was an experience of a small drug company getting into joint negotion with BENELUXA, 'Big Pharma' was reluctant to get into negotiations (GL).
Reimbursement agreements	There was agreement that reimbursement decisions should remain at national level (FG, SL).
Purchasing and procurement	Joint procurement was challenging and experience in Europe was limited and only just recent (GL)
Post-marketing authorisation studies	The policies for the use of real-world data differed across agencies (SL). Recently there was a proposal that generation of real-world data was to be done together as one output to increase volume and variety. This was a new concept and it was being presented as data being used for implementation of a learning healthcare system (SL).
Generation of real-world data	

5.5 Evidence from different methods on perceived impacts (benefits and risks) from collaboration between national health authorities for pricing and reimbursement

The themes of the 'Framework' and the indicators for each theme for the perceived impacts supported the strategic aggregation of the evidence from the different sources and standardisation with the relevant theme. The themes were divided into social health impacts and economic impacts in line with the Guidelines for Better Regulation of the European Commission. The aggregated evidence from the different sources for each indicator was presented in Table 5.3. At times the same information could fit for different themes. The evidence available about each indicator was classified as benefit or risk in line with the impact and the perspective of the specific stakeholder concerned.

The scientific literature mainly reported the positive experiences and perspectives (benefits) in relation to improved quality of output and the benefits from joint methodology and tools. 'The Study' specifically studied the perspectives of impacts for different stakeholder groups and was the most informative method in this respect. 'The Study' showed that there were conflicting perspectives between and within stakeholder groups. The industry (and also the authors of 'the Study') considered economical benefits as key, while the MSs emphasised the social impacts such as access, sustainability of health care systems and public health. 'The Study' considered that there would be improved governance, improved quality of assessment, standardisation of tools and methodology and reduced administrative burden for MSs (SIA). Contrastingly the scientific literature (Vella Bonanno et al. 2019), the focus group discussion, and the grey literature, showed that while the countries with no resources favoured collaboration, countries which had well-established systems for HTA considered collaboration as a deterrent whereby they would lose their autonomy and potential for local contextualisation and possibly there would be waste of time for access to medicines. The latter perception was also being reflected by a number of Member States during the actual discussion of the Proposal on HTA at Council. It was important to note that the perspective of the 'stronger' MSs was not expressed in 'The Study'. Industry classified all themes for PO5 (i.e. joint economic assessment) as negative while the MS representatives were supportive of PO5. The final Proposal for a Regulation on HTA did not include PO5.

Table 5.3 Evidence from different methods on perceived impacts (benefits and risks) from collaboration between national health authorities for pricing and reimbursement

Social health impacts from collaboration		
	Benefits	**Risks**
Employment	Increased possibility of funding of joint research work, payment for assessment work, specialisation and consultancy (SL). No / minimal changes in employment (SIA).	
Governance, participation and good administration	Methodological guidelines and joint assessment were considered to increase the quality of assessment and improve decision making, particularly in countries with less-developed HTA systems, low capacity and expertise (SL). Practitioners from HTA organisations considered that collaboration would lead to: increased harmonisation, standardisation and quality of assessment, HTA would be conducted according to agreed standards and methodology, decreased duplication of work, increased efficiency, attainment of critical mass of evidence (SL). Quality of assessments required defined tools, processes and methods (SL). EUnetHTA achieved joint standardised methodologies and tools (SL; GL). There would be increased expertise through the sharing of information and expertise (SL). The European Commission considered that the legal proposal on HTA provided a legal and organisational framework for sustainable HTA cooperation, improved scientific quality of joint work and mitigated conflicts of interest (GL). Patient organisations considered that joint HTA reports would increase the quality of reports (GL). The Authors of 'the Study'' considered that a legislative framework and a permanent secretariat will enable strong governance and faster assessment of more health technologies as compared to current joint work. Industry considered that mandatory uptake of joint outputs would	Harmonisation of REA was considered to have the potential of losing local context and introduce standards which were not universally accepted (SL). The authors of 'the Study' considered that national adaptations of joint reports were time consuming and problematic for joint REA (SIA).

	lead to a swifter process (SIA). Industry stressed on the expected increase in predictability of HTA related processes for REA (SIA). The Authors of ‚the Study' considered that legislative structure could create institutional capacity and more streamlining of expertise (SIA). Public administrations considered stricter regulations to be key for successful collaboration (SIA). Patients considered that transparent HTA processes required consideration of all stakeholder perspectives including patients' to increase efficiency and prevent conflict of interest (SIA). Industry and public administrations considered the standardisation of patient involvement in HTA processes positively (SIA). It was considered by patient organisations that the independence of the HTA process must be ensured, influence of stakeholder groups should be limited and HTA should be funded through public funds (SIA). Public administrations considered that countries with no or little HTA activities were likely to benefit most from joint output and central governance, as they had not implemented major investments in building national systems. These were more likely to use centralised resources and adopt joint results (SIA). Public administrations stressed on the need for a legislative framework (SIA). The authors of 'the Study' considered that the policy options were not expected to have an impact on the responsibility of the MSs and would not interfere with the autonomy of the public administrations in this area (SIA). These authors considered that the introduction of a MS expert committee and the active involvement of national HTA bodies increased output (SIA).	
Access to social protection and	Collaboration was expected to bring increased strength and negotiating power for health care systems (SL).	

health systems	Patient organisations considered that cooperation on HTA would increase equity, scientific standards and efficiency of the decision-making process (GL). The industry considered that the legislative proposal would lead to faster patient access to medicines (GL). Industry considered benefit from collaboration because national methodologies led to substantial variations in outcomes (SIA). Industry considered positive impact for access for PO3 and PO4, negative for PO5 (SIA). The 'authors' considered that mandatory joint REA provided input for decision-making and that uncertainty would be lower (SIA). Public administrations expected positive access to medicines with PO3, 4 and 5, and that collaboration would lead to better selection of products with value added (SIA).	
Sustainability of health systems	It was considered that collaboration and pooling of information increase the quality of real-world data, particularly for effectiveness (SL). Collaboration would lead to pooled purchasing power (SL). Policy makers considered that MS collaborations address imbalances in negotiation power, limited transprency and market fragmentation. Joint procurement was expected to offer opportunities, particularly for small populations and rare conditions, due to a larger market size and economies of scale. Collaboration for procurement was considered to help countries attain economies of scale and socio-economic gains (GL). Certain areas such as rare diseases and personalised medicines could benefit from collaboration to ensure access, quality, affordability and sustainability of health systems (GL; FG). The Council Conclusions considered that collaboration enhanced transparency through sharing of information, sharing of experience, strengthening bargaining power and sharing of information on shortages (GL).	Policy makers considered that larger and high-income countries were likely to get less benefit from pooled procurement (GL).

	Industry considered that the Proposal for a Regulation on HTA would lead to synergies in the generation of clinical evidence and assessements (GL). Public administrations considered that POs with legislative framework were more likely to influence sustainability (SIA). Authors considered that countries with no structured HTA would be supported to make more efficient decisions (SIA). While public administrations considered that joint assessment would increase negotiating power, industry considered that all POs would have no effect on MSs' power on setting prices (SIA).	
Public health	Collaboration was considered to facilitate timely production of national HTA reports and to support decision making (SL). Collaborative research was considered to increase the number of patients studied and statistical power (SL). Collaboration was considered to possibly lead to increased access to medicines in low income countries, although access highly depends on affordability (SL). Decreased uncertainty on the actual added value of a technology (SL). MS representatives considered that involvement of patients ensured consideration of endpoints relevant to patients (SL). Policy makers considered that joint public procurement which takes into account the needs of the countries has public health benefits (GL). Public administrations considered increased availability of health technologies particularly with PO 4.1. The Authors considered that patient empowerment may affect public health positively (SIA).	Industry considered that PO5 had negative impact on public health (SIA).

Economic impacts		
	Benefits	**Risks**
Costs The costs related to the processes	Industry considered that the EUnetHTA core model (first four domains) provides a useful framework for pharmaceutical companies to optimise generation of evidence for assessment (SL). Industry considered that having joint REA with set dossier requirements will reduce spending on the generation of a global value dossier which is generated by indutry for each product and in particular the costs for additional generation of evidence (SIA). The Authors of 'the Study' expected that there would be overall savings for the MSs and for industry from collaboration on REA (SIA). The Authors considered that having a permanent secretariat would lead to larger savings compared to project-based cooperation (SIA). The Authors considered that additional generation of evidence due to requests by national HTA bodies will be limited when joint REAs are produced and this was considered to produce potential savings (SIA).	High costs were expected for coordination between MSs because MSs have different regulations, legislation, marketing practice and languages. Differences on types of national regulations on prices and procurement can hinder collaboration (GL). Public administrations considered that staff will be needed for collaborative work and this will be at a cost. HTA-related costs were not expected to change irrespective of the PO. The Commission was expected to bear any additional costs for cooperation (SIA).
Administrative burden	The EUnetHTA core model was expected to increase the transferability of HTAs across countries (SL). Development of joint outputs such	MSs considered that collaboration on REA may initiallially slow

	as tools, methodologies, standardisation of assessment facilitated collaboration (SL). Sharing of information through EUnetHTA database allowed partners to share information on ongoing projects (SL). The Commission considered that the HTA proposal will enable authorities to pool resources and expertise resulting in quality and efficiency gains (GL). The Authors and the industry considered that mandatory production and uptake of assessment will decrease the costs (SIA). The Authors considered that there will be decreased duplication in assessment and the evidence considered across settings is 'by and large' the same (SIA). The industry considered that fragmented HTA systems require companies to cater for a range of demands (SIA). Public administrations considered that joint assessment has the potential to cover more health technologies than separate essessments (SIA). Some HTA bodies expected that joint assessment will reduce their costs (SIA).	down the process in countries with well-established HTA systems (SL). Some HTA bodies considered that joint assessment will not reduce their costs becasue national procedures will still remain in some form (SIA). Public administrations expected slight increase in administrative burden and increased challenge particularly to reach agreement on economic aspects (SIA).
Competitiveness of the EU health technology sector	Industry considered that collaboration and unification of common criteria for REA will apply for MSs and for companies and this would support joint submission by industry (SL). The Commission considered that the health technology industries will benefit from more clarity in the requirements of evidence for HTA across the EU (GL). Industry saw harmonisation of REA throughout the EU as a benefit (GL). Public administrations perceived that joint assessment REA as well as full HTA will increase predictability of the HTA system and competitiveness (SIA).	The industry expected negative effect from full HTA (PO5) (SIA).

	The industry considered positive effect for REA (SIA).	
Innovation and research	The Commission considered that establishing the requirements for the dossier which will be submitted by industry will ensure that HTA bodies have access to clinical evidence (GL). Industry considered that harmonisation of evidence requirements and processes, acceptability of indirect comparisons and predictability of assessment outcomes facilitate investment (SIA). Public administrations considered increasingly positive effect from PO2 to PO5 (SIA).	HTA agencies considered that collaboration for REA could lead to increased time to market because the national processes still needed to take place and REA is part of the reimbursement decision (SL) Industry considered negative effects from PO5 (full HTA) (SIA).
International trade innovation and research	Industry considered legislative options as leading to increased predictability (SIA).	
Functioning of the internal market and competition	Practitioners considered that the costs of new orphan drugs are much higher than their production costs and Europe should take advantage of its total volume of market and team up to have one joint negotiation (SL). The Commission considered that the legislative Proposal for a Regulation on HTA was expected to bring benefits for the industry (GL). The industry stressed that the Proposal on HTA will remove divergences in the internal market through harmonisation at the EU level (GL). Industry considered a legal obligation to increase the functionality of the internal market (SIA).	
Consumers	The Commission considered that the Proposal for	Industry considered

	a Regulation on HTA will support involvement of stakeholders to exchange views (GL). Public administrations considered all POs to increase the number of health technologies assessed (SIA). Industry expected slight positive effect for PO3 and PO4 (SIA).	negative effect for PO5 (SIA).
Macroeconomic environment	The authors of 'the Study' considered the macroeconomic environment to be influenced by the legal framework (SIA).	

5.6 Evidence from different methods on negative motivational factors (challenges / barriers) and positive motivational factors (drivers / facilitators) for collaboration between national health authorities for pricing and reimbursement

The evidence about the motivational factors for MS collaboration from the different sources was aggregated in Table 5.4. The themes in the 'Framework' were considered adequate for the presentation and aggregation of the available evidence. There was some overlap between the concept of motivational factors and perceived benefits and risks. The grey literature was the main source of evidence on motivational factors and gave an insight mainly from the point of view of MS organisations. There seemed to be more evidence on challenges than facilitators for collaboration. The main driver for collaboration for MSs was increased access to medicines. The main challenges were not of technical nature but concerned mainly cultural, national and political factors such as safeguarding national jurisdiction, autonomy over activities for pricing and reimbursement, problems with harmonisation across MSs, the national level of engagement, building of trust, national legislations, the need for specific resources for collaboration and political will and commitment.

Table 5.4 **Evidence from different methods on negative motivational factors (challenges / barriers) and positive motivational factors (drivers / facilitators) for collaboration between national health authorities for pricing and reimbursement**

Theme of Factors	Factors which act as challenges / barriers	Factors which act as drivers/ facilitators
Social	There were conflicts of interest between stakeholders because of lack of alignment of purpose; while MSs sought inititiatives to reduce expenditure on medicines, EU policies were trying to boost innovative industry (GL).	Generation of added value was considered as a major motivator by industry (SL). The main objective for collaboration for MSs was better access to medicinal products and sustainability of national healthcare systems (GL). Patient organisations supported collaboration for rare diseases and complex technologies (GL).
Economic	Flexibilities offered by the agreement on trade-related aspects of intellectual property rights have not been exploited to their full extent for joint procurement. Small countries were concerned that products will not be placed on their national markets by the industry (SL). Regulatory limitations concerning data and market exclusivity (SL). Some larger countries believed that they benefit from confidential price agreements and that they can exert power over negotiations, while small coutries can benefit from humanitarian or corporate policies (GL). Differences of opinions between payers (GL). Industry did not want to adopt new ways of working which could impact its profit margin (GL). Paticipants of	The value of real-world data could be translated into economic incentives (SL). Sharing of experiences on strategic collaborative procurement was considered to be of benefit (SL). Individual countries were concerned with irritating the industry; and considered that collaborating together will overcome this concern (SL). Collaboration was considered to be driven by economics and not all countries are in the same economic situation (GL). Regional collaborations were considered to help governments to get organised (GL).

	regional collaborations considered that industry has a negative attitude towards regional collaborations (GL). Industry considered that external reference pricing has undermining effects (GL). Some policy makers considered that transparency of prices and of information are essential for joint procurement (GL) but participants of FG were reluctant to share information on prices.	
Behavioural	MSs considered “inherent difficulty” with not communicating in national language although they were competent to communicate in English (SL). Mechanisms of quality control for collection of real-world data needed to balance the needs of the research and concerns such as data protection and privacy (SL). Use of common websites and sharing of information were considered to have challenges of “not being invented here” syndrome, confidentiality of information, completeness and quality for filling forms, the level of diffusion of technologies in different countries (SL). The European Commission was criticised by the organisations as placing itself in a position of conflict of interest with respect to the Proposal on HTA (SL). Lack of transparency regarding prices and disclosure of discounts and difficulties with joint negotiation by MSs were considered major challenges (SL).	Technical experts from different countries participating in EUnetHTA Joint Action were considered skilled and motivated for cross-national work (SL). Council Conclusions stressed that MS collaboration should be voluntary and MS driven (GL).

	Collaboration was considered to require strong commitments from governments and from policy makers (GL). There was need for an authority / body to take the lead to organise collaboration (GL). Political will, mutual trust and mutual confidence were considered essential for collaboration (GL). Collaboration requires flexibility and openness from all parties (GL). Countries do not see issues in the same way and some countries are less experimental than others (GL).	
Organisational	There were challenges for the uptake of the HTA Core Model and gudelines for REA at national level (SL). There was lack of transparency in national processes (SL). The EC proposed a position of power for itself in HTA (SL). Clarity on management responsibility was considered necessary for joint procurement; the level of engagement (ministerial or technical) was crucial. It was essential to consider the national legal framework, synchronisation of national procedures, resource planning, timelines and a business case for industry was needed (GL).	EURORDIS (a patient organisation for orphan diseases) considered that only a permanent structure could guarantee long-term collaboration of all EU HTA agencies (GL).
Contextual	Competence and jurisdiction of MSs over activites of HTA (SL). Previous initiative for collaboration between the big EU MSs (2014) failed (GL).	Collaboration on communication platforms was considered important in countries with less-developed pathways for decision making (SL).

		EU legislation and policies were considered to support collaboration (GL). The European Commission considered that EU HTA cooperation brings upward convergence for standards of quality, transparency and independance for all MSs (GL). EU legislation on public procurement supported joint procurement (GL). Directive on cross border heath care supported cross-border cooperation, while respecting MS competence (GL).
Factors related to purpose	Patient organisations considered need for harmonisation of guidelines for economic evaluation and the need for alignment by MSs over willingness to pay (SL). There were differences between countries in criteria for prioritisation of reimbursement (SL) and in time-tables for assessments (SL). There was lack of harmonisation of policies for the use of real world data for HTA, and differences in choice of comparators and preferred endpoints (SL). It was considered that there needed to be a balance between the competence of the EC and the MSs (GL). Joint procurement needs good governance (GL). Collaboration was considered to need true political will,	MSs considered achievement of objectives and work plans (SL), quality and timely availabilty of assessments and transparency in REA reports (SL) as positive motivators. Article 168 of the Treaty specified that the Commission shall encourage cooperation between MSs in the field of Public Health and if necessary lend support in their actions (GL). Council Conclusions considered access to health technologies as the main outcome for voluntary cooperation for MSs (GL).

	ownership, commitment by policy makers and politicians, equity flexibility and standardisation (GL). MSs considered that collaboration should be MS driven (GL). Regional cooperations considered identification of lead partner for procurement, communication, language of official documents as challenges (GL). EFPIA believed that collaboration on price should be confined to countries with similar economic and health-related needs (GL).	
Implementation climate	It was considered that no country would foresake its autonomy in decision making. The technical domains of REA were considered less conflicting although coordinated assessment could lead to loss of autonomy in deciding the outcome of relative assessment (SL). Building trust between countries was considered important (SL). There were legal, logistical and methodological challenges for buiding of registries (SL).. Countries with well-established systems for HTA wanted to preserve their systems (SL). Legislative requirements impeded transferability of joint HTA reports (SL). Countries with more legalised structures were considered to have more difficulty (SL). Collaboration requires legal provisions and specific resources for collaboration (GL). Setting a policy for differntial	The following factors were considered as facilitating factors for collaboration: an environment conducive to collaboration (SL), increased motivation for collaboration in areas of increased benefit e.g. orphan diseases (SL), having countries with no or less well-established systems (SL).

	pricing and the setting of joint procurement required political will to agree mechanisms and principles (GL). It was questioned whether hard indicators were needed as a mechanism for measurement of success (GL). Regional collaborations experienced reluctance from the industry to negotiate, leading to lack of concrete results and making communication to the public challenging (GL). Clear political commitment and mandate were necessary (GL). Some countries believed that alignment of HTA will interfere with MS responsibility for national health systems (GL). EFPIA insisted that collaboration should guarantee confidentiality of pricing and reimbursement agreements (GL).	
Cultural	MSs considered the following factors as challenges for collaboration: getting to know each other and how to work together (SL); variance in interpretation of methods between assessors / countries (SL); national requirements due to historical events, local politics and funding models of national healthcare services (SL); ethical and cultural considerations of HTA (SL); different health technologies can challenge moral and cultural beliefs and values (SL). Regional collaborations and joint procurement were considered challenging because of divergence in	MSs conisdered the following as motivators for collaboration: transfer of ‘examples of good practice from other countries‘ (SL); high congruence in the level of evidence requirements for HTA (SL).

	legal, regulatory and organisational procedures (GL).	
Resources / physical	Challenges for collaboration included: availability of funding, information management systems, tools and guideline development, methodology, resources, infrastructure to support collaboration, logistical difficulties; the working language, organisational differences, time-frames, project management, lack of financial support (SL). MS considered that collaboration will not reduce the staff requirements for national processes (SL). Work on cross-border assessments needs to start very early (SL). GDPR requirements for real-world data needed to be coordinated at national level (SL). Regional collaborations had no allocated budgets for collaboration work, and funding was needed (GL). Experience of BENELUXA showed that collaborative processes are more resource consuming (GL). It was expected that countries with well-developed systems do most of the work initially and other countries develop competence later (GL).	Sharing of data in a standardised manner was considered to reduce resource requirements (SL). Ongoing initiatives such as EUnetHTA and MoCA support co-ordination across healthcare systems (SL). Co-ordination was expected to increase speed of implementation of the learning healthcare system (SL), reduce duplication of HTA output and increase capacity to produce common and high-quality information (SL). Development of common tools and methodologies particularly benefits countires with less-developed systems (SL). Collaboration was considered to support quality assurance and high level of expertise and standards, particularly as technologies become more complex and evaluation more challenging (GL). The European Commission considered that the legal framework, the organisational structure and financial support from the Proposal on HTA, will contribute to convergence (GL).

5.7 Corroboration and robustness of the evidence

It was important to note the timing of the evidence because the activities were dynamic. The 'Study on impact analysis of Policy Options for strengthened EU cooperation on health technology assessment Final report', 'the Study', was published in 2017, at a point where there were just the policy options set by the European Commission. The Proposal for a Regulation on HTA was published in 2018.

The major lack of congruence and corroboration in the evidence was on the attitude of public administrations regarding the nature of the collaboration for the Proposal on a Regulation for HTA. In 'the Study' the public administrations are reported to favour policy option 5 (PO5) which included a legislative framework and mandatory participation and uptake. The scientific literature, particularly the publication by Vella Bonanno et al. (2019), and the focus group discussion showed that there were divergent preferences between MSs. In the focus group, the position for voluntary participation was dominant. This lack of corroboration could depend on the extent of response of the MSs for the different methods and, in particular, which countries responded for each method. The divergent positions by the MSs, particularly with regards to MS jurisdiction, were also evident in the discussions at Council. It was surprising how this major issue was not highlighted in 'the Study' which was aimed to direct the way forward on collaboration.

The collaborated papers, Vogler et al. (2017) and Vella Bonanno et al. (2019), and the focus group discussion revealed organisational perspectives which were not specifically expressed during interviews and questionnaires with practitioners from the organisations. The media reports were also quite revealing of these issues. The publication by Vogler et al. (2017), which was driven by WHO, recommended for increased transparency of prices, while the participants of the focus group were totally opposed to transparency of prices.

The researcher classified the attitudes, the perceived impacts and the motivators in accordance with the relevant stakeholders. At times it was difficult to classify a perceived impact into a benefit or risk. The motivational factors, barriers and facilitators, were more tangible and specific as compared to perspectives. There was a balance in representation of barriers and motivators. While from a technical point of view practitioners seemed to be motivated to work together (this is particularly evident through the published scientific literature), there were major organisational and political barriers including the need to secure autonomy in decision making and to protect national jurisdiction. The organisational perspective won over the professional perspective, and as seen in the focus group discussion, practitioners were expected to align with the position of their organisation and not their personal point of view.

In the compilation of the Logic Model for the process of pricing and reimbursement (Model 3), the evidence from the different methods corroborated for the achievement of the full picture. The evidence for the building of the Logic Model came mostly from the scientific literature and was considered robust. Some concepts were still in development and it appeared that the scientific literature had surges of articles about specific topics which were timed in line with the evolvement of new concepts and new initiatives. The latest concept introduced was the use of real-world data to generate evidence for medicines approved through adaptive licensing.

The evidence in the scientific literature on attitudes on the Proposal for a Regulation on HTA came mainly from one paper, Vella Bonanno et al. (2019) which collated opinions of practitioners and academics from different Member States. The researcher declares that she was the main author of this paper. The experience of collating the opinions of practitioners was very challenging because there was a wide variation in opinions and interests of practitioners and of organisations. It took a lot of effort to ensure that a consolidated opinion was achieved by as many co-authors as possible.

When there were varying opinions, these were represented as clearly as possible. As could be seen from the positioning of the information on perceived impacts from the scientific literature in Appendix 4, the evidence from the scientific literature on impacts was almost all positive. This could indicate that the scientific literature has a tendency (bias) towards the publication of positive perspectives. The scientific literature was very informative and insightful regarding barriers and facilitators for collaboration.

The grey literature included the perspective of policy makers and these seemed to dare say what the professionals who worked with organisations were afraid to say. Also the grey literature showed more clarity and transparency of opinions particularly for barriers and motivators for collaboration. While the scientific literature mainly emphasised on the benefits and experiences of working together (mainly on a technical level) the grey literature corroborated well with the focus group and highlighted the differences in the political interests of MSs.

The information collected from the review of 'the Study', as presented in Appendix 6, contained perspectives of different stakeholders as this was a planned study with multiple methods. The limitations of the presentation and the representation of 'the Study' which were described in Chapter 4 were reflected in the presentation of the perspectives on impacts of the different stakeholders.

Most of the information from the focus group discussion concerned attitudes and there was an insight into the issues and a strong expression of organisational perspectives which were not openly expressed in other sources.

5.8 Perspectives of the different stakeholders and power mapping of the stakeholders

As explained by Barends and Rousseau (2018), the power of stakeholders to influence decisions depends on the power the stakeholder can exert on the decision-making process. The power of the different stakeholders concerned with MS collaboration was assessed and mapped in Figure 5.2.

While the activities progressed over time, most of the attitudes of the stakeholders regarding collaboration remained engrained. The changes, such as the publication of the Proposal for a Regulation on HTA, at times served to make the stakeholders more reactive, adamant, strong in their attitude and possibly resistant to change. In spite of the evident high prices being charged by the industry, the organisations/ practitioners remained reluctant to consider sharing of confidential price information. The industry stakeholders were also adamant that pricing information should not be transparent. 'The Study' showed that the industry stakeholders were adamant that MSs were to be forced into mandatory collaboration on HTA which was to be regulated by legislation. On the other hand patient organisations seemed to evolve in their perspective. While 'the Study' expressed the concerns of patients regarding the quality of the evidence used for marketing authorisation, patient organisations later became strong advocates for access to medicines, and seemed to have lost their concern on quality.

There were clear conflicts of interest between stakeholders. While MSs sought initiatives to reduce expenditure, EU policies prioritised economic initiatives that boosted innovative industry. While the main objectives of the MSs for collaboration were increased access to medicines and sustainability of healthcare systems, the main objective of the industry was economic. The main objective of the Proposal for a Regulation on HTA as originally published by the Commission was clearly just economic.

The industry considered that there is a “tension” between regulators who promote early access and pricing and reimbursement authorities who are “cautious due to uncertainty in evidence and resource constraints” (SIA). The issue of adaptive pathways was controversial and the industry played the game to push influential authorities to act in its favour and to divide and rule.

Industry was adamantly negative of PO5 and favoured PO4 throughout ‘the Study’; this was reflected in all answers. The public administrations were more in favour of PO5. The Authors of ‘the Study’ were generally more supportive of the position of the industry and the final recommendation and the subsequent Legislative Proposal which was published by the Commission reflected this.

Based on this aggregated evidence, the researcher mapped the level of power and the interests of different stakeholders. These were presented in Figure 5.2. The power positions of the stakeholders differed widely. For example in the classification of benefits and risks, the authors of ‘the Study’ and the industry considered the fact that there was to be no additional evidence generation as a benefit from collaboration on REA. In the paper by Vella Bonanno et al. (2019) and in the focus group, MS representatives considered it unacceptable that they will not be allowed to ask the industry for additional evidence generation according to national requirements.

Industry is the owner of the medicinal products and therefore it has power over what to do with its products and with the setting of prices. The ‘stronger’ MSs considered that they had economic power and felt that they were getting good negotiated prices from the industry. These countries did not feel the need to collaborate and considered that they benefitted from lack of transparency of prices. The countries with low economies of scale, the ‘weaker’ MSs, felt that that they were at the mercy of the industry and also felt bullied by the ‘stronger’ MSs. The ‘weaker’ MSs were in favour of a legislative proposal and supported the mandatory attitude because they considered that these would force the ‘stronger’ MSs to collaborate.

The practitioners working within the organisations reflected the views of their organisations and were very cautious to speak because of the political implications of their positions. This was particularly evident from the focus group discussion, where the practitioners did not consent to publication. Academics and policy makers, who were in a position to express an independent opinion, tended to see outside the box and express alternative views, for example they were not afraid to say the truth about the transparency of prices.

The European Commission was particularly questioned by the organisations on its conflicting interest with respect to its regulatory function and its role at the top of the hierarchy, as proposed in the Proposal for a Regulation on HTA.

The WHO seemed to be taking up an empowering role to support the MSs to address certain challenges where the MSs were weak and where the European Commission maintained a non-committal position such as for joint procurement and transparency of prices.

Influence High		**'Stronger' MS Authorities for P&R** (do not support mandatory collaboration for REA)		**Industry** (support mandatory collaboration for REA) **Media**
Some			**Regulatory (EMA)** (joint scientific advice, production of real-world data) **Patient organisations**	**'Weaker' MS Authorities for P&R** (support mandatory collaboration for REA) **European Commission** (only for REA)
Little		**Health care professionals**		**World Health Organisation** (pricing, negotiation, REA)
		Little	Some	**Interest** High

Figure 5.2 **Influence / interest mapping of different stakeholders on collaboration between Pricing and Reimbursement Authorities**

5.9 Summary

This Chapter presented the aggregation of the evidence by the researcher. The sourcing of evidence from multiple sources and aggregation and corroboration of the evidence within themes helped to achieve a comprehensive picture and also insight into the subject. This aggregation enabled corroboration of the evidence and comparison of perspectives of stakeholders. Areas where there was lack of corroboration on evidence indicated the need for specific attention. Although the researcher was also a practitioner and academic in the area, this comprehensive exercise showed additional insights and highlighted areas of risk and bias.

The most significant evaluation on MS collaboration up to the time of this research was 'the Study'. Comparison of the position of the public administrations as given in 'the Study' with that obtained from the aggregated evidence of this research showed areas where the evidence did not corroborate. The divide in perspective and in motivation between the MSs, which was not apparent in 'the Study', is a very significant challenge in practice and is a main decisive point for the way forward, particularly due to the vote which needs to be taken at Council.

Industry pushed hard to get the legislative Proposal for a Regulation on HTA through in line with its attitude of mandatory participation and uptake of HTA. Industry is not supporting the activities which are prioritised by the MSs in the regional collaborations, particularly joint negotiation and procurement. The industry is keeping a low profile and surreptitiously divides and rules. The position of industry was mainly reflected through the media.

The patient organisations shifted their perspective and were more aligned with the perspective of industry.

One major lesson learnt by the researcher through the experience of this research was the risk of bias when reading literature and interpreting studies. When 'the Study' was published, as a practitioner the researcher had given it a good viewing. With hindsight, the researcher realised

that she had given the document a read through, mainly focusing on the sections of the overview, the summary and the conclusions as written by the authors. After a thorough evaluation of ‘the Study’ as part of this research, it was clear that although the methodology of ‘the Study’ was clear and according to the rules, the final outcome of ‘the Study’ gave a strong prominence to the position of industry.

The actual mapping out of the stakeholder influence / interests will help the prediction of future developments and the possible risks, and will support planning and strategies for ongoing and proposed initiatives.

Up to this stage the researcher restricted her urge to come to subjective conclusions or make inferences. Inferences for the application of the evidence were presented in Chapter 6.

6. Application of Evidence-Based Management and of the Evidence from this Study

6.1 Introduction

This research was a case study for the implementation of the method of evidence-based management in line with the methodology detailed by Barends and Rousseau (2018). In this Chapter, the experience of the application of principles of evidence-based management and the relevant methodology were discussed. Some considerations and recommendations on the application of this methodology to reduce risks and consequences from uninformed or biased decisions were presented.

The researcher used the evidence gathered and aggregated in Chapter 5 and the theoretical framework presented in Chapter 2 to make inferences for the application of the evidence regarding the attitudes, perceived impacts and motivational factors for Member State (MS) collaboration for pricing and reimbursement of medicines, and to support future decisions in this regard. Initiatives for collaboration between MSs were a relatively new concept, therefore there was limited experience with MS collaboration and to date, few decisions were made as part of ongoing initiatives. The researcher assessed the outcome of two major decisions taken: the publication of the Proposal for a Regulation on HTA by the European Commission and the formation of a number of regional collaborations by MS authorities for pricing and reimbursement. The evidence used to update the Logic Model for the Process of Pricing and Reimbursement (Model 3) was used to update the General Logic Model presenting the Pharmaceutical Framework, which was the original baseline for the Logic Model for the Process of Pricing and Reimbursement (Model 1).

Conclusions and inferences for current and future initiatives for MS collaboration for pricing and reimbursement of medicines were presented.

6.2 Evidence–based management methodology and its application in academia and in management practice

This project was carried out as an academic research and needed to address the requirements of an academic dissertation. It also followed the specific methodology of evidence-based management from Barends and Rousseau (2018) (Refer to Section 2.3). The two complemented each other; however, there were major differences from the traditional format of an academic dissertation. As for academic dissertations, this project included a Chapter on the theoretical framework (Chapter 2), but the rest of the Chapters followed the Steps of the methodology for evidence-based management. The process was detailed in Table 3.1.

In contrast to academic dissertations, in the case of evidence-based management, the scientific literature and the grey literature on the subject of the research question directly contribute to part of the evidence. Thus in this case, the evidence on Member State Collaboration for pricing and reimbursement which was obtained from scientific literature and grey literature, was part of the results and not part of the chapter on the theoretical framework.

This dissertation showed that the pragmatic methodological approach of evidence-based management is robust, systematic and appropriate for management decisions, particularly for practitioners. The approach by Denyer and Rousseau (2009, p. 19) for the “conscientious explicit and judicious use of the best available evidence” as explained in Section 2.3, was highly applicable. The method of this study was ‘conscientious’, and great effort was dedicated to obtain what was considered to be the best available evidence. The collection and aggregation of evidence was very time consuming, systematic and laborious; and it was ‘explicit’, particularly through the use of the ‘Framework’ with clear themes and specific indicators for the themes. The ‘Framework’, which was built with the support of the literature presented in Section 2.7, was adequate to support the study of the concepts of attitudes, perceived impacts and motivational factors. The ‘Framework’ supported the different steps of the study including collection of the

evidence from the different methods and the aggregation of the evidence. The judicious use of the evidence came through the appraisal and aggregation of the evidence.

As shown in Section 2.3, evidence-based decision making involves the intersection of evidence from the 'four sources of evidence'. The prioritisation of the methods for collection of evidence and the adoption of a "fit for purpose" approach (Briner and Denyer 2012, p. 328) for addressing the research questions and for comprehensive coverage of evidence from the four sources, rather than according to the hierarchy of the pyramid of evidence, was found to be plausible for evidence-based management. The methods used for this study often covered more than one source of evidence (refer to Table 3.2).

Although the focus group did not proceed as originally expected, in actual fact the outcome from it was very insightful of the divided political climate for collaboration between MSs. The aggregation of the evidence from the different methods, the corroboration of the evidence and the consideration of the appraisal of the different sources of evidence within the process enabled the building of a holistic and realistic picture.

As the researcher was a practitioner in the field of study, she already had some evidence and pre-conceptions before starting the research. From her involvement as a researcher and as a practitioner, it was clear to her that she had gaps in evidence, particularly with respect to insight on opinions of practitioners. The main reasons for embarking on this study were to build a comprehensive picture of evidence and remove biases. The evidence-based approach adopted for this study confirmed that this original picture was not complete and was also distorted by biases.

The biggest gaps in evidence identified through this research included the identification of the recommendations which were made by the WHO on how to break the barrier of lack of transparency of prices and of related confidential information (Vogler et al. 2017) and the need to clear the misconceptions that joint negotiation and procurement were not permitted by EU

legislation (Espin et al. 2016). As shown from the focus group, practitioners from MSs were set in certain beliefs, such that lack of transparency of prices was beneficial. Practitioners were cautious not to appear as contradicting the industry.

The researcher identified a recent wave of literature pushing forward the concept for the use of real-world data, which is of particular interest to payers who are directly affected by the implementation of adaptive pathways by the regulators. Getting evidence about this concept from different sources enabled transparency of the 'web' being built, and showed how key opinion leaders, who were previously vocal against the concept of adaptive pathways, were being actively involved and championed to drive this new concept through participation in industry-funded projects and by involvement in joint publications, amongst others. The evidence showed the possibility of risk of the stronger stakeholders, particularly industry, exerting power; and it is important to keep vigilant and if possible take timely actions to direct the developments in this area. If payers consider collaborating on initiatives for real-world data, they should take heed both of the technical aspects as well as the practical arrangements such as who will pay for stocks of medicines and who will be responsible to cover the cost of the collection of data.

The biggest bias identified by the researcher through this project concerned her 'misunderstanding' of the 'Study on an Impact Analysis of Policy Options for strengthened EU cooperation on Health Technology Assessment Final Report', 'the Study', at the time when this was published. At that time, the researcher had just read the summary of the report and the conclusion by the authors, but did not study the evidence which was presented in the raw data of the results. This evaluation of 'the Study' showed that important evidence was 'lost' through the restrictions and assumptions of the methodology. While the researcher was aware of the risk of bias, it was quite surprising and intuitive to find one self at fault on such an important issue. This experience will make the practitioner more vigilant of possible biases in the future. Moreover the researcher realised that as a practitioner she was not keeping abreast with all the

literature that was published. Systematic search of the literature helped the identification of articles which had otherwise been missed.

The dissertation showed that the evidence from the scientific literature prioritised technical outputs e.g. the building of joint tools and methodologies for HTA and the possible sharing of resources as positive impacts from collaboration. Evidence on organisational and political insights of collaboration was scarce, and attitudes and motivational factors were not openly discussed outside national organisations. This corroborated with the outcome from the focus group discussion.

The divergence in attitude of Member States towards collaboration is a major determinant of the success or otherwise of MS collaboration. In the scientific literature this challenge was only reflected by an opinion paper by Vella Bonanno et al. (2019). Opinion papers are usually considered low in the pyramid of hierarchy of evidence, but were found very useful for the study of perspectives. The grey literature (which is also low in the hierarchy of the pyramid of evidence) and the focus group discussion gave insights into attitudes and into organisational perspectives, including on the divide in attitude between MSs. For the purpose of measurement of attitudes and perspectives, the grey literature was considered as very useful. It is recommended that a different 'pyramid for the hierarchy of evidence' is drawn, specific for the study of attitudes and of perspectives, with methods that feed insight being ranked high in this pyramid.

'The Study', which followed the methodology of EU Better Regulation, was aimed to determine the Policy Option to be adopted for the future of Member State collaboration on HTA. 'The Study' focused on the perceived impacts of the intervention; and totally missed out on the attitudes of the main stakeholders and on the challenges and motivators related to the intervention. This shows a major deficiency with the EU Better Regulation methodology of the European Commission. The resulting legislative 'Proposal for a Regulation on HTA' which was

published by the Commission, adopted the Policy Option which was most favourable to industry: the most influential stakeholder. During the discussions by MSs at Council (which by end August 2019 were still ongoing), progress was achieved on the articles of the Proposal related to technical and administrative aspects. However debate was still ongoing on the main issues related to attitude identified in this study: voluntary/mandatory participation in collaboration and in the uptake of the joint output, and the application of the principle of Member State jurisdiction in areas of public health.

6.3 Other methodological outputs of this project

This project produced tangible methodological outputs: the updated Logic Model of the system for pricing and reimbursement (Model 3) and the 'Framework' for studying of attitudes, perceived impacts and motivational factors (Figure 3.2).

The Logic Model of the EU Pharmaceutical Framework which was presented in Figure 2.1 was the foundation for the preparation of the first Logic Model of the Process for Pricing and Reimbursement (Model 1). During the course of this project the evidence collected was used to update Model 1 into Model 3. This evidence was also used to update the Logic Model of the EU Pharmaceutical Framework and the updated model was presented in Figure 6.1. The changes to this model were highlighted in grey. The main explanations for these changes were in line with the evidence collected to update Model 3 (Refer to Section 5.5). Model 1 and subsequently Model 3, did not consider the 'external factors', while the Logic Model of the EU Pharmaceutical Framework Model included them. The experience of this dissertation showed that a number of 'external factors' such as national governments, new policies and the European Commission have a great impact on processes and interventions. The section on external factors for the General Logic Model of the EU Pharmaceutical Framework was updated accordingly. External

factors are significant to a process and the addition of 'external factors' to the Logic Model representing a process is recommendable.

Resources		**Activities**	**Stakeholder (customers reached)**	**Outputs**	**Outcomes**				
Legislation & policy	**Structural & human**				Unmet medical needs	Quality, safety, efficacy	Affordability	Access & availability including shortages and market failures	Rational use
European legislation European policy National Legislation National policy	Academia Investigators Pharma industry	Research &Development, clinical trials Application for Marketing Authorisation	Regulators Policy makers Pricing and reimbursement authorities Pharmaceutical industry Healthcare professionals Patients Health Service providers Payers	Risk governance Free movement of goods Innovation Intellectual Property Protection Public health Allocation of resources Equity Sustainability of healthcare systems Joint / agreed tools, templates and methodologies Information as input to decision making					
	Regulatory agencies: EMA National agencies	Scientific advice to industry pre-authorisation Evaluation for marketing authorisation Post-authorisation monitoring							
	National pricing bodies	Setting of national price (where a price is set prior to placing on the market)							
	P&R authorities HTA bodies Collaborations between P&R Authorities such as Regional collaborations and EUnetHTA Service Organisations	Early dialogue / joint scientific consultation to industry pre-authorisation Horizon scanning Needs assessment Health technology assessment, Reimbursement decisions, Appraisal Setting of maximum price and financing models Monitoring of outcomes							
	Payers D&T Committees Procurement agencies	Procurement, negotiation, managed entry agreements, monitoring of outcomes of treatment							
	Operators of the supply chain	Manufacture, distribution, storage, supply							
	Health care professionals	Prescribing, dispensing, administration, monitoring of treatment							
	Patients and carers	Access to medicines, Administration, Monitoring of treatment Generation of real-world data, collaboration between national registers and collaborative research Optimisation and disinvestment							
External Influences									
The Treaties; The European Commission, the Council and the European Parliament; Regulatory governance framework set by the pharmaceutical legislation; Associations/groupings for stakeholders; Pricing and Reimbursement bodies; Pressures by/on different stakeholders; Research and funding initiatives; national governments and politics; international politics									

Figure 6.1 General Logic Model representing the EU Pharmaceutical Policy Framework as in August 2019, updated from the General Logic Model in Figure 2.1

The concepts of ‘attitudes’, ‘perceived impacts’ and ‘motivational factors’ were considered adequate. As discussed in Chapter 5, the building of a ‘Framework’ with specific themes for each concept, and the use of this ‘Framework’ for collection of evidence from different methods and for aggregation of the evidence was laborious but systematic and useful. The literature described in Section 2.7 was informative for the identification of the themes for Parts 2, 3 and 4 of the ‘Framework’. Different stakeholders had different perspective for the same theme and therefore it was important to specify the stakeholder from whom the evidence originated.

The themes of social impacts and economic impacts of the EU Better Regulation Guidelines (European Commission 2017) were adequate for the measurement of impacts for this study. ‘The Study’, which was conducted using the methodology for Better Regulation measured only impacts. It was evident from the literature used to prepare the ‘Framework’ (refer to Section 2.7), that to plan new initiatives and to propose changes it is not enough just to have evidence on perceived impacts. It is also important to obtain evidence on attitudes and on motivational factors. The ‘Framework’ for studying attitudes, perceived impacts and motivational factors used in this research can be adapted to study these concepts for different research questions, not just for MS collaboration. This is another output of this dissertation.

6.4 Attitudes, perceived impacts and motivational factors for Member State collaboration for pricing and reimbursement

The Research Questions were set to study the attitudes, perceived impacts and motivational factors for Member State collaboration for pricing and reimbursement.

The main aspects of attitude for collaboration were voluntary / mandatory participation in collaboration, the uptake of the joint output from collaboration, and the attitude towards the formation of regional collaborations. The governance of an activity by an EU Regulation makes

the activity mandatory, forced and liable to enforcement; this will have major impact on the MSs and on the collaboration. As seen from the focus group discussion, there was a divide between MSs, particularly on their attitude on voluntary and mandatory collaboration. The ‘stronger’ MSs preferred to retain their power, independence and full jurisdiction. As reported by Vella Bonanno et al. (2019) the ‘weaker’ MSs were opting for mandatory participation for the Proposal for a Regulation on HTA because they wanted to force the ‘stronger’ MSs to participate in collaboration, so that the ‘weaker’ MSs could ride piggy-back on them. This attitude was parasitic.

The attitude for mandatory collaboration was only considered for relative effectiveness analysis (REA), the attitude for all other activities of pricing and reimbursement was for voluntary collaboration. Minimal evidence was found to show positive outcomes from collaboration and these mainly resulted from the sharing of information. There was minimal progress on joint negotiation.

From the evidence on attitudes gathered it was clear that all MSs had a negative attitude for ‘hierarchical’ modes of collaboration. The regional co-operations showed that a number of countries were willing to collaborate as a ‘network’ as described by Baldwin, Cave & Lodge (2012), (refer to Section 2.6). Networking is recommendable, as long as there are concerted efforts for agreed actions. The parasitic approach adopted by ‘weaker’ MSs was not a correct attitude for networking. Ideally all MSs come to a point where they feel that they will benefit from collaboration, possibly for different reasons and in different ways. Forming smaller groups, such as the regional cooperations, may make it easier for the collaborating MSs to find an aligned scope and benefit. The regional co-operations are being formed by MSs voluntarily and therefore these only form if the MSs feel that they are mutually benefitting from the collaboration in one way or another.

The researcher favours voluntary collaboration. There is no point in forcing countries to go into mandatory collaboration; if collaboration is forced, the synergies and the outcomes will not be achieved.

This study demonstrated the three aspects of attitudes as described by Edelmann (2000), (Refer to Section 2.7.1). The emotional component was highly evident in the focus group discussion. A cognitive component whereby MS professionals are strong and consistent in their positions on collaboration, was evident through the corroboration of the evidence from different sources and through the active discussion on the Proposal for a Regulation on HTA at Council. The action / behavioural component was demonstrated by MS representatives' active participation in the regional collaborations and in EUnetHTA.

In the 'Framework' for the study, the impacts were divided into social health impacts, with the main themes being governance and administration, sustainability of healthcare systems and public health; and economic impacts, with the main themes being administrative burden, competitiveness and innovation. Most of the evidence on the theme of governance was collected from 'the Study'. A high emphasis was placed on benefits for 'governance and administration' in terms of improved quality of assessment, standardisation and harmonisation. This was in line with the results of the systematic review by De Freitas, De Oliveira and Alcantara (2018) which reported on the primary and secondary benefits from company collaboration and ranked governance, participation and good administration as high impacts. Other sources of evidence, particularly the grey literature and the focus group discussion, showed that from the perspective of the MSs the main benefits from collaboration were improved public health outcomes, (particularly increased access to medicines) rather than improved outputs (governance and good administration). While the healthcare systems of the MSs differ and there are different levels of affordability, all MSs have challenges with access to new medicines (to different extents) and all support the concept of collaboration to increase access to medicines.

‘The Study’ reported that MSs were mainly supportive of PO5, which included collaboration on financial evaluation and possibly joint negotiation; which MSs consider to increase access to medicines. In contrast, industry was totally against PO5 and wanted collaboration only on REA. This corroborates with the situation of the regional collaborations whereby the MSs are pushing for joint negotiation and the industry is not playing ball. There are distinct differences in perspectives and interests between MSs and the industry. The Proposal for a Regulation on HTA was mainly supportive of PO 4 and of the economic impacts, reflecting the power mapping of the stakeholders, including the high power and influence of industry and the strong imbalance of the European Commission towards the agenda of competitiveness as compared to public health interests.

In the Proposal for a Regulation on HTA, which followed from ‘the Study’, the Commission strongly and directly linked the aspects of governance, a social health impact, with having the criteria for REA set by the legislation. Having rigid criteria was considered by the industry to increase competitiveness and innovation (improved economic impacts). In reality these concepts are separate and the linkage was introduced by the industry in ‘the Study’ and was reflected by the European Commission in the Proposal. This emphasis on harmonisation of criteria for REA is a wolf (industry want control over REA) being presented in sheep’s clothing (as governance, a social health impact).

All MSs were critical of harmonisation of the criteria for REA and this was one of the areas where MSs strongly disagreed with the Proposal for a Regulation on HTA. Rigid criteria were considered to disable contextualisation and to force standards which were not adaptable. Looking at the system of pricing and reimbursement holistically, through the view and the logical framework afforded by the Logic Model, the researcher considers this manoeuvre of major concern because freezing of the criteria for evaluation will block the MSs from adapting their evaluation to consider the uncertainties from lack of evidence on medicinal products due to adaptive pathways.

The themes for motivational factors for collaboration were collated from studies of different organisational scenarios: an evaluation of the systematic review on companies in a supply chain (De Freitas, De Oliveira and Alcatraz 2018), a study on collaboration between educational institutions (Kezar 2006) and a study of forest owners (Gorriz-Mifsud et al. 2019). The final set of themes was included in the 'Framework' and was considered comprehensive. The researcher termed the themes as 'motivational factors' and it was considered that each theme could act as a positive motivator (driver / facilitator) or as a negative motivator (challenge / barrier) depending on the approach and the perspective of the stakeholder concerned. There was a link between the concepts of the themes for the perceived impacts and for the themes for motivators. Perceived impacts will result in positive or negative motivation to implement an intervention.

This study showed that 'factors related to purpose', cultural factors, and the implementation climate were key motivators for MS collaboration. The results of this study were aligned with the factors mentioned by Kezar (2006) who identified culture, shared values, relationships and priority from senior management as main motivational factors for collaboration between educational institutions.

The differences in attitude on voluntary/mandatory collaboration between the 'stronger' MSs and the 'weaker' MSs could be explained in terms of motivational factors. The 'stronger' MSs considered that their economical strength gave them enough power for negotiation with the industry, and thus they were not motivated to collaborate with other MSs, while 'weaker' MSs needed to build power for negotiation through grouping. Kezar (2006) recommended that successful implementation of collaboration involves redesign and learning of collaboration skills and unlearning of non-collaborative practices. This may be a reason why the practitioners in the larger and well-established organisations were reluctant to collaborate; they were resistant to redesign and change what they had, over years, painstakingly built to minimise risks. Moreover, well established systems support practitioners to build their niches and experts may not want to

lose their prima-donna positions within their organisations and to get diluted within a pool of experts.

Collaboration requires the building of organisational structure (Baldwin, Cave and Lodge 2012). The power and attitude of the MSs involved will determine whether countries will be willing to collaborate together and which model of organisational structure will be chosen. The regional collaborations were voluntarily formed between groups of MSs and demonstrated the motivators in the formation of collaboration. The BENELUXA was constituted of countries of medium size and of the same economic strength, with a history of working together. Possibly the main motivators for BENELUXA were economic (joining together to form a larger market), cultural and historical, and a common purpose for increased access to medicines. The Valletta Declaration was made up of ten big and small MSs, mostly from the south of Europe, where the main motivators for collaboration were probably cultural (countries from the same geographic area), economic (joint negotiation) and the sharing of resources (MSs with well-developed systems supporting others with less well-developed systems). Both collaborations were formed through Ministerial decision, and the main push came from the Ministers who sought to address the problem of access to medicines, which is a major and realistic challenge for MSs. Another reason for this Ministerial motivation may be political. As shown by Koeing-Archibugi (2010) one reason for international cooperation may be a blame-management and blame-shifting incentive and ministers may want / need to show that they are tackling the challenge of access to medicines. As shown in the grey literature, some of the Ministers of countries participating in regional collaborations used the media to relay the message that action was being taken to address challenges with access to medicines: O' Donnell (2015) received comments from a spokesperson of a Minister; EURACTIVE (2017) reported an interview with a Minister; and Kenny (2019) reported feedback from a government advisor.

The main external factors which motivated MSs towards the formation of the regional co-operations included the lack of power of the MSs with respect to the pharmaceutical industry,

the financial difficulties being faced by MSs for the sustainability of healthcare systems and the challenge of ensuring access to medicines for citizens.

6.5 Use of the evidence to support assessment of decisions already taken in relation to Member State collaboration

To date two main decisions on initiatives for Member State collaboration have been taken. The first decision was taken by the European Commission, and resulted in the publication of the Proposal for a Regulation on HTA. As at end August 2019, this Proposal was still being discussed at Council. The divergence in political position of MSs regarding the attitude on voluntary / mandatory cooperation during the discussions of the Proposal for a Regulation on HTA at Council corroborated well with the evidence on attitude on collaboration obtained from the focus group discussion and from the grey literature. The ongoing discussion at Council clearly showed the divide between the 'stronger' MSs that are self-sufficient and do not want mandatory collaboration and the 'weaker' MSs that do not have well established HTA systems and expertise. While with good will a level of consensus may be reached by MSs on the technical aspects of HTA assessment such as the methodology, tools and guidelines, the final decision on the Proposal for a Regulation on HTA will mainly be determined on the basis of the political will and power of the MSs. With reference to the influence / interest mapping of stakeholders presented in Figure 5.3, the ongoing political power struggle involves a tug of war between the 'stronger' MS authorities that have high influence but little interest in collaboration and the 'weaker' MS authorities that have high interest in collaboration but possibly less influence. At the end there will be a vote. 'The Study', on which the Proposal for a Regulation on HTA was based, did not clearly reflect this important divergence in attitude between MSs.

Article 168 of the Treaty on the Functioning of the European Union specifies that the European Union shall encourage co-operation between MSs in the field of Public Health and if necessary

lend support in their actions, and that Union action shall fully respect the responsibility of the MSs (Council of the European Union 2016). Whatever the outcome of the vote at Council on the Proposal for a Regulation on HTA, the Commission should consider supporting the infrastructure needed for collaboration for HTA for the countries that are willing to participate, even if this collaboration is driven by MSs and if it is voluntary. So the basic premise adopted by the Commission and by the authors of 'the Study' that Member State driven collaboration cannot be supported by the Commission, was not valid and the position should be reconsidered. Collaboration on REA may support the objective of the regional collaborations with regards to negotiation on prices, and thus these two initiatives may complement each other.

The Proposal for a Regulation on HTA highly favoured the agenda of competition as driven by industry and as supported by the European Commission. As discussed by Baldwin, Cave and Lodge (2012) the main consideration of regulation should be public interest and the authors referred to the 'contest' between different interest groups. Capture theories highlight the attempts of organised interests to shape the regulatory process to their own ends, and the fact that the industry and the Commission emphasised on the need for a legal framework for collaboration is a good example of this. Considering this from another point of view, the experience of this research showed that the political situations in certain countries were unstable and governments changed quite often. This lack of national political stability could affect the sustainability of MS collaborations and having an EU legislative framework would guarantee stability for the collaborations.

Institutional theories stress that regulatory developments are driven by institutional structures and arrangements. If HTA were to be governed through legislation, the regulatory framework will change completely and the regulatory power of the MSs over HTA will decrease. In spite of the reassurance by the Commission and by the industry that collaboration on REA will not affect the final national reimbursement decision, capture theories predict differently. Legislation will

probably reduce the power of the MSs and increase the control of the industry over national decisions, particularly if the criteria for REA were set by the legislation. The industry could object and trigger enforcement action if it considers that national decisions are not based on the criteria set by the legislation. The legislation could turn out to be a Trojan horse for the MSs.

Organisational politics relate to the personal and aggregate power to influence others and to secure personal and aggregated interests (Vigoda-Gadot & Drory 2004). Short-sightedly, the 'weaker' MSs want the collaboration on REA to be governed by legislation in order to change the organisational politics and become at par with the 'stronger' MSs. The resource dependency theory (Kezar 2006) explained an alternative reason why the 'weaker' MSs, which have limited resources and expertise, are motivated into collaboration which enables sharing of resources. MSs should communicate between themselves to find a solution which suits them all, without resorting to external factors such as EU legislation. In reality, the real power game and the highest risk, extend beyond the MSs and depend on the influences and pressures of other stakeholders, mainly those with high interest and high power, particularly industry and the European Commission.

Powerful entities have different ways of exerting influence, for example by influencing politicians and key people in authorities and in stakeholder organisations. The study showed a number of ways for exertion of influence such as key opinion leaders collaborating in industry-funded studies, involvement in joint publications and the award of advisory positions. The evidence showed that a high level of influence was exerted by the media. The 'game' was also influenced by external influences such as the outcome of the elections at the European Parliament and the timing of Brexit with respect to the decision at Council.

The second major initiative for Member State collaboration was the formation of a number of regional MS collaborations during the last three years**.** These collaborations have been successful mainly in the sharing of information but the impact on outcomes in terms of access to

medicines and sustainability of national healthcare systems has been minimal. As corroborated from the sources which provided insights (the focus group discussion and the grey literature) the big pharmaceutical industry is not playing ball; and as the owner of the medicinal products, this stakeholder is in a position of power. As seen in the evidence on motivational factors related to purpose (Section 5.6) unless these collaborating countries have strong political willingness to break the *status qou*, there will not be further progress.

The principle of bounded rationality (Simon 1991) considers that one individual or organisation has limited capacity to process all information within the existing constraints; resulting in decisions being inherently bounded. Voluntary collaboration and having different contributors to the evidence for a decision, as practised by the regional collaborations could have the potential to improve decision making. Strengthening the evidence for decisions, particularly through sharing of information on prices (which to date is not transparent) will also empower decision making. The Valletta Declaration demonstrates the applicability of the principle of bounded rationality whereby the MSs with systems which are not well-developed will benefit from collaborating with countries with robust resources for evaluation. The principle of bounded rationality will also apply if the regional collaborations manage to progress to joint negotiation (which is their main objective). Unless the countries within the regional collaborations take a strong political position to act jointly and to stop industry from blocking joint negotiation, joint negotiation will not be successful. Another possible bold consideration for the regional collaborations is to introduce transparency of prices of medicines between themselves. It is not possible for all the Member States to be gaining from the current confidentiality on prices. The Member States are in the dark regarding the true picture, while the industry knows the prices and the terms for negotiation which it achieves with each Member State. Transparency should be between the countries that agree to the terms of the collaboration and should not extend beyond the countries participating within the regional collaboration, because of the system of reference pricing.

In spite of progress achieved, MSs still have much to learn about the possible benefits and synergies from collaborating together. Strong political will is needed. There is lack of trust and of motivation among MSs to collaborate. In the meantime, the other stakeholders tend to benefit from this rift between Member States. Unfortunately, it takes little effort to divide and rule. The ongoing collaborations should take the bold steps to surmount the main hurdles and fears. They need to be assertive; they need to trust each other and they must address the fears of the unknown. It takes time to build trust and political will. Ideally the main ongoing regional collaborations take actions at the same time, if not jointly. The other MSs that currently do not participate in regional collaborations and prefer to wait and see how current initiatives will progress, will hopefully eventually come to a point where they also consider benefits in public health outcomes from collaboration. This will be the ultimate indicator that Member State collaboration is successful. In the meantime bold strategic steps should be taken and the efforts should be escalated to overcome the hurdles.

6.6 Summary and conclusion

This dissertation was an informative, educational and formative experience for the researcher both from an academic point of view as well as a practitioner. With some adaptation, the methodology of evidence-based management was applicable as an academic exercise. The main adaptations required included the structuring of the study in line with the steps of the methodology for evidence-based management and the use of the scientific literature and the grey literature as sources of evidence and as part of the aggregation of the evidence (the results).

This dissertation showed that the methodology of evidence-based management as presented by Barends and Rousseau (2018) was robust and systematic and appropriate for management practice, particularly for practitioners of evidence-based management. Methods which are

considered as weak sources of evidence in the pyramid for hierarchy of evidence, such as opinion papers and grey literature, were found to be strong sources when it came to studying concepts like attitudes, perceptions on impacts and motivational factors, particularly if the methods collected evidence from a comparatively representative sample of stakeholders. This study showed an inversion of the hierarchy of evidence when measuring these concepts. Thus the choice of method depends on the best available evidence for the concept being studied.

The Logic Model for the process of pricing and reimbursement and the General Logic Model for all the processes of the Pharmaceutical Framework covered the same themes / components for processes. The experience of using Logic Models of this research was very positive and the use of Logic Models to represent complex real life processes is commendable.This research showed that it is important to also consider the 'external factors' which impact the process, such as stakeholders, political influences etc.

The 'Framework' set by this research for measurement of attitudes, perceived impacts and motivational factors can be adapted to measure these concepts for other research questions. 'The Study' reflected that the methodology of Better Regulation addresses only perceived impacts and does not consider attitudes and motivational factors of stakeholders. It is recommended to revise the methodology for Better Regulation to include attitudes and motivational factors and to ensure that during evaluation there is balanced consideration of the evidence from all stakeholders, not on the basis of stakeholder power. The 'Framework' used for this research can be used to update the methodology of Better Regulation of the European Commission.

This project was a good case study for evidence-based management in the area of health policy and regulation. The experience showed that evidence-based management in line with the methodology by Barends and Rousseau (2018) is labour intensive and takes up time and resources. The methodology brought out gaps in evidence and biases which would have been

of great detriment to future decisions on collaboration. In practice, it would be recommendable to reserve this methodology for the decisions which are of highest strategic importance. As collaboration among Member States for pricing and reimbursement is a major strategic decision, particularly for MSs, it was worth investing in evidence-based management methodology for this topic.

The evidence showed that the main determining motivational factor for the final decision on the 'Proposal for a Regulation on HTA' will be political. It is important that the methodology for proposing change also evaluates political factors because these are major determinants for the success of new initiatives, particularly for national organisations.

It was very important to understand the different political positions and powers of the stakeholders concerned. The exercise of influence / interest mapping should be done formally, using the best evidence and incorporating the involvement of the different stakeholders concerned whenever a main strategic decision is to be taken. The power / impact analysis helped to predict the changes that were likely to take place. In the case of the Proposal for a Regulation on HTA, the first determining decision will need to be taken by the MSs by a vote at Council. Unfortunately, the main consideration for this decision ended up being the organisational tug of war between the 'stronger' MSs and the 'weaker' MSs. In reality, the biggest perceived impact and de-motivator for this decision to be considered by MSs should be the loss of power for all MSs if a Regulation, which strictly regulates their jurisdiction on HTA decisions, comes into force. The industry is a very strong stakeholder and exerts influence over the different players / stakeholders. In this case, the 'stronger' MSs, some of which are usually aligned with industry on economic impacts, were on the opposite end of the influence / interest map to the industry. The MSs that prefer mandatory collaboration are adopting a risky long-term position for short-term gain.

Whatever the outcome of the final vote of the MSs regarding the Proposal for a Regulation on HTA, it is important that the work done through EUnetHTA to-date and the outcomes achieved with regards to building of methodology, tools and guidelines for HTA are not lost and continue to be developed.

The European Commission should support MS collaboration, whichever Policy Option or alternative option is finally decided. The European Commission is mandated by the Treaty to support collaboration between MSs, even if the Model for collaboration is set and managed by the MSs. The EC needs to revise its original position that it will not support MS driven collaboration. Hopefully, with the change in the European Commission in the third quarter of 2019, there will be a change in the approach of the Commission regarding the Proposal for a Regulation on HTA and regarding the Commission's prioritisation of economic impacts over public health impacts.

The regional co-operations are a model for voluntary cooperation which achieved some success but still faces major challenges. The objectives of the main regional co-operations extend beyond joint HTA and their primary objective is joint negotiation. Joint negotiation requires the willingness of the industry to participate, and currently the industry is reluctant to participate in joint negotiation. Thus, even the regional co-operations are highly affected by the influence/interest mapping of the stakeholders.

Collaboration requires political support and willingness, and the frequent changes in national governments may withdraw the participation of individual countries from established collaborative initiatives, leading to instability. The industry, as the owner of the medicinal products has a monopoly. For the current *status quo* to dissolve, the MSs within the regional collaborations need to take major decisions, such as sharing of price information among themselves (but not externally) and finding ways to 'force' industry to go into joint negotiation. The MSs seem to be reluctant / afraid to get into the bad books of industry because of possible repercussions whereby the industry would not supply them with its medicinal products. Strong

collaboration between MSs would empower the MSs to act. Collaboration between the different regional collaborations, particularly those with the same mandate, will also strengthen the position of the MSs and should be considered. To collaborate at this level the MSs need to come to a position where they trust each other and where they collaborate to achieve synergy rather than to prioritise individual interests.

This dissertation gave the researcher hands-on experience with conducting and appreciating a case study in evidence-based management. This methodology is highly recommendable particularly to answer major strategic decisions and to reduce the risks from decisions, thus minimising unwanted consequences from risks and increasing effectiveness of decision making. To date, progress with initiatives for MS collaboration has been slow, and not much has been achieved with regards to the tangible outcomes of the pharmaceutical framework. The challenges can be addressed, particularly if the MSs take informed decisions based on the best available evidence. The final decision on the 'Proposal for a Regulation on HTA' is not yet taken and hopefully the MSs consider the holistic picture and adopt a long-term view. Once a legislation is in place there is no turning back or changing the situation, and the MS will have to face enforcement action against them. Considering the aggregated evidence from this study, the researcher recommends that MSs should not accept to be bound by legislation into mandatory cooperation. This will weaken their position in relation to the industry. The model of the regional cooperations may work. If voluntary collaboration is successful, eventually more countries will be motivated to participate and join in. However the regional cooperations are stunted unless they join forces and combine their power to remove the barriers for collaboration.

The evidence gathered in this project can be used for current and possible future initiatives for Member State collaboration. The method of evidence-based management is recommendable to support decision making for future initiatives in the area of healthcare services and regulation.

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Appendices

Appendix 1 Faculty Research Ethics Committee (FREC) Approval

L-Università ta' Malta

Patricia Vella Bonanno <patricia.vella-bonanno.15@um.edu.mt>

Ethical Clearance

3 messages

Josian Grech <josian.grech@um.edu.mt> 29 May 2019 at 10:01
To: Patricia Vella Bonanno <patricia.vella-bonanno.15@um.edu.mt>

Dear Ms Vella Bonanno,

Please note that FREC has reviewed your forms and has approved your proposal. You may continue with your research project.

Regards

--

Josian Grech

Administration Specialist
Faculty of Economics, Management & Accountancy
Dean's Office
Room 425
Humanities B (FEMA)
University of Malta
Msida
☎ +356 2340 3417

josian.grech@um.edu.mt

Patricia Vella Bonanno <patricia.vella-bonanno.15@um.edu.mt> 29 May 2019 at 10:06
To: Josian Grech <josian.grech@um.edu.mt>
Cc: Vincent Cassar <vincent.cassar@um.edu.mt>

Dear Ms Vella Gera,

Thank you for your e-mail.

Regards

Patricia
[Quoted text hidden]

Josian Grech <josian.grech@um.edu.mt> 29 May 2019 at 10:07
To: Patricia Vella Bonanno <patricia.vella-bonanno.15@um.edu.mt>

Welcome.

Regards
[Quoted text hidden]

Appendix 2 Identification of records from scientific literature through database searching

Details of the Search Strategies for the Published Scientific Literature

(Refer to Section 3.6.1)

Strategy 1

MEDLINE COMPLETE (EBSCO)		**No. of articles**	**No. of articles selected based on abstract**
1.	Horizon scanning AB AND cooperat* AB	7	2
2.	Horizon scaning AB AND cooperat* OR network OR collaborat* AB	38	9
1.	Real world data AB AND cooperat* OR network OR collaborat* AB AND pharm* All Text	68	8
2.	Early dialogue AB AND cooperat* OR network OR collaborat* AB AND pharm* All Text	4	1
3.	Health technology assessment AB AND cooperat* OR network OR collaborat* AB AND pharm* All Text	147	28
4.	Reimbursement AB AND cooperat*OR network OR collaborat* AB AND pharma* OR medicine AB	269	48
5.	Procurement AND cooperat*OR network OR collaborat* AB AND pharma* OR medicine AB	105	5
6.	Scientific advice AND cooperat*OR network OR collaborat* AB AND pharma* OR medicine AB	8	0
Limit	English, abstract available, human, peer reviewed, dates 2000 to 2019		
Date	04.04.2019		

Strategy 2

Pro Quest ABI/INFORM Global		**No of articles**	**Number of articles selected based on abstract**
3	Pharm* OR medicine TI AND cooperat* OR collabor* OR network TI	16	2
Limit	English, abstract available, human, peer reviewed, dates 2000 to 2019		
Date	04.04.2019		

Strategy 3

Cochrane Database of Systematic Reviews		No. of articles	No. of articles selected based on abstract
	Health technology assessment	44	nil
	reimbursement	13	nil
	Horizon scanning	nil	nil
	Pric*	38	nil
Limit	English, dates 2000 to 2019		
Date	04.04.2019		

Strategy 4

EBSCO host		No of articles	Number of articles selected based on abstract
	Health technology assessment OR reimbursement OR pric* TI AND cooperat* OR collaborat* OR network TI AND medicine OR pharma* AB	6	4
	Reimbursement AB AND cooperat* OR collaborat* OR network AB AND pharm* OR medicine AB	11	6
	Pric* AB AND cooperat* OR collaborat* OR network AND medicine OR pharma*	48	9
Limit	English, abstract available, human, peer reviewed, dates 2000 to 2019		
Date	04.04.2019		

Consolidation of Strategies 1 to 4

All selected abstracts removing doubles – 102

Classification of abstracts:

- Directly relevant to the subject of collaboration: 53

- Not relevant to collaboration but possibly relevant to introduction: 27

- Not relevant to the dissertation: 22

Strategy 5

PLOS ONE (includes PLOS Medicine)		No. of articles	N. of articles selected based on abstract
1.	Reimbursement AB	148	3
2.	Health Technology Assessment AB	27	4
3.	Horizon scan* AB	4	0
4.	Real world data AB	68	0
5.	Pric* AB AND medicine AB	63	4
6.	Pric* AB AND pharm* AB	54	4
Limit	English, abstract available, dates 2000 to 2019		
Date	05.04.2019		

Consolidation of Strategy 5

All selected abstracts removing doubles – 10

Classification of abstracts:

- Directly relevant to the subject of collaboration: 1

- Not relevant to collaboration but possibly relevant to introduction: 6

- Not relevant to dissertation: 3

Strategy 6

	collaborat* OR network OR cooperat* OR cross border OR international	AB
AND	Barrier OR benefit OR challenge OR facilitat* OR motivat* OR opinion OR attitude OR belie* OR perspective	AB
AND	Health technology assessment OR reimbursement OR horizon scanning OR real world data OR pric* OR early dialogue	AB
AND	Pharm* OR medicine	AB
Limit	English, all documents, peer reviewed, dates 2000 to 2019	
Date	5.04.2019	

Data base		Number of articles	No. of articles selected based on abstract	Number of articles directly relevant to the subject of collaboration	Number of articles for introduction
Medline complete		573	71	28	34
PRO Quest ABI/INFORM Global		59	14	5	9
EBSCO Host		69	12	nil	12
SCOPUS		nil	0	nil	0
Psychology and Behavioural Science Collection		27	3	nil	3

Strategy 7

	collaborat* OR network OR cooperat* OR cross border OR international				AB
AND	Health technology assessment OR reimbursement OR horizon scanning OR real world data OR pric* OR early dialogue				AB
AND	Pharm* OR medicine				AB
Limit	English, all documents, peer reviewed, dates 2000 to 2019				
Date	5.04.2019				
Data base		Number of articles	Number of articles selected based on abstract	Number of articles directly relevant to the subject of collaboration	Number of articles for general
PRO Quest ABI/INFORM Global		142	17	6	11

Consolidation of Strategy 6 and 7

All selected abstracts removing doubles – 111

Classification of abstracts:

- Directly relevant to the subject of collaboration: 38

- Not relevant to collaboration but possibly relevant to introduction: 55

- Not relevant to dissertation: 18

Consolidation of strategies 1 to 7

Abstracts from the database search directly relevant to the subject of collaboration after removal of duplicates: 78

Appendix 3 Letter and focus group guide sent to all possible participants of the focus group

XXX Meeting XX April 2019

Dear participants of the XXX meeting

I am currently doing a project for an MA in Management with the University of Malta. The title of my project is: **Attitudes and perceived benefits and barriers for Member State collaboration for pricing and reimbursement of medicines: a review of the evidence.** I ask you to participate in a focus group discussion which will contribute to this project.

If you accept to participate you will be kindly asked to fill the Consent Form / Agreement in **Annex 1**, which will be circulated during the XXX meeting.

Annex 2 contains an introduction with background information and explains the problem, the scope and the aims of the project.

A focus group guide has been prepared (refer to **Annex 3**) and is being circulated prior to the meeting to give you time to consider the questions, prepare for the focus group, fill the questionnaire and make notes. You can fill the form electronically, as a word document, or print it and fill it in writing. If you would like to send me the filled forms or send me feedback before the meeting, you are welcome to do so.

A focus group discussion, based on this guide, will be conducted during the XXX meeting on the XXth of April. The focus group is aimed to generate interaction between participants and to support participants to clarify their views and consider alternatives. You are encouraged to participate actively during the focus group meeting. During the focus group discussion you are asked to update / fill in the guide and to give it to the researcher at the end of the focus group meeting.

The information from the focus group will be collated and presented. Confidentiality and anonymity will be maintained. There will be no identification of any individual contributor in the write up. The only information given will be global and will include the total (global) numbers of participants, the number of different countries which they came from, a breakdown of how many came from large, medium and small countries and the areas of practice (HTA bodies, insurances etc.). The information collated will be circulated to the participants and they will be asked for any further feedback. The information will be presented and used in the project.

If the information from the focus group will be used for the publication of a co-authored paper, the draft paper will be circulated for feedback to all participants and consolidated as done for previous papers (such as the paper on Adaptive pathways and the paper on the HTA Proposal). Participants may opt to be included or not included in the final paper.

Thank you for your consideration, participation and valuable contribution.

Regards, Patricia Vella Bonanno, Researcher

pvellabonanno@gmail.com Mobile 00356 xxxxxxxx

Annex 1: Consent Form / Agreement for participation in the project

If you agree to participate in the Focus Group and to fill the Focus Group Guide in Annex 3 kindly fill and sign this Consent Form / Agreement for participation in the project. This Form will be circulated and signed during the XX meeting.

I agree to:

- participate in the focus group discussion and to fill the Focus Group Guide

- the use of the information as specified in the letter

- the recording of the focus group session and to its transcription

Name (capital letters)	Country	Do you consider your country as small, medium or large?	Area of practice (HTA body, reimbursement authority, health insurance)	Signature	E-mail address

Annex 2: Background information, an explanation of the problem and description of the scope and the aims of the project

Attitudes and perceived benefits and barriers for Member State collaboration for pricing and reimbursement of medicines: a review of the evidence

1. Introduction

Member State collaboration for pricing and reimbursement

Member States have extensive experience of collaboration in systems, processes and activities related to medicines regulation, which are regulated by EU legislation. For the system of pricing and reimbursement and the related activities (such as horizon scanning, early dialogues, coordination of patient registries, health technology assessment (HTA), economic evaluation, national pricing of medicines, reimbursement decisions, pricing decisions, negotiation and procurement, follow-up of negotiated conditions and effectiveness and generation of real world data) collaboration between the relevant Member State authorities is voluntary and is less systematic. For over ten years there have been various initiatives to increase collaboration between Member State reimbursement and pricing authorities.

One of the main motivators for governments to pursue initiatives for Member State collaboration within the system for pricing and reimbursement is to address challenges with the sustainability of their healthcare systems and the need to address the challenge of lack of access and affordability to new medicines to cater for the medical needs of their population. All governments within the European Union, including those of high-income countries, are experiencing increasing challenge to provide sustainable access to medicines. Concerns on universal coverage have instigated a number of initiatives by governments and by public authorities for pharmaceutical pricing and reimbursement. These initiatives have included new models to better manage the entry of new medicines, horizon scanning, new models for financing of innovative medicines, strategies to improve prescribing and use of medicines and initiatives for collaboration between Member States.

There have been initiatives for collaboration between Member State pricing and reimbursement authorities. A number of authorities have collaborated on a voluntary basis within the European Network for Health Technology Assessment (EUnetHTA) on differnt activities and have developed joint tools and guidelines. Over the last five years Member States have developed regional co-operations (e.g. BeNeLuxAIr, the Valletta Declaration, FINOSE and the Fair Pricing Initiative), to collaborate on different activities including horizon scanning, health technology assessment, negotiation of prices of medicinal products and sharing of information.

On the 31st of January 2018, the European Commission published a legislative proposal 'Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU'. The Proposal was discussed by the European Parliament is currently being discussed at Council.

2. The problem

Although there are is a concerted motivation for Member State collaboration and there are a number of ongoing and proposed initiatives for collaboration between Member States within the system for pricing and reimbursement, in practice participation in collaboration and the adoption of joint work and tools can be difficult and slow.

In spite of all the motivation and 'support' for collaboration, some initiatives lack a strong governance structure and there may be attitudes, interests and barriers which hinder progress. The impact of collaboration on costs and administrative burden can be quantified to some extent; however the impact on public health and on access to medicines is not so clearly measured and quantified. Other stakeholders of the pharmaceutical framework will be affected by Member State collaboration directly or indirectly and support or hurdle the initiatives according to their perspectives and priorities. The collaborations exist in the context of a real-life European environment which is continuously in flux and currently in turmoil and this can have significant and sudden impact on the initiatives for collaboration.

Internal and external stakeholders have different perspectives, attitudes and perceptions of benefits and barriers for Member State collaboration for pricing and reimbursement of medicines. Knowledge of the attitudes and perceived benefits and barriers for Member State collaboration will shed an insight of the drivers and challenges for collaboration and will support inferences which may support further action.

3. Scope

This study will review the evidence on attitudes and perceived benefits and barriers for Member State collaboration for pricing and reimbursement of medicines, to support inferences for future initiatives for collaboration between Member States in this system. The study will consider the different activities holistically. During the course of the study the context of the system will continue to evolve and there may even be major events such as the vote at Council regarding the Proposal on HTA.

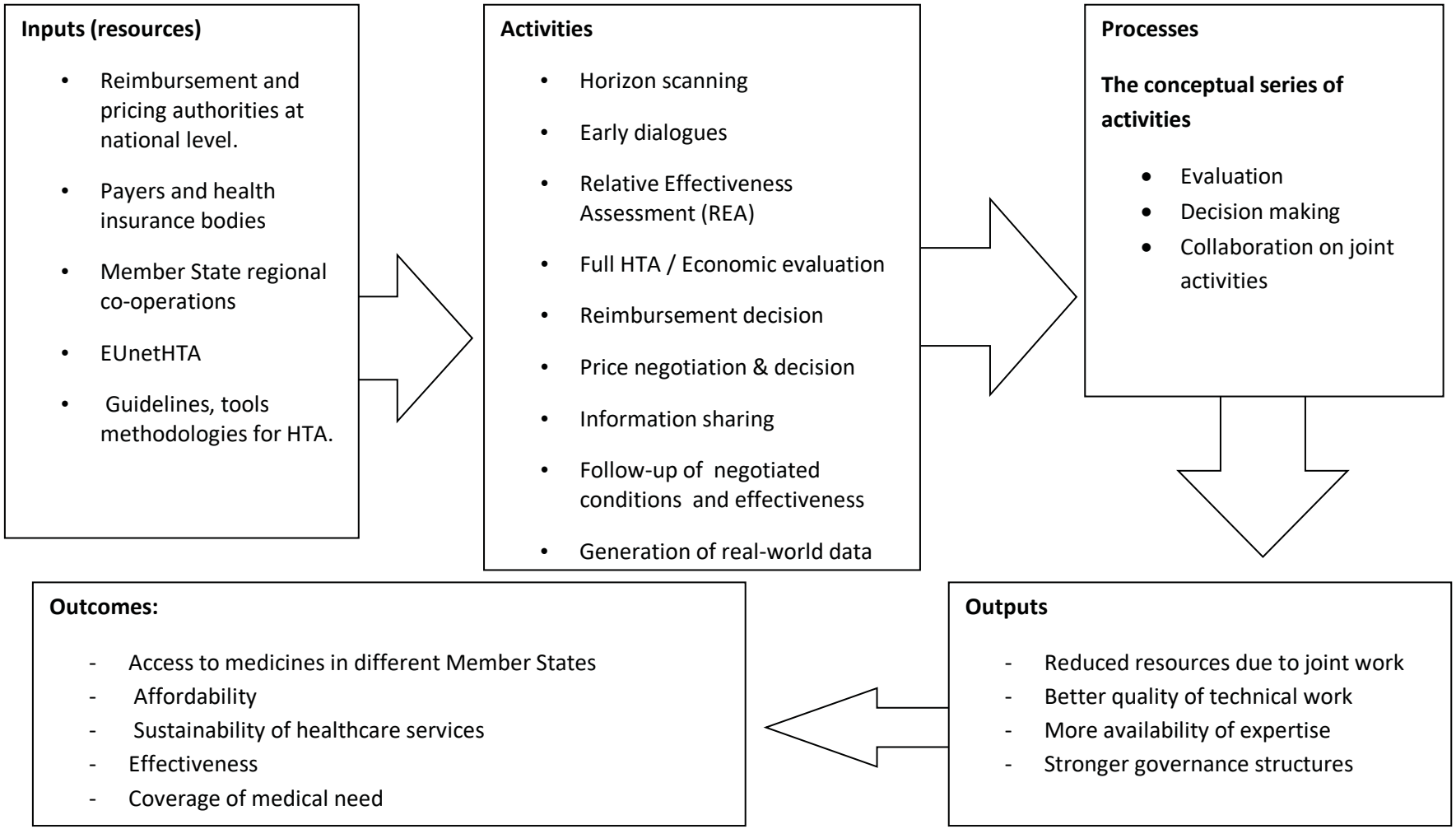
4. Aims

To study the attitudes and perceived benefits and barriers for Member State collaboration for pricing and reimbursement of medicines

To make inferences for collaboration between Member States for activities related to pricing and reimbursement of medicines

Annex 3: Focus Group Guide To be considered and filled before the meeting; updated and finalised during the meeting and given to the researcher at the end of the meeting

1. **Feedback on the draft Logic Model for the System of Pricing and Reimbursement.** Please print the model and write on it.



2. Attitudes on collaboration between national health authorities for pricing and reimbursement

Attitudes are a way of describing differences between people with reference to their different opinions (likes and dislikes). Attitudes are not transient feelings or moods but consistent thoughts that people have about a particular object or intervention (in this case collaboration between national health authorities) and the action they take towards it.

Attitudes consist of 3 aspects: (1) an emotional or evaluative component, (2) a belief or cognitive component, (3) an action or behavioural component

a. Should collaboration between national health authorities for pricing and reimbursement be:
   i. voluntary participation and voluntary adoption
   ii. mandatory participation and voluntary adoption
   iii. mandatory participation and mandatory for adoption

   Explain your choice _____

b. Should collaboration between national health authorities for pricing and reimbursement be regulated through:
   i. soft regulation (e.g. . guidelines set by the collaborating countries)
   ii. EU legislation set by the European Commission
   iii. legislation set by the collaborating countries

   Explain your choice: _____

c. What is the role of the European Commission with regards to collaboration between national health authorities for pricing and reimbursement?
   i. to set legislation to regulate the collaboration
   ii. to support a structure for governance

2. (contd.) Attitudes on collaboration between national health authorities for pricing and reimbursement – specific activities

Activity	Do you agree with collaboration between national health authorities for this activity? Yes/No	If you agree with collaboration:		If you do not agree with collaboration, why not?	Prioritise the activities for collaboration	Action to be taken
		Which authority should be responsible?	Type of collaboration: voluntary, regulated by legislation, governed by authority		Start with 1 for the highest priority	
Horizon scanning						
Early dialogues with industry						
Sharing of information						
Health technology assessment (REA)						
Full HTA (with economic evaluation)						
Price negotiation						
Reimbursement agreements						
Post-marketing authorisation studies						
Generation of real-world data						

3. Perceived impacts (benefits and losses) from collaboration between national health authorities for pricing and reimbursement

Social health impacts: Governance, good administration; access to social protection and health systems; sustainability of health systems; public health

Economic impacts: Costs related to processes; administrative burden; competitiveness; innovation and research; functioning of internal market

Social health impacts	Indicators	Benefits	Losses
Employment			
Governance, participation and good administration	Indicators: i. Impact of collaboration on involvement of different stakeholders in processes ii. The responsibilities of public administrations and other organisations at MS level iii. The uptake of joint outputs (e.g. HTA reports, early dialogues, tools) iv. Resource efficiency of processes v. The sustainability of European cooperation (sustainability of processes)		
Access to social protection and health systems	Indicator: The potential effect of collaboration on the access to treatments that could be considered as 'innovative'		
Sustainability of health systems	Indicators: i. The effect of collaboration on the financing of expensive treatments with little or no added value ii. The negotiating power of MSs in setting prices		
Public health	Overall public health i. Availability of health technologies on the market ii. Access to medicines		

Economic impacts	Indicators	Benefits	Losses
Costs The costs related to the processes	Variability in methods and processes currently employed by national health authorities across the EU; Possible duplication of efforts; Areas for improvement in consistency and transparency in the criteria used for decision making; What clinical and economic evidence is used in processes.		
Administrative burden	Administrative burden derived from processes: overall administrative burden; repeated processes/products across European countries; time needed for process; complexity of processes e.g. HTA assessment processes		
Competitiveness of EU health technology sector	Competitiveness of SMEs; revenues for the industry; predictability of national systems in Europe		
Innovation and research	Effect of the intervention on: research climate ; innovation in the European market; predictability of the market; reduction in fragmentation		
International trade innovation and research			
Functioning of the internal market and competition	Fragmentation of the system in Europe; convergence of methodologies; attractiveness of European market for industry		
Consumers	The availability of medical technologies for patients		
Macroeconomic environment	Overall economic growth; labour market		

4. Motivational factors which act as barriers (challenges) and factors which act as facilitators (facilitators, drivers) for collaboration between national health authorities for pricing and reimbursement

Category of Factors	Factors which act as barriers (challenges)	Factors which act as facilitators (motivators)	Comments / Details e.g. specific activities
Social Access to social protection and health systems, sustainable health systems, access to medicines			
Economic External factors arising by an economic factor or by a market event e.g. more intense competition, globalisation, market reaction, competitive advantage			
Behavioural Trust, ability or willingness to share information, resistance to change, mutual respect, ability to compromise, communication, personal interests			
Organisational Internal factors related to the form of organisation: supply chain problems, pressure from trading partners, flexibility, development of clear policy and guidelines			
Contextual History of collaboration			
Factors related to purpose Concrete attainable goals, shared vision, unique purpose, membership characteristics, sharing a stake in process and outcome			
Implementation climate Political and social climate			
Cultural Difference/similarities in goals and objectives, relationship, capacity to share risks, integration of key processes, flexibility of organisational system, compatibility of organisational culture			
Resources / physical Investments, financial resources, funds, staff, expertise, skilled leadership			

5. Recommendations and proposals for action with respect to collaboration between national health authorities for pricing and reimbursement	
What are your recommendations on the following?	**Recommendations and considerations for action (possibly consider collaboration for different activities, as applicable)**
Implementation of Member State collaboration	
Prioritisation of areas for collaboration	
Extent of collaboration	
Recommendations for improvement of ongoing collaboration	
Proposals for change of attitude regarding collaboration	
Proposals for change in behaviour related to collaboration	
Removal of barriers/ overcoming challenges	
What actions can be taken to motivate industry to participate and cooperate with initiatives for collaboration between national health services for pricing and reimbursement e.g. negotiation of prices of medicines, post-marketing authorisation effectiveness studies and generation of real-world data	
Involvement of patients in initiatives for collaboration between national health services for pricing and reimbursement	

Thank you for your contribution and support to this project.

Appendix 4 Data collected from published scientific literature

1. Update to the draft Logic Model for the System of Pricing and Reimbursement

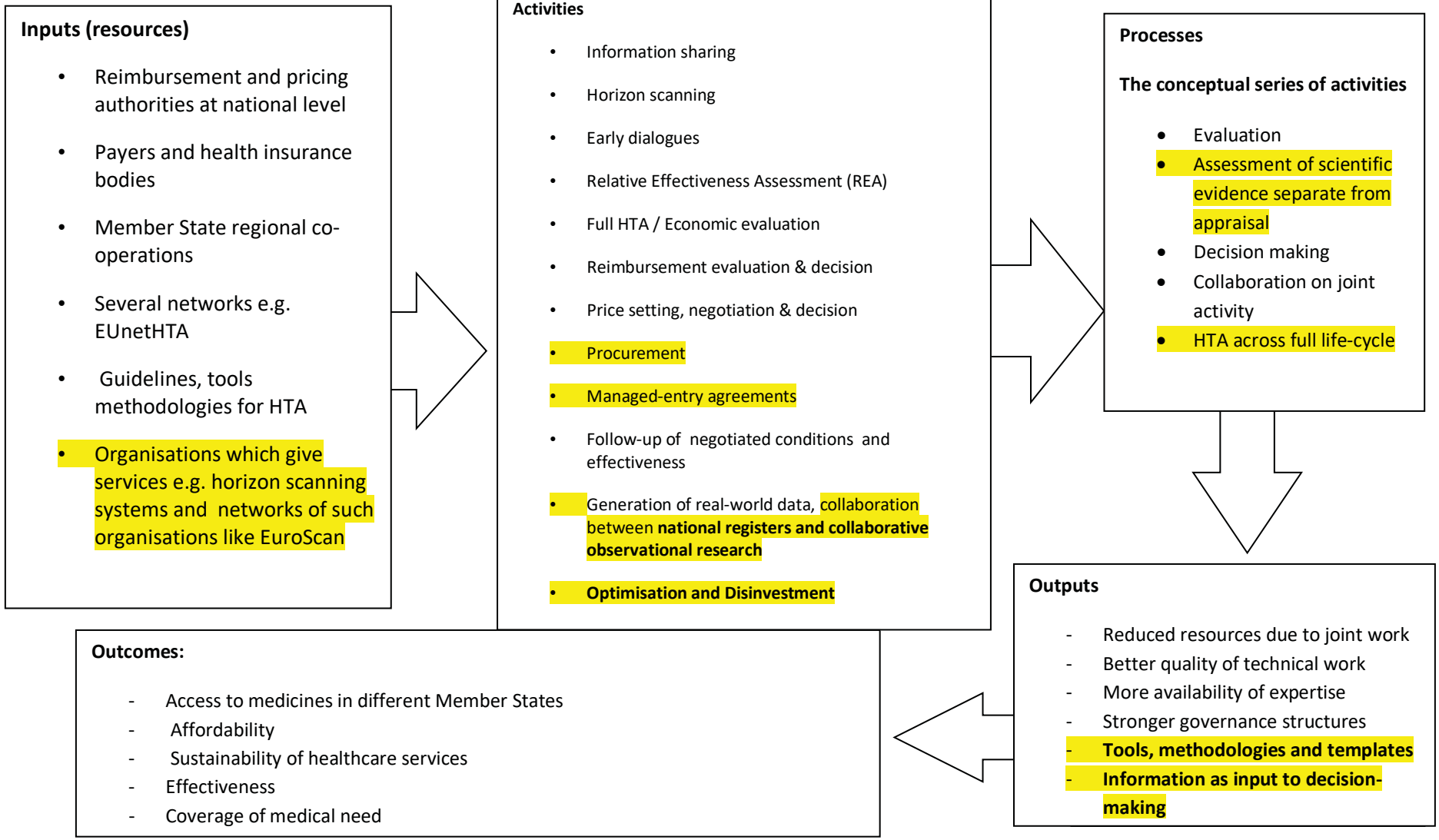


Figure 1. Draft Logic Model for the system of pricing and reimbursement updated with the data collected from published scientific literature (highlighted in yellow) (Model 2)

Description of the updates to the system for pricing and reimbursement reflected through the updates to the Logic Model from Model 1 to Model 2

Inputs (resources)

Loblova (2016) classified health technology assessment agencies in Europe into three streams: forerunners (well established agencies established since the 1980's and 1990's – five countries); mainstreamers (agencies established between 2004 and 2010 – 11 countries, including 4 EEC; non-adopters (12 countries – including 7 EEC).

There are sevaral collaboration networks aimed at increasing international collaboration in HTA both at European and at international level: EUnetHTA, International Network of Agencies for Health Technology Assessment (INAHTA), Health Technology Assessment international (HTAi), and HTAsiaLink (Woodford Guegan et al. 2014; Panteli et al. 2015)

EUnetHTA has been set since 2006 and coordinates European countries in the evaluation of HTA. It is co-funded by the European Commission (Wild and Langer 2008). In Europe projects have been funded to promote collaboration of MSs on HTA: EUnetHTA project 2006-2008, EUnetHTA Joint Actions. EunetHTA developed common tools and methodology, and the HTA Core Model. The POP database contains information on current and ongoing projects and enables collaboration on projects (Huic et al. 2013).

There are several well-established networks for the regular sharing of information and experiences on information on prices, reimbursement and rational use of medicines e.g. the Network of Competent Authorities for Pricing and Reimbursement of Medicines; the Medicines Evaluation Committee; the Pharmaceutical Pricing and Reimbursement Information Network; Piperska Group. There are collaborative initiatives e.g. BeNeLuxA, the European Network for Health Technology Assessment, EuroScan International network, the Nordic Pharmaceuticals Forum, the Vesegrad Group (Ferrario et al. 2017).

Horizon scanning systems (HSSs) usually directly serve a customer. EuroScan is an international collaborative network of publicly funded member organisations of HSSs involved in early awareness and alert systems for health technologies. The information is used by national governments, health services, healthcare professionals, purchasers etc (Douw & Vondeling 2006; Packer et al. 2015). Euroscan played an important role in the harmonisation process so that effective collaboration , to reduce duplication and for the development of procedures. The common understanding between participants contributes to stability and integration across the functions of horizon scanning systems. The main issues, such as an implicit prioritisation process' are susceptibe to subjectivity (Wild & Langer 2008).

In some countries the same agencies are in charge of marketing authorisation and reimbursement e.g Denmark, Greece, Iceland and Italy (Panteli et al. 2015).

Activities

In 2017 there was the establishment of EMA-EUnetHTA parallel consultation for early dialogue with the intention of aligning the data requrements along the life-span of the product (Eichler et al. 2018a).

Pricing: While the logic model does not dictate the order, sequence of the activities, there are countries where pharmaceuticals are evaluated for reimbursement based on an established price which is set in advance, and countries where reimbursement and the price are set after evaluation (Panteli et al. 2015). External reference pricing is frequently applied in European Countries. Vogler at al. (2017) considered that external reference pricing is capable of providning some benchmarking for policy makers and was shown to generate some savings. It implementation has been considered challenging. For high-priced medicines managed entry agreements and being used inclreasingly as they allow policy makers to manage uncertianty and obtain lower prices. However MEA raise concerns due to transparency becasue they include confidentiality clauses. Tendering as used by hospitals and off-patent out-patient departments has been proven to reduce prices of medicines but requires a robust framework (Vogler et al. 2017).

The paper by Souliotis et al. (2016) considered recommendations for a new pricing policy in Greece. External reference pricing was considered to have 'indigenous weaknesses' that might cause distortions and barriers to the sustainability of care. It was considered to raise 'ethical and political' concerns. Pricing models that fit prices to income and affordability were considered better and fairer. It was recommended that small sets of reference countries were preferred to large baskets, and were considered to increase transparency of markets (Souliotis et al. 2016). Of 28 European countries analysed in the study by Leopold et al. (2012), 24 applied external price referencing (EPR) in 2010. EPR is still highly used in Europe (Leopold et al. 2012). The PPRI network started as a project funded by the EU between 2005 and 2007 and continues as a European network of competnet authorities on pricing and reimbursement (Leopold et al. 2012).

Managed-entry agreements: the use of financial managed entry agreements (rebates and discounts) was common in Europe but outcomes-based managed entry agreements were not frequently used for medicinal products with a conditional marketing authorisation (Bouvy et al. 2018).

Procurement: of medicines goes beyond obtaining the lowest price for a product, but also includes the creation of a health market. Procurement requires a strategic approach (Ferrario et al. 2017).

Regulatory initiatives for earlier licensing of medicines: the FDA Breakthrough Therapy Designation and the Priority Medicines (PRIME) scheme was launched by the EMA in Europe. Some countries such as the UK introduced the Early Access to Medicines Scheme. New terms are now being connotated in the literature such as 'flexible regulatory pathways'. There are also calls for such intitiatives for reimbursement, flexible access and reimbursement pathways (FARPs), for the management of new medicines through pathways that decrease uncertainty due to accelerated marketing authorisation, addressing return on investment e.g. through payment for performance and flexible reimbursement mechanisms and the possibility for managed disinvestment (Mc Auslane et al. 2019). The increased use of adaptive pathways leads to motivation for collection of real-world data throughout the life-cycle of the medicinal product. Big data analytics on RWD can be used for insights

into effectiveness of medicines. The four V's: volume, variety, velocity and veracity (Geldof et al. 2019). Stress on the transformation of healthcare data to actionable information. A new concept of the 'learning healthcare system' was presented where real-world data is translated to real-world evidence in particular to address the question of relative effectiveness (Eichler et al. 2018b). Another concept which is technically basic but which was much less practised is international collaboration of registers and increase in collaborative observational research (Chatzidionysiou et al. 2018).

Optimisation: involves assessment or re-assessment of a technology and disinvestment involves stoppping/restricting technologies with low-benefit uses. The term managed exit is also used. The objective is to improve patient health outcomes, and fascilitate introduction of technologies which offer high value, thus increasing sustainability of healthcare. The concept of promotion of the value of HTA across the full life-cycle of the technology (Henshall, Schuller & Mardhani-Bayne 2012).

Processes

The assessment of scientific evidence is a different and separate step from appraisal. Assessment of scientific evidence is usually done by scientists and includes study of the relative effectiveness of pharmaceuticals compared to other treatment. Appraisal for reimbursement decision making is usually done by committees which include other staff such as representatives from ministries, healthcare provider organisations, health insurers representatives of patient organisations (Panteli et al. 2015).

Outputs

Tools, methodologies, HTA Core Model from EUnetHTA and application and field-testing of applicable tools and methds (Woodford Guegan et al. 2014).

Outcomes

It was considered that issues of differences in access, affordability and availability of medicines throughout European countries will remain inspite of initiatives for collaboration because different countries have significant differences in affordability and the lack of collaboration on HTA on the prices of medicines. Other initiatives (for pricing) would also be required (Vella Bonanno et al. 2019). Drug prices vary significantly between EU MSs, there was almost eleven fold difference in the price of interferon beta 1a between Germany and Croatia. Some medicines are still unaffordable for many EU citizens. Full price of olanzapine was higher in Bulgaria and for instance in Belgium. The authors recommended that prices of medicines should be adjusted to local economies. Differences in prices may lead to impaired access due to parallel trade or policies of pharmaceutical companies (Zaprutko et al. 2017).

2. Attitudes on collaboration between national health authorities for pricing and reimbursement

Attitudes are a way of describing differences between people with reference to their different opinions (likes and dislikes). Attitudes are not transient feelings or moods but consistent thoughts that people have about a particular object or intervention (in this case collaboration between national health authorities) and the action they take towards it.

Attitudes consist of 3 aspects: (1) an emotional or evaluative component, (2) a belief or cognitive component (3) an action or behavioural component

Notes on attitudes:

It is important to develop a general strategy and business model for sustainable European collaboration on HTA (Woodford Guegan et al. 2014).

WHO considered that the first steps for Member State collaboration should be sharing of information for HTA, the managed introduction of new medicines and practices for procurement (Ferrario et al. 2017).

The EUnetHTA has taken a number of work streams and work packages to foster alignment: parallel HTA consultations with the EMA, particularly linking to PRIME to select the products which would mostly benefit from facilitated access pathways; joint REA conducted in parallel with EMA assessment; collaboration on additional collection of data to increase the number of patients included in registries; the authors consider that pricing, reimbursement MEAs and exit schemes will remain at national competence for the foreseeable future (McAuslane et al. 2019).

There are two main perspectives for collaboration – traditionally (refer to papers up to 2014 – 2015) the Member States collaborated together to set tools, guidelines and methodologies and these can be used at national level. This brings about a degree of harmonisation and standardisation, promotion of best practices etc. but allows for differences between the MSs. Such collaboration is considered to facilitate exchange of knowledge, improve efficiency in the production of information and strengthen systems and processes. Organisational networks (refer to resources) lead to dialogue between expert stakeholders and help to contribute to challenges in methodology and procedures (Panteli et al. 2015). More recently there is the concept of doing things together as one output. This is most dominant for REA (through the Proposal on HTA) and also recently being promoted for generation of evidence throughout the medicinal product life-cycle e.g. registries and the generation of real-world data (Panteli et al. 2015).

Collaboration was always 'assumed' to be voluntary. The Proposal on HTA introduced the concept of mandatory participation and voluntary /mandatory uptake of the output by Member States. There was only one paper in the review concerning the Proposal on HTA (Vella Bonanno et al. 2019).

There was one paper which considered the Proposal on HTA. This paper gave different opinions of MS practitioners and academics on the Proposal when it was published. This paper considered the pros and cons of collaboration. However this paper went into aspects concerning the implications of the collaboration as set in the Proposal. The respondents were practitioners from reimbursement authorities as well as academics. The paper considered the power holding within the collaboration. There was concern that the participants in the collaborations would be restricted from having jurisdiction over the methodology. There was concern that having the methodology set through legislation would restrict the collaborators from evolving and adapting the methods. The implications of having collaboration governed by legislation and the concept of mandatory participation and mandatory implementation were also a major concern for some participants. It was considered important that although there is collaboration there is flexibility and adaptability (Vella Bonanno et al. 2019).

The paper considered that with the legislation regulating collaboration 'the position of the Member States in the power balance will change'. It was considered that the legislation will make the MSs more susceptible to interference from the industry (Vella Bonanno et al. 2019). A main consideration for collaboration was the perspective of possible gain and risks from collaboration. Countries with well-established national systems who considered their national system superior to the system after collaboration were reluctant to collaborate, while those with no or less advanced systems were willing to collaborate (Vella Bonanno et al. 2019).

The Proposal advocated for greater patient and stakeholder involvement in the collaboration, compared to the level of involvement in some Member States. Different countries have different level of patient involvement and participation in decision making and the experience is different countries. There was concern that once there is a collaborated system, it will be easier for other stakeholders to exert power over the whole system of decision making (Vella Bonanno et al. 2019).

If there is collaboration there is more strength and this can act positively or negatively depending on whose side the bias is strongest. The Proposal on HTA as originally published had the economic perspective of the single market as its main legal basis and less consideration to the public health perspective (Vella Bonanno et al. 2019).

If there is a joint assessment there may be more pressure on the countries to take a common decision, even though some countries have more financial constraints for reimbursement (Vella Bonanno et al. 2019).

While the Proposal on HTA gives a framework for cooperation, the processes were going to be detailed in the delegated and implementing acts. This was considered to restrict and include detail in the methodology, thus reducing the possibility for flexibility and adaptation (Vella Bonanno et al. 2019).

The experience of EUnetHTA involved investment of time and resources from Member States and funds from the European Commission. Progress was achieved in the setting of tools and methodology. However the main stumbling block was that on a voluntary basis, full collaboration was not achieved. Member States were not willing to collaborate on all processes (Vella Bonanno et al. 2019).

Member States have jurisdiction over the HTA evaluation within their health systems and have the right to decide whether and how to collaborate between themselves on these activities. To date MSs have considered and proposed MS driven voluntary cooperation and all collaborations to-date were voluntary. The collaboration in the Proposal is more coercive and is tightly regulated by legislation. It is difficult to consider how MSs have difficulties to collaborate fully on a voluntary basis and will then happily collaborate under a coercive legislative regime. Even within a network of voluntary cooperation there are still elements of hierarchy and power struggle. Those who feel less strong in the hierarchy may rather be at par with other MSs (through legislation) than feel 'bullied' by some more powerful MSs (Vella Bonanno et al. 2019).

While there are advantages in collaboration, including producing of evaluation of a high quality, it is considered important to safeguard the needs of individual MSs, and to take local contexts into consideration, without compromising national healthcare systems (Vella Bonanno et al. 2019)

2. (contd.) Attitudes on collaboration between national health authorities for pricing and reimbursement – specific activities

Activity	Attitudes
Horizon scanning	One of the main networks for horizon scanning is the EuroScan International Network. EuroScan network was not considered as a Member State collaboration for pricing and reimbursement because it consists of an international network of publicly funded agencies doing horizon scanning which are not necessarily national agencies for pricing and reimbursement but include different types of agencies such as public health agencies. Members of EuroScan are often service providers for Pricing and Reimbursement agencies and can compete with each other to give services. Barriers to collaboration between agencies within this network include differences in aims, purposes, requirements of systems; lack of finance, opportunity and staff; differences in language; problems with dissemination (Packer et al. 2015). There is limited evidence on the impact of horizon scanning, and it was considered that current horizon scanning systems mainly identify health technologies at a late stage of development, mainly with the objective of information selection of topics for HTA. It was recommended to improve horizon scanning by clearly identifying the end users, consider the long-term effects for the full health system, and to consider smart data systems and international collaboration to improve the efficiency of horizon scanning systems. It was considered that new skills will be required to improve HSS (Oortwijn et al. 2018). Horizon scanning and forecasting tended to be implemented as an academic exercise disconnected from policy and from practice. There were a few examples ('rare exceptions') where horizon scanning was used to support decision making (Vogler et al. 2017). Cooperation platforms such as Beneluxa and the Nordic Pharmaceutical Forum aim to work together on horizon scanning (Vogler et al. 2017).
Early dialogues with industry (joint scientific advice)	Early dialogue is considered to coordinate data collection in a lot of countries and to facilitate outcomes-based agreements (Bouvy et al. 2018). Collaboration between Member States for early dialogues is considered very important for companies and reimbursement agencies, particularly for orphan drugs (Mincarone et al. 2017). The experience of joint scientific advice for HTA for applicant MAHs was considered positively (Vella Bonanno et al. 2019). EUnetHTA follows the concept of the lifecycle and starts with early dialogues to advise the manufacturers on study designs, comparators and outcomes for HTA (Erdos et al. 2019).
Sharing of information and generation of evidence	EUnetHTA partners considered three levels of collaboration for promising health technologies: sharing of information on generation of evidence (this is considered to entail a low level of commitment); coordinated action – based on an agreed common core protocol but actions being done independently at national level (considered to require an intermediate level of commitment) and joint action – involving cross-border joint study and prospective data collection (high level of commitment) (Quentin et al. 2009). EUnetHTA calls for reduction in duplication for generation of evidence. In EUnetHTA JA 3 WP5 is responsible for evidence generation pre- and post authorisation (Erdos et al. 2019).

Health technology assessment (REA)	Interviews with members of HTA organisations showed that cross-border REA meets in particular the needs of smaller- and middle-sized European countries and countries with less well-developed HTA systems. It was considered that the potential quality gains and efficiency would be the highest for these countries. It was considered that in the shorter term national adoption of cross-border assessments would be highest in these countries. It was considered that as with time more experience would be gained with cross-border assessment, the success would be more tangible and some larger countries may also be motivated to join in collaboration on REA (Kleijnen et al. 2015). As European countries have significant differences in their health care systems, they may have different challenges and perspectives towards collaboration on REA (Kleijnen et al. 2015). Collaboration on different steps in the process of REA was generally considered positively although some respondents wanted to limit the collaboration to exchange of information while others were in favour to extending to production of assessments which can be used for decision making. A mandatory cross border production of assessments was not accepted by any of the respondents (Kleijnen et al. 2015). There are similarities in the methodologies for REA in different countries and collaborations on assessments were considered feasible (Kleijnen et al. 2015). The desired extent of collaboration on REA varies between countries (Kleijnen et al. 2015). Smaller and middle sized countries and countries whose HTA systems are less well-developed are more willing to support collaboration. This may relate to higher efficiency gains (Kleijnen et al. 2015). EUnetHTA was considered to be able to deliver tangible achievements in terms of development of tools and methodologies, which was the original basis for collaboration between MSs. The cooperation for joint assessment is considered as sustainable and avoids duplication and inefficiency, however progress in this regard is slow and the objective of jointly produced assessments is a target for the future and this is considered to 'realise economies of scale' with increased quality, consistency and transparency for health systems. There were three joint actions, the current JA period is 2016 - 2020 (Erdos et al. 2019). One major concern of a number of countries with the Proposal on HTA was that MSs were expected to transfer the authority for conducting REA to a single body and then have to abide by this decision. Moreover the purpose and responsibility for reimbursement of medicines remained national competence (Vella Bonanno et al. 2019). The Proposal was consider to have a significant impact and was considered to overpower national legislation (Vella Bonanno et al. 2019).
Full HTA (with economic evaluation)	Interviews with practitioners from eight HTA organisations agreed that Member States should initially prioritise collaboration on REA before progressing to economic considerations (Kleijnen et al. 2015). There was a general consensus that reimbursement decisions should be taken within the national and local context, however there are efficiency gains through collaboration for collection of evidence required for these decisions (Kleijnen et al. 2012).
Price negotiation and pricing policy	Vogler et al. (2017) showed that confidential discounts and MEAs have been increasingly used, particularly for new patented medicines. The industry argued that because of the wide-spread use of external reference pricing, affordable pricing could only be

	possible through discrimination through confidential discounts. Policy-makers are in a type of 'prisoner's dilemma'. The authors recommended increased cooperation on pricing between countries, between regulatory authorities and pricing and reimbursement agencies, through sharing of experiences and by improving transparency of price information, including real price information and disclosure of confidential discounts. No European country has pioneered in disclosing discounted prices. The authors believe that a possible solution could lie in cooperative approaches by public agencies, even if only a few countries as prices would reduce due to stronger purchasing power and larger purchasing power and larger markets in case of joint negotiations or possibly joint procurement (Vogler et al. 2017). The authors recommended the need for all-European solutions which will guarantee the affordability of medicines and profitability for companies and support national pricing negotiations. They should contribute to bringing prices of medicines to levels adequate to domestic economic factors and lead to achievement of the main goals of the European public health policy (Zaprutko et al. 2017).
Reimbursement agreements	There is general acceptance that decision making should remain at national/local level in Europe (Allen et al. 2017). In Canada there is a centralised HTA agency that enables regions to include evidence generated at the national level to be considered at a local context. Also the regulatory environment of the EMA shows an example that collaboration can work (Allen et al. 2017).
Procurement	
Post-marketing authorisation studies	
Generation of real world data	Cross-network and cross-border collaboration is important for the generation of real-world data in order to increase volume and variety, adopting a hybrid approach linking multiple databases and getting information from different countries (Geldof et al. 2019) International cooperation will increase the speed of implementation of the use of actionable information for the implementation of a learning healthcare system (Eichler et al. 2018b). Policies for the use of RWD in HTA evaluation differed across HTA agencies. It was considered that this dissuaded from the use of RWD for HTA. The authors recommended for more alignment of policies for the use of RWD. The project proposals by EUnetHTA were considered as a positive starting point for alignment (Makady et al. 2017).
Optimisation and disinvestment	Recommendations for need for international collaboration to learn from experiences, share information and disseminate methods of good practice (Henshall et al. 2012)

3. Perceived impacts (benefits and risks) from collaboration between national health authorities for pricing and reimbursement

Social health impacts: Governance, good administration; access to social protection and health systems; sustainability of health systems; public health

Economic impacts: Costs related to processes; administrative burden; competitiveness; innovation and research; functioning of internal market

Social health impacts	Indicators	Benefits	Risks
Employment		Collaboration is considered to increase the possibility of funding for joint research projects, payment for assessment work done and some experts may consider collaboration as an opportunity for specialisation and consultation in specific areas. HTA may continue to develop into an interdisciplinary science (Vella Bonanno et al. 2019).	
Governance, participation and good administration	Indicators: i. Impact of collaboration on involvement of different stakeholders in processes ii. the responsibilities of public administrations and other organisations at MS level iii. the uptake of joint outputs (e.g. HTA reports, early dialogues, tools) iv. resource efficiency of processes v. the sustainability of European cooperation (sustainability of processes)	Availability of database of planned and ongoing projects encourages cross-agency collaboration by identifying similar projects across agencies (Woodford Guegan et al. 2014). Methodological guidelines e.g. on selection of endpoints lead to improved decision making (Woodford Guegan et al. 2014). Collaboration between different agencies enables piloting of tools and provides lessons in logistics and trade-offs between resources and duplicated work (Woodford Guegan et al. 2014). Collaboration is considered to increase harmonisation of the assessment (Kleijnen et al. 2015). Most respondents felt that the general quality of decision making will improve through cross-border assessments in certain countries, although not in countries with a very high current level of assessment (Kleijnen et al. 2015). Increased knowledge and experience of participants, increased quality and number of HTA reports (Huic et al. 2013). It was considered that with increased collaboration on HTA there will be increased motivation to find estimates to measure relevant therapeutic	Collaboration and harmonisation on REA was considered to have the potential of losing local contextualisation and introducing standards that are not universally accepted (Kleijnen et al. 2015).

		and financial impacts of HTA. Increased collaboration and increased usage of reports by international agencies will require a broad definition of impacts of HTA. The impact needs to be captured in policy decisions and this is difficult and time consuming. International uptake by HTA agencies requires development of common tools and processes. Consideration of international impact and the responsiveness to external factors are crucial (Nachtnebel et al. 2016). EUnetHTA developed a website (EUnetHTA Interface to facilitate furthering of evidence level for use by the partners to enable transfer of information). Benefits include easy storage of information, avoidance of duplication of work and more efficient transfer of information, attainment of critical mass of evidence (Quentin et al. 2009). Authors considered that countries with less-well developed HTA systems (like Slovakia) significantly benefitted from participation within the Joint Action projects of EUnetHTA through improvement in the quality of the process for HTA, use of tools and methodological standards and the use of the information technology and communication tools (including the POP (Planned and Ongoing Projects) database. REAs prepared at the EU level were considered as 'very useful' for the Slovak healthcare system. Reuse of joint work was considered useful (Tesar et al. 2017). Collaboration ensures that HTA is conducted according to agreed standards and methodology of high level (Vella Bonanno et al. 2019). Significant agreement was achieved on joint standardised methodologies and tools through EUnetHTA and other EU funded projects and this was considered positively (Vella Bonanno et al. 2019) International collaboration leads to transparent, standardised and high-quality assessments. This requires clearly defined tools, processes and methods (Nachtnebel et al. 2015).	

Access to social protection and health systems	Indicator: The potential effect of collaboration on the access to treatments that could be considered as 'innovative'	Collaboration is considered to result in increased strength and negotiation power, which is important for new high-priced medicines (Vella Bonanno et al. 2019).	
Sustainability of health systems	Indicators: i. the effect of collaboration on the financing of expensive treatments with little or no added value ii. the negotiating power of MSs in setting prices	Increases in volume and variety of data from different databases from different countries were considered to increase the quality of real-world data, particularly for effectiveness. The insights and the evidence generated from big-data analytics are only as 'high-quality as the data being analysed' (Geldof et al. 2019). There was experience of consolidation of purchasing power across different countries, and there are 'pooled procurement models' in different parts of the world. These resulted in reduction in unit purchase price, improved quality assurance, reduction of corruption in procurement, better-informed selection and standardisation, increased equity between members, utility of the role of the host institution that administered the system. Pooled purchasing power is a determinant of pooled procurement arrangements (Huff-Rousselle 2012).	
Public health	Overall public health i. Availability of health technologies on the market ii. Access to medicines	Improving the quality of healthcare through improved quality, removing duplication, facilitating timely production of national HTA reports and supporting sound decision-making process (Woodford Guegan et al. 2014). Improvement of national reports by using information from the cross-border assessment e.g. literature review, multiple comparisons, information about treatments available in other countries, modelling. One respondent recommended that there should be sharing of information on price (Kleijnen et al. 2015). Collaborative observational research increases the number of patients involved and statistical power (Chatzidionysiou et al. 2018). Some stakeholders positively linked collaboration on HTA with increased access to medicines, particularly in countries with low access, while some	

		opinionated that access is mainly dependent on affordability (Vella Bonanno et al. 2019). Mayer et al. (2017) considered that European collaboration decreases uncertainty with the actual added value of a technology through early dialogues, harmonised and transparent assessments improve the quality of reports, division of work between authorities allows more efficient use of resources and assessment of more technologies, involvement of patients ensures consideration of endpoints relevant to patients (Mayer et al. 2017).	

Economic impacts	**Indicators**	**Benefits**	**Risks**
Costs The costs related to the processes	Variability in methods and processes currently employed by national health authorities across the EU; Possible duplication of efforts; Areas for improvement in consistency and transparency in the criteria used for decision making; What clinical and economic evidence is used in processes.	Ducournau et al. (2019) described how employees within a pharmaceutical company developed tools based on the first four domains of the EUnetHTA Core Model, and found that the EUnetHTA Core Model provided a 'useful framework' for a pharmaceutical company to optimise generation of evidence and for assessment.	
Administrative burden	Administrative burden derived from processes: overall administrative burden; repeated processes/products across European countries; time needed for process; complexity of processes e.g. HTA assessment processes.	Development of outputs such as HTA tools and methods, HTA Core Model for standardisation of assessment, guidelines, development of principles, methodological guidance; application and field-testing on developed tools and methods. Importance of online version of tools and simplification of tools to facilitate collaboration. Adoption of the Core model could increase the transferability of HTAs across countries; collaboration can decrease work load (Woodford Guegan et al. 2014). The proportion of responders who predicted that they would find the HTA tools useful in practice varied between two-fifths and one-half depending on the tool (Woodford & Cook 2014).	Some respondents from HTA agencies considered that collaboration on REAs may initially slow down the process in countries which have well-established procedures (Kleijnen et al. 2015).

		Collaboration and harmonisation on REA may save resources and prevent duplication of work for industry and for payers (Kleijnen et al. 2015). All respondents agreed cross-border collaboration would lead to increased expertise through the sharing of information and expertise (Kleijnen et al. 2015). In countries with limited resources or expertise for REA cross-border assessment could result in faster assessment (Kleijnen et al. 2015). Collaboration on HTA is considered to reduce duplication and improve efficiency (Vella Bonanno et al. 2019). EUnetHTA has a POP database that allows partners to share information with each other on planned and ongoing projects conducted in individual agencies, this database helps to reduce duplication and facilitates collaboration between partners on similar projects. Collaborative activities usually focus on exchange of information and literature search protocols, extraction tables, information on technical description of a technology. Agencies wait for each other to finish their projects when they fins a topic on the database. Within the first two years of JA3 there are about 20 jointly produced assessments (Erdos et al. 2019).	
Competitiveness of EU health technology sector	Competitiveness of SMEs; revenues for the industry; predictability of national systems in Europe	Collaboration and unification of common criteria for REA will apply to MSs and to companies, and this is considered to streamline activities, avoid duplication, support synergies between experts from different authorities and support one joint submission by the industry. New products require competence, expertise and specialisation for evaluation and collaboration can support this (Vella Bonanno et al. 2019).	
Innovation and research	Effect of the intervention on: research climate ; innovation in the European market; predictability of the market; reduction in fragmentation	Respondents from HTA agencies considered that collaboration would not lead to decreased time to market new drugs because the national processes will still need to take place and REA is only part of the process for reimbursement decisions (Kleijnen et al. 2015).	
International trade innovation and research			
Functioning of the internal market and	Fragmentation of the system in Europe; convergence of	Luzzatto et al. (2018), showed that the costs of new orphan drugs are so much higher than then the production costs and strongly recommend	

competition	methodologies; attractiveness of European market for industry	that Europe should take advantage that it covers 500 million inhabitants and has such a significant position as a customer of new medicines that price negotiation should take place at the European level and no by individual MSs. Some European countries have teamed up to do joint negotiation on the price of OMPs.	
Consumers	The availability of medical technologies for patients		
Macroeconomic environment	Overall economic growth; labour market		
Other impacts	**Indicators**	**Benefits**	**Risks**
Behavioural		Networking with contacts made was considered to be the highest benefit from collaboration at EUnetHTA. Optimal involvement of external stakeholders (Woodford Guegan & Cook 2014) Respondents considered that frequent contacts between experts from different agencies help to build trust (Kleijnen et al. 2015).	

4. Motivational Factors which act as barriers (challenges) and factors which act as facilitators (drivers) for collaboration between national health authorities for pricing and reimbursement

Category of Factors	Factors which act as barriers, challenges	Factors which act as facilitators, enablers
Social Access to social protection and health systems, sustainable health systems, access to medicines		Generation of added value (Woodford Guegan & Cook 2014).
Economic External factors arising by an economic factor or by a market event e.g. more intense competition, globalisation, market reaction, competitive advantage	As yet no international initiatives for joint procurement specifically associated with the procurement of medicines. The authors from the WHO considered that the flexibilities offered by the agreement on trade-related aspects of intellectual property rights seem not to have been exploited to their full extent. Reasons include inadequate 'infrastructural and-or technical capacity and too much negative pressure from the industry'. Many European countries consider the pharmaceutical industry as an important employer and tax payer and the countries fear 'annoying' the industry and having retaliation from the industry. Smaller countries may be concerned that their full exploitation of the agreement on trade-related aspects of intellectual property rights will limit the release of new products on their markets by the pharmaceutical industry. There are also regulatory limitations concerning data and market exclusivity (Ferrario et al. 2017).	The value of real-world data can be translated into economic incentives so that collection of data is not only seen as a cost centre. Incentives need to be implemented across Europe (Geldof et al. 2019). The WHO considered that few countries perform well in all areas of strategic procurement and considered that international cooperation and sharing of experience can be of benefit (Ferrario et al. 2017). Individual country concerns of irritating the pharmaceutical industry might be overcome if the countries collaborate together (Ferrario et al. 2017).
Behavioural Trust, ability or willingness to share information, resistance to change, mutual respect, ability to compromise, communication,	How to stimulate collaboration (Woodford Guegan et al. 2014). Engagement may not involve just members from partner agencies but also a variety of external agencies and stakeholders (Woodford Guegan et al. 2014). Most respondents did not experience significant problems when communicating in English, however it was recognised that there was 'inherent difficulty' with communicating in English, which was not most of the participants' native language (Woodford Guegan & Cook 2014).	Effective communication (Woodford Guegan & Cook 2014). Continuous cooperation of the competent members (Kleijnen et al. 2015). Experience of collaboration during EUnetHTA Joint Action showed that human resources from the participating countries were open and skilled for cross-national work

personal interests	Tools for the collection of real-world data should be designed carefully and need to be tested, there should be site-coordinators who are trained to ensure the quality of data. Mechanisms for quality control should be in place to support the identification and the solving of any issues. It is important to balance the needs of the research and the concerns such as data protection and privacy to ease the linkage of data (Garrison et al. 2007). While web-site serves as a means to sharing information it will only be as relevant as the relevance, accuracy and update of the information included in it. Challenges to using a web-site for the sharing of information by EUnetHTA partners included the 'not invented here syndrome' whereby users are reluctant to use information that did not come from their own mechanisms because they could not control the quality of the information. Another challenges included the transferability of information due to differences in technology use; terminology, training and consideration of population risk. Other challenges include the confidentiality of information, the completeness and quality for filling forms and the level of diffusion of a technology in different countries (Quentin et al. 2009). The Commission was considered to place itself in a position of conflict of interest in the Proposal on HTA because it wanted to have power over the conclusion of the joint assessment and it has the decision making role in regulation (Vella Bonanno et al. 2019). EUnetHTA emphasised on the involvement of stakeholders and the presentation of interests was encouraged because it was considered to promote the utilisation of HTA in national and regional policy (Erdos et al. 2019). It was considered as mandatory to involve healthcare providers (clinicians) in scoping and in the review phase of assessment (Erdos et al. 2019). Transparency is a major challenge for MS collaboration. Discussions about transparency concern not only price transparency and disclosure of discounts	(Lo Scalzo et al. 2014).

	but also concern joint negotiation and procurement. Cooperation, even if by a few countries, will be expected to have an impact (Vogler et al. 2017). Experience of the EUnetHTA JA showed that working in small groups enabled more exchange. Coordination of large and heterogenous groups was considered challenging (Lo Scalzo et al. 2014).	
Organisational Internal factors related to the form of organisation: supply chain problems, pressure from trading partners, flexibility, development of clear policy and guidelines	Respondents identified a number of challenges for the uptake of the HTA Core Model and guidelines for REA in national settings including: national assessments may have different content from those based on core model/guidelines, may apply methodology less strictly, may use less or more advanced methodology; there may be differences in methodology e.g. with the choice of comparators or in accepting indirect comparisons (Kleijnen et al. 2015). Lack of transparency observed at national processes can be an obstacle for collaboration. Institutions should be clear on their consideration of confidential information (Panteli et al. 2015). The European Commission proposed to take up a powerful role within the collaboration for the original Proposal on HTA including determination of the final conclusion of any joint assessment of REA. This brought a negative reaction from MSs (Vella Bonanno et al. 2019).	
Contextual History of collaboration	The Proposal on HTA brought up the context of activities that are within EU competence and what is within Member State jurisdiction. A number of stakeholders considered that HTA (including REA) was of Member State competence (Vella Bonanno et al. 2019).	The Nordic countries Denmark, Finland, Norway and Sweden had started active collaboration in HTA in the 1980s and 1990s and they established a collaborative body Nordic Evaluation of medical technology. INAHTA dates back to the 1990s (Huic et al. 2013). Participation in ISPOR (International Society for Pharmacoeconomics and Outcomes Research) facilitated HTA collaboration of Hungry (a middle-income country with low capacity and expertise for HTA) with other countries of the Central European and Eastern Region (Kalo et al. 2013).

		Collaboration on communication platforms and exchange of knowledge were considered more important in countries which have less well-developed pathways for decision-making (Panteli et al. 2015).
Factors related to purpose Concrete attainable goals, shared vision, unique purpose, membership characteristics, sharing a stake in process and outcome	Allen et al. (2017) distinguished between the technical evaluation and the final reimbursement decision. They considered that there can only be harmonisation on the technical evaluation but not the final reimbursement decision. Guidelines could be aligned but considerations such as willingness to pay are specific to each jurisdiction and thus the reimbursement decision cannot be harmonised (Allen et al. 2017). Different countries have different position / priority on the level of reimbursement. Some countries introduced different criteria for diseases such as cancer, possibly due to its emotive nature (Vella Bonanno et al. 2019). Different standard treatments are available in different countries (Vella Bonanno et al. 2019). The relevance of topics for individual HTA institutes and the timing of joint assessments in line with the time-table of the country is a challenge (Nachtnebel et al. 2015). Experience with EUnetHTA Joint Action considered that the procedure for selection of topics for joint evaluation was not clear and was not managed well (Lo Scalzo et al. 2014).	Achievement of objectives according to work plan, achievement of progress, good communication and clear work stream management act as motivators (Woodford Guegan et al. 2014; Woodford & Cook 2014). Interviews with practitioners from eight HTA organisations considered quality and timely availability of assessments as a critical success factor for collaboration on REA (Kleijnen et al. 2015). The Joint REA reports should be transparent, there should be agreement on methodology and there needs to be room to meet demands of individual countries (Kleijnen et al. 2015). Methodology of REA is very similar in many countries, making collaboration on assessments feasible (Kleijnen et al. 2015) The authors consider that comparison of reimbursement recommendations by eight reimbursement agencies, classified system taxonomy showed a level of concordance in HTA recommendations and the authors consider that such alignment could support a more collaborative HTA in Europe (Allen et al. 2017). Lack of harmonisation of policies regarding the use of RWD for HTA was considered as a deterrent from using RWD for HTA. Collaboration on policies for the use of RWD through EUnetHTA is expected to increase incorporation of RWD in HTA (Makady et al. 2017). Kleijnen et al. (2012) evaluated differences and

		similarities in methodology of relative effectiveness assessments of pharmaceuticals in 29 jurisdictions and found that there are more similarities than differences particularly related to choice of comparators, and preferred end points. This was considered to increase the possibility and 'feasibility' for collaboration and development of methods and best practices for REA across jurisdictions.
Implementation climate Political and social climate	Most respondents considered coverage in healthcare was a politically sensitive issue. Respondents considered that no country would forsake its autonomy in decision making. The technical domains were considered less sensitive and most respondents considered that the production of cross-border REAs does not conflict with the principle of subsidiarity. Some respondents considered that if part of the joint assessment was included in national procedures, it would still influence the autonomy of HTA organisations. Use of coordinated assessments may lead to loss of autonomy in deciding the outcome of relative effectiveness assessments (Kleijnen et al. 2015). Collaboration between registers of inflammatory arthritis in Sweden, Denmark, Norway, Finland and Iceland requires harmonisation and standardisation of the individual data repositories due to legal, logistic and methodological challenges. This leads to the need to assess the viability of different logistical approaches to data protection, to investigate analytical approaches to multisource data and to perform collaborative studies on effectiveness of treatment, safety and health economic outcomes. Analytical protocols need to be harmonised, and data sources need to provide information on an established set of desired variables. The research question needs to be agreed (Chatzidionysiou et al. 2018). Countries which have well-established systems for HTA wanted to preserve their systems and considered collaboration negatively. They considered that collaboration could reduce the quality of assessment and reduce the speed, compared to their systems (Vella Bonanno et al. 2019).	Political aspects, building trust between countries, the quality of the process and its management are critical success factors for collaboration (Kleijnen et al. 2015). An environment conducive to collaboration needed e.g. enforcement of legislation on intellectual property rights (Ferrario et al. 2017). It is considered that there is increased benefit and thus motivation to collaborate in the area of orphan diseases, because there is low volume in each country. Cooperation needs to be fostered in the EU through standardisation in the approach for the creation of registries and ensuring coordination between what is required at EU level as compared to what is needed at Member State level (Denis et al. 2010). Countries with no or less established systems considered collaboration as an opportunity to improve, learn, standardise the systems and share work (Vella Bonanno et al. 2019).

	Nachtnebel et al 2015 described that experience during JA 2 showed that preparation of HTA assessments took 7 to 9 months. A survey conducted showed that 28 HTA institutes wanted to use the common assessments for national HTA reports in their own context. The HTA Agency in Austria prepared two HTA reports based on EUnetHTA assessments. The use and transferability of the standardised assessments for national / local HTA reports was considered to be a challenge. The development of methods in national HTA institutes is 'impeded by legislative requirements' (Nachtnebel et al. 2015).	
Cultural Difference/similarities in goals and objectives, relationship, capacity to share risks, integration of key processes, flexibility of organisational system, compatibility of organisational culture	Practitioners across Europe getting to know each other and how to work together (Woodford Guegan et al. 2014). Practitioners working in HTA organisations identified challenges with implementation in the respective national processes as a challenge (e.g. because of legal restrictions) (Kleijnen et al. 2015). Legal restrictions may hinder the use of the core model / guidelines in REA (Kleijnen et al. 2015). There may be variance in the interpretation of the methods of the core model between assessors or countries (Kleijnen et al. 2015). Countries with highly legalised structures have more difficulty to adopt collaboration (Kleijnen et al. 2015). A concern of the Proposal on HTA was different peculiarities between countries such as size of the country Gross domestic product, and thus 'roadmaps' cannot be transferred between countries (Vella Bonanno et al. 2019). HTA has a technical aspect and also ethical and cultural considerations. Although the Proposal on HTA considered only the technical domains of the HTA model, a number of authors considered that the clinical part and the economic part cannot be separated from each other (Vella Bonanno et al. 2019).	Rajan et al. (2011) considered 'examples from other countries' and the 'transfer of good practices to different local contexts' as a main enabler for collaboration on HTA. The fact that evaluation showed quite a high level of congruence in the evidence requirements for HTA was considered positively. It is important to understand and accept that a number of differences in evidence requirements are 'justified as necessary' to support context-specific analysis and to address criteria for decision making. Other national requirements may be the result of historical events, of local politics and also due to the funding of the national healthcare services (Oyebode et al. 2015).

	Different health technologies can challenge moral and cultural values and beliefs (Vella Bonanno et al. 2019).	
Resources / physical Investments, financial resources, funds, staff, expertise, skilled leadership	Availability of funding for collaboration, e.g. EU funding is needed for EUnetHTA (Woodford Guegan et al. 2014). Enhancement of the information management system by testing various solutions to improve collaboration (Woodford Guegan et al. 2014). Tool and guideline development brought a number of challenges: technical challenges, legitimate differences in HTA methodology across agencies, guidelines needed to strike balance between being sufficiently broad to achieve consensus on content and being specific enough to give concrete guidance; creating infrastructure to support collaboration e.g. the use of different languages (Woodford Guegan et al. 2014). Interviews with practitioners involved in REA consider methodology and resources as a challenge for collaboration (Kleijnen et al. 2015). Logistical difficulties for a collaboration needs resources for coordination, dissemination, evaluation and strategic development (Woodford Guegan et al. 2014) None of the respondents from HTA agencies considered a reduction in the number of staff that would be needed for national processes. More resources may be needed to adapt to the Core Model's outcomes to the national procedure (Kleijnen et al. 2015). All respondents agreed that work on a cross-border assessment needed to start very early in order for results to be available for national decision making. Resources and time are needed to achieve consensus between countries. Extra resources (costs) may be needed to do reports in English (Kleijnen et al. 2015). When collaborating to gather real-world data, GDPR should still be regulated at Member State level, even for international systems (Geldof et al, 2019). An underlying 'federated data provider infrastructure' is necessary to stimulate collaboration and data science-based innovation at a European scale (Geldof et al. 2019).	HTA is a resource intensive activity with heavy burden of evidence gathering. Sharing of data in a standardised manner can reduce resource requirements (Woodford Guegan et al. 2014). In 2018 the Innovative Medicines Initiative (IMI) started EHDEN - the European Health Data and Evidence Network to create a sustainable and trustworthy European ecosystem. The network is based on a federated data platform (Geldof et al. 2019). Ongoing initiatives such as EUnetHTA and MoCA (Mechanisms of Coordinated Access to Orphan Medicinal Products) support coordination across health care systems for post-marketing collection of data (Eichler et al. 2018a) EUnetHTA helps to facilitate early dialogues (Eichler et al. 2018b). IMI PROJECT Big Data for Better Outcomes was aiming to support efforts for coordination of multi-country data collection (Bouvy et al. 2018). International cooperation on the use of electronic health records and eHealth is needed to reduce resource requirements for individual actors , reduce uncertainty and associated concerns about the adoption of new approaches and methods and help sharing failures and success. Cooperation will increase the speed of implementation of the learning healthcare system (Eichler et al. 2018b).

	Barriers to international collaboration included the working language, organisational differences, differences in time-frame, difficulties in project management and lack of financial support (Huic et al. 2013). Countries have different requirement s for REA and REA done by EUnetHTA may be considered inferior to national REA in some countries, particularly those countries with an advanced national methodology (Vella Bonanno et al. 2019). Barriers to re-use of EUnetHTA assessments included timing constraints because the EUnetHTA assessments were still in progress at the time of the policy request for a national assessment not being up to data, differences in the scope of the EUnetHTA assessment and the national assessment, the reporting structure used by EUnetHTA and language (Erdos et al. 2019). Experience of working in the EUnetHTA JA showed that sifting of researchers involved in HTA production due to change in their position within an agency or if they left the agency could create difficulties and gaps in the availability of expertise in particular domains of the Core Model. For certain domains it was more difficult to find trained and experienced researchers (Lo Scalzo et al. 2014). The use of different languages, lack of experience with the use of the online tool and different ways for producing HTAs and for conducting processes were also considered as barriers for collaboration. There were differences in practice within agencies (Lo Scalzo et al. 2014).	As far back as in 2009, Belgian National institute for Health considered that international cooperation would increase efficiency in the production of HTAs and reduce duplication of assessments (Cleemput & Van Wilder 2009). International cooperation on HTA reduces redundancy and avoids duplication of HTA outputs, increases the capacity to produce common and high quality information, and increases the number of national reports (Huic et al. 2013). The experience of setting up and piloting of the HTA Core Model was described. This experience may give some elements which can also apply to other experiences of joint setting of tools. The tool provides standardised production and transparent reporting of RE information. There are more similarities than differences in the methodology used for RE in different countries and this supports a collaborative tool (Kleijnen et al. 2014). EUnetHTA has led to the development of tools and methodologies for HTA which allow joint assessment using agreed tools and methods. This was considered particularly useful for countries with limited expertise and resources, as these are considered to benefit most from joint assessment (Vella Bonanno et al. 2019). The standardisation of methods is generally considered positively (Vella Bonanno et al. 2019). Evaluation of horizon scanning assessments done by different international stakeholders showed a high level of overlap in the topics assessed. The authors considered that there would thus be benefit from international

		collaboration on horizon scanning. Subsequently there were 'calls for collaboration' and joint reports were published. It was recommended to further facilitate collaboration and usability of horizon scanning reports by other agencies. Development of tools at European level was considered to enable adjustment of reports to make them usable by a wider range of agencies to tailor the output to fit the needs of a wide range of users (Nachtnebel et al. 2016). There is a high level of support for collaboration on HTA in MSs as collaboration increases the efficiency of HTA by avoiding duplication, improving the quality of assessment (Vella Bonanno et al. 2019). Approximately 4 months of staff time are saved when an agency re-uses a EUnetHTA report (Erdos et al. 2019). EUnetHTA has also the Evidence Database on New Technologies (EVIDENT) Database which is a tool to promote additional evidence in the post-launch phase (Erdos et al. 2019).

5. Recommendations and proposals for action with respect to collaboration between national health authorities for pricing and reimbursement

Recommendations on the following:	Recommendations and considerations for action (possibly consider collaboration for different activities, as applicable)
Implementation of Member State collaboration	Use of outputs (e.g. tools) from European collaboration can increase sustainability of national and regional cooperation (at country level) (Woodford Guegan et al. 2014). Differences in methodological approaches may be solved by identifying the differences at an early stage and by scoping. A collaborated report should be compiled by at least two countries (an author and a co-author)(Kleijnen et al. 2015).
Prioritisation of areas for collaboration	
Extent of collaboration	
Recommendations for improvement of ongoing collaboration	
Proposals for attitude regarding collaboration	Vella Bonanno et al. (2019) were of the opinion that a lot of good work has been done through EUnetHTA and other initiatives and this should be used as a foundation for future collaboration on HTA.
Proposals for change in behaviour related to collaboration	
Removal of barriers/ overcoming challenges	Much needs to be learnt to improve willingness to work together (Vella Bonanno et al. 2019).
What actions can be taken to motivate industry to participate and cooperate with initiatives for collaboration between national health services for pricing and reimbursement e.g. negotiation of prices of medicines, post-marketing authorisation effectiveness studies and generation of real-world data	
Involvement of patients in initiatives for collaboration between national health services for pricing and reimbursement	
Supporters/ facilitators of collaboration	Knowledge of each other's work plans, use of common templates and methodology, using a common scientific and working 'language' (Woodford Guegan et al. 2014).

	A case study of four cases of collaboration showed that facilitators for collaborative initiatives included: predefined project management, early identification of collaborators, commitment to the project, adherence to timelines, relevance of technology, common understanding of the methods applied, experience in the technical work, merging of methodological and clinical expertise, agreement on the process and standard applied, acceptance of reports written in English (Huic et al. 2013). A paper on the experience of the HTAsiaLink network , which was set up in 2011, identified key determinants of success and challenges for this network . Collaboration benefitted from 'systemic factors' including a favourable outlook on HTA to set priorities for reimbursement; 'organisational factors' such as the high number of newly established HTA agencies with similar needs for capacity building and peer-to-peer support; 'interactional aspects' including ownership, trust and team spirit among members of the network. Challenges of this network included financial sustainability and management of the expanded network (Teerawattananon et al. 2018).

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Appendix 5.1 List of types of documents used for grey literature and documents used

Type of document	Examples of documents from this source of evidence	
Policy Briefs Policy Briefs are documents prepared by a group of designated authors to address a specific policy question. They are aimed to provide evidence and different policy options to policy makers and do not contain policy advice. They are published by the WHO Regional Office for Europe as the host organisation for the European Observatory on Health Systems and Policies. They adopt systematic methodology and undergo a formal process of peer review. The Policy Briefs were specific to an area of practice. These policy briefs gave a lot of insight and perspective. The information is factual. The policy briefs bring different information together: literature, case studies, narrative review. Some briefs also include semi-structures interviews e.g. with policy officers, professionals with experience in the field and experts. They are subjected to a process of rigorous peer review to ensure that the evidence presented is independent. With respect to the sources of evidence in relation to the model from Barends & Rousseau (2018), refer to Figure 2.1, the Policy Briefs contain information from the scientific literature, from practitioners and possibly also from the organisations (the Member State authorities for pricing and reimbursement).	Espin, J. et al. 2016, *How can voluntary cross-border collaboration in public procurement improve access to health technology in Europe?*, Policy Brief 21, WHO Regional Office for Europe, Copenhagen.	This policy brief was prepared in support of the Maltese Council Presidency in 2017.
	Panteli, D. & Edwards, S. 2018, *Ensuring access to medicines: How to stimulate innovation to meet patients' needs?* European Observatory on Health Systems and Policies, World Health Organisation, Policy Brief 29, WHO Regional Office for Europe, Copenhagen.	This policy brief was prepared in support of the Austrian Council Presidency in 2018.
	Vogler, S. Paris, V. & Panteli, D. 2018, *Ensuring access to medicines: how to redesign pricing, reimbursement and procurement?* European Observatory on Health Systems and Policies, World Health Organisation, Policy Brief 30, WHO Regional Office for Europe, Copenhagen.	This policy brief was prepared in support of the Austrian Council Presidency in 2018.
Council of the European Union The Council of the EU adopts legal acts as well as other types of documents such as conclusions, resolutions and statements,	Council of the European Union. 2016, *Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States*	These Council Conclusions were published in 17/06/2016 as part of the Presidency of the Council of the Netherlands.

which are not intended to have legal effects. The Council uses these documents to express a political position on a topic related to an area of activity of interest. The Conclusions of the Council of the European Union are set and approved by the Member States. The Council also has a role in the co-legislative process and new legislation needs to be approved by the Council. The Proposal for a regulation for HTA is being discussed by the Council. With respect to the sources of evidence in relation to the model from Barends & Rousseau (2018) (refer to Figure 2.1), these Conclusions mainly relate to information from the organisation internal data.	https://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-balance-pharmaceutical-system/ Council of the European Union, 2017*, Council conclusions on encouraging Member States-driven voluntary cooperation between Health Systems* https://publications.europa.eu/en/publication-detail/-/publication/c527e567-5d5c-11e7-954d-01aa75ed71a1 Report by the Austrian Presidency on the *Proposal for a Regulation on health technology assessment and amending Directive 2011/24/EU* Council of the European Union Doc 14694/18 30 November 2018 http://data.consilium.europa.eu/doc/documents/ST-14694-2018-INIT/en.pdf	These Council Conclusions were published on the 30.06.2017 as part of the Presidency of the Council of Malta. As at end August 2019 the Proposal was still being discussed at Council.
Research study on impact and benefits of cross border collaboration in WHO European region With respect to the sources of evidence in relation to the model from Barends and Rousseau (2018) (refer to Figure 2.1), these Conclusions mainly relate to information from organisation internal data. This study was commissioned by the WHO Regional Office for Europe on cross-country collaborations in Europe. This study was performed by the WHO Collaborating Centre for	The objectives of this study were to 'identify and assess the country collaboration initiatives, their motivations and objectives; to assess performance of the initiatives, to identify facilitating and challenging factors, to identify gaps where country collaborations could provide important opportunity to promote equitable access to medicines' This research consisted of a document review and semi-structured interviews with key staff of	By the end of May 2019 this study was not published by the authors and the only information about this study was published through the presentation delivered by Sabine Vogler and Fatima Suleman during the INFARMED Conference. The researcher was one of the interviewees for this study on behalf of the Valletta Declaration.

Pharmaceutical Policy and Regulation, Utrecht; WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, Vienna and WHO Collaboration with WHO Collaborating Centre for Pharmaceutical Policy, Boston.	authorities from 5 cross-country collaborations. Document and interview data were analysed using a matrix with predefined domains.	
International Conference 'Facing the Challenges: Equity, sustainability and access' This International conference was held in INFARMED, Portugal in collaboration with WHO EUROPE to commemorate the 25th Anniversary of INFARMED on the 29-30 of November 2018. By the 19th of May the Conference proceedings were not yet published however the abstracts / presentation of this conference are available online on the conference web-site. The conference presented a number of contemporary activities related to collaboration as shown by the presentations listed. The researcher attended this conference and was moderator for the session entitled: 'Benefits of country collaboration '. Reference: INFARMED 2018, Medicines Facing the Challenges: equity, sustainability and access, 29 – 30 November 2018 http://www.infarmed.pt/web/infarmed/25-anos/eventos/international-conference-facing-the-challenges-equity-sustainability-and-access With respect to the sources of evidence in relation to the model from Barends and Rousseau (2018) (refer to Figure 2.1), these Conclusions mainly relate to information from organisation internal data.	Presentation title: Research study on impact and benefits of cross border collaboration in WHO European Region Presentation of the study described above	Vogler, S. & Suleman, F. 2018, *Research study on impact and benefits of cross border collaboration in WHO European Region.*
	Presentation title: Making the case for horizon scanning Presentation of the International Horizon Scanning Initiative (IHSI). Initiative is open to all countries, not limited to Beneluxa	Golja, A . 2018 Making the case for horizon scanning.
	Presentation title: EUnetHTA ongoing and future development Update on EUnetHTA joint action 3: 81 partners, 29 countries. Aim to increase collaboration, production and usage.	Guardian, M. 2018. EUnetHTA ongoing and future developments.
	Presentation title: The Valletta Declaration	Testori-Coggi, P. 2018. The Valletta Declaration.
	Presentation title: Nordic Pharmaceutical Forum	Sonne, F. 2018. Nordic Pharmaceutical Forum.
	Presentation title: Joint health economic assessment in FINOSE	Stromgren, A.2018, Joint health economic assessment in FINOSE.

	Presentation title: Fair and affordable pricing (FAAP)	Dziurda, D. 2018, Fair and affordable pricing.
Information from the Regional cross-country collaborations. With respect to the sources of evidence in relation to the model from Barends and Rousseau (2018) (refer to Figure 2.1), these Conclusions mainly relate to information from organisation internal data.	Nordic Collaboration (Nordic Pharmaceuticals Forum) The Nordic Collaboration have a page within the website of Amgros, the Danish pharmaceuticals organisation.	Nordic Collaboration, 2019 www.amgros.dk/en/areas/nordic-collaboration/ accessed 13/05/2019.
	BeNeLuxA This initiative has a dedicated website. The website publishes activities, news, links, information.	Beneluxa Initiative on Pharmaceutical Policy http://www.beneluxa.org/ accessed 13/05/2019.
	The Valletta Declaration The Valletta Declaration does not have a website. The VD prepared a standard document with information which is given to all stakeholders asking for information. The VD started issuing a press release after each meeting in order to give information proactively .	The researcher performs the role of the secretariat of the Valletta Declaration.
Interdisciplinary Platform on Benefit Assessment This Interdisciplinary Platform is set by discussion between clinicians and experts from a variety of disciplines and is supported by an open consortium of sponsors including pharmaceutical companies. They produce a publication series, each volume on a different topic. This is published by: Kienberg, Germany: Springer	Ampelas, A.E. & Schmitz, J. 2019, Strengthening EU cooperation on Health Technology Assessment pp. 8 – 13.	Article gives the latest update on the Proposal on HTA by the European Commission.
	Haas, A. & Ermisch, M. 2019, Common European benefit assessment – Ways and aberrations, Interdisciplinary Platform on Benefit Assessment, vol. 8, April 2019, pp. 26 – 36.	This article gives the perspective of the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) on the draft Regulation.

Medizin Verlag GmbH Volume 8 April 2019 'European Benefit Assessment – Opportunities and Risks' This publication contained opinions and insights of different stakeholders including the European Commission, academics, National Association of Statutory Health Insurance Funds (Germany), the Department of Pharmaceuticals at the Federal Joint Committee, Institutes for Medicines Regulation. It contains information on the progress and opinions of the Proposal on HTA. https://www.aerztezeitung.de/politik_gesellschaft/gp_specials/plattform_zur_nutzenbewertung/ With respect to the sources of evidence in relation to the model from Barends and Rousseau (2018) (refer to Figure 2.1), these Conclusions mainly relate to information from stakeholders.	Behring, A. 2019, National versus European benefit assessment: pros and cons from the G-BA's perspective pp. 38 – 45.	This article gives the perspective of the Federal Joint Committee G-BA on the draft Regulation.
European Commission	In September 2018 the European Commission organised a workshop for the sharing of experiences from the Regional Co-operations. This workshop was confidential.	By the end of May 2019 no report of this meeting was provided. The notes from the meeting were confidential and were not included in the analysis.
	Legislative proposal on HTA European Commission, 2018, *Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU (2018/0018(COD)*, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM%3A2018%3A51%3AFIN	

Innovative Medicines Initiative https://www.imi.europa.eu/ A public-private partnership in the life-sciences. Funding comes from the European Union's Horizon 2020 research and innovation programme (EU tax payers) and the pharmaceutical industry.	ADAPTSMART http://adaptsmart.eu/home/ An enabling platform for the coordination of Medicines Adaptive Pathways to Patients (MAPPs) activities.	Interview with Ad Schuurman published on the ADAPTSMART website on 19/03/2018. http://adaptsmart.eu/has-adapt-smart-been-successful-in-changing-the-way-we-think-about-approving-new-therapies-interview-with-ad-schuurman/
On-line magazines With respect to the sources of evidence in relation to the model from Barends and Rousseau (2018) (refer to Figure 2.1), information from this source mainly relates to information from stakeholders.		A few examples of articles from the press were chosen to show media coverage.
Politico https://www.politico.eu/ A global nonpartisan politics and policy news organisation, launched in Europe in April 2015. In June 2018 a survey ranked POLITICO the most influential publication on European affairs.	Belgium, Netherlands team up to take on pharma over prices	Peter O'Donnell 21/04/2015 https://www.politico.eu/article/belgium-netherlands-team-up-to-take-on-pharma-over-prices/
	Europe struggles to face down Big Pharma	Carmen Paun 28/03/2018 https://www.politico.eu/article/drug-pricing-big-pharma-even-facing-big-pharma-together-countries-still-struggle-to-haggle/
Pharmaphorum https://pharmaphorum.com/	Late to the Party but we brought friends: BeneLuxA's horizon scanning initiative	21/11/2018 https://pharmaphorum.com/views-analysis-market-access/joint-horizon-scanning/
Euractive https://www.euractive.com/	Southern EU states present unified front in drug talks	9/05/2017 https://www.euractiv.com/section/health-consumers/news/southern-eu-states-present-unified-front-in-drug-talks/

	EU southern alliance on drug pricing expands	31/01/2018 https://www.euractiv.com/section/health-consumers/news/eu-southern-alliance-on-drug-pricing-expands/
Pink Sheet https://pink.pharmaintelligence.informa.com/	Biogen Pours cold water on cross country Spinraza pricing talks with Norway and Denmark	Francesca Bruce 28/12/2018 https://pink.pharmaintelligence.informa.com/PS124478/Biogen-Pours-Cold-Water-On-Cross-Country-Spinraza-Pricing-Talks-With-Norway-And-Denmark
	EU cross-country coalition targets new products for joint pricing talks	Maureen Kenny 15/02/2019 https://pink.pharmaintelligence.informa.com/PS124764/EU-CrossCountry-Coalition-Targets-New-Products-For-Joint-Pricing-Talks
Stakeholder feedback on the HTA proposal The website of the European Commission under the area EU cooperation on Health Technology Assessment includes feedback on the Proposal by different stakeholders. Examples: https://ec.europa.eu/info/law/better-regulation/initiatives/com-2018-51/feedback/F11065_en?p_id=168597	EURORDIS https://www.eurordis.org/ EURORDIS-Rare Diseases Europe is an alliance of 798 rare disease patient organisations	EURORDIS 30 March 2018 issued feedback on the EC Proposal on HTA and called for the EC Proposal on HTA. The Organisation posted this information on their website and as feedback on the European Commission website: Transparency and Health Technology Assessment cooperation as proposed by the Regulation are the only real antidote to secrecy and political games
	EFPIA European Federation of Pharmaceutical Industries and Associations	Feedback from EFPIA
Patient Associations	Joint Statement by 14 Patient Associations	EFNA, 2018, *Patients call for meaningful*

	EFNA – European Federation of Neurological Associations (Patient associations)	*involvement in European cooperation on HTA, Joint statement,* 12 November 2018, https://www.efna.net/patients-call-for-meaningful-involvement-in-european-cooperation-on-hta/
Industry opinion on cross-country collaborations	EFPIA	EFPIA, 2019, *Policy Principles on Cross-country Collaborations on medicines' Pricing and Access*, 17 January 2019, https://www.efpia.eu/media/412513/policy-principles-on-cross-country-collaborations-on -medicines-pricing-and-access.pdf

Appendix 5.2 Data collected from analysis of grey literature

1. Update of the draft Logic Model for the System of Pricing and Reimbursement.

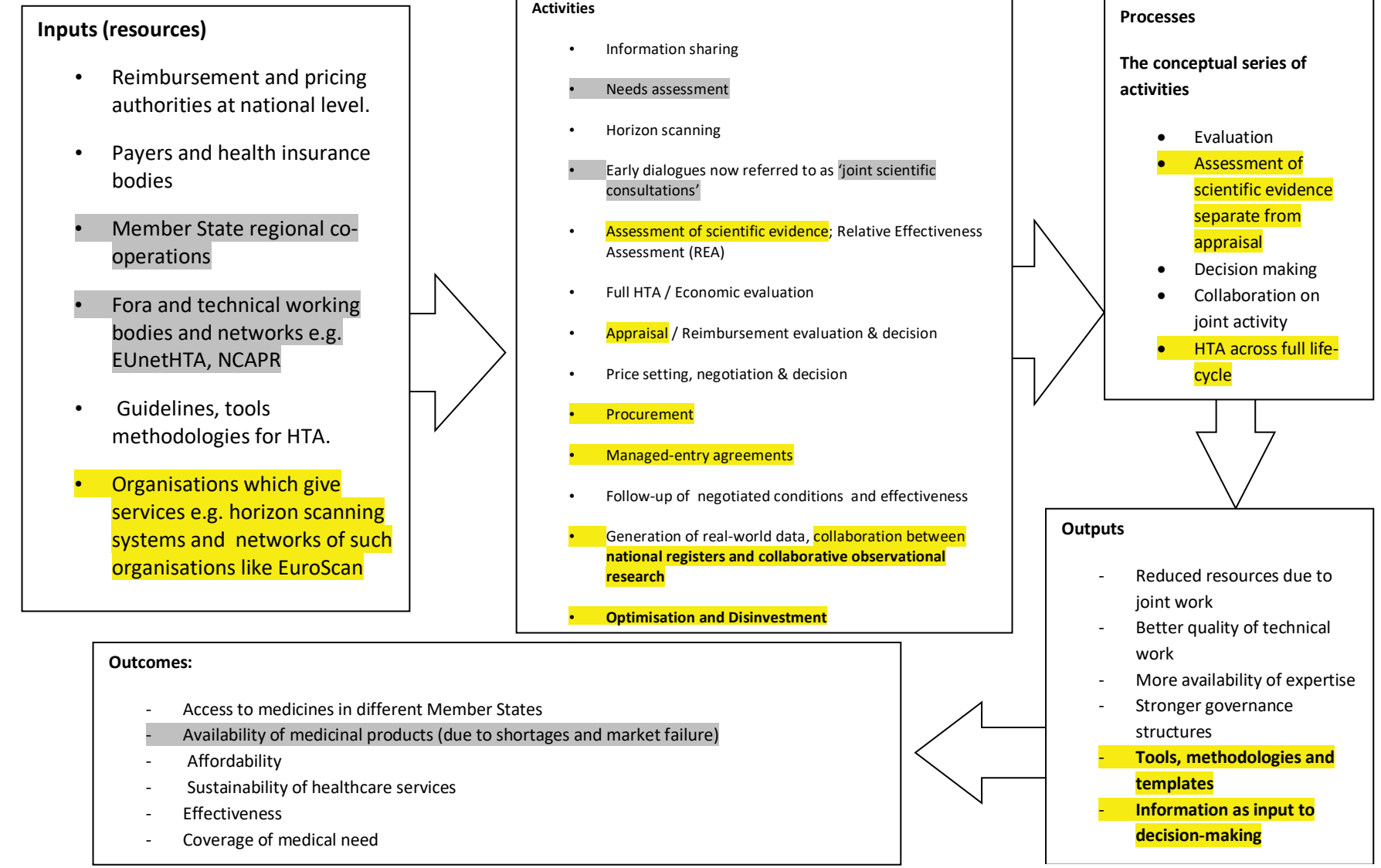

Figure 2. Draft Logic Model for the system of pricing and reimbursement updated with the data from the published scientific literature presented in Model 2 (highlighted in yellow) and from the grey literature (highlighted in grey) Model 3

Description of the updates to the system for pricing and reimbursement reflected through the updates to the Logic Model from Model 2 to Model 3

Needs assessment involves data collection at country level to inform prioritisation of research and development (Espin et al. 2016).

Early dialogues are recently being referred to as 'joint scientific consultation'. Joint scientific consultations are expected to provide advice on the design of clinical studies in order to facilitate the generation of appropriate evidence for HTA purposes (Ampelas & Schmitz 2019; Haas & Ermisch 2019).

There are different methods for public procurement including open tender, restricted tender, competitive negotiation and direct procurement (Espin et al. 2016).

There is a motivation towards 'coordinated collaboration alongside the life-cycle'. This requires coordination between different stakeholders (which is outside the scope of this dissertation). The authors consider that the collaboration for those collecting real world data is not sufficiently organised and structured (Vogler, Paris and Panteli 2018).

Shortages and market failure of medicinal products are not considered within the scope of this dissertation. In the Draft Logic Model availability has included as an outcome in Model 2.

The Council of the European Union invites the MSs and the Commission to improve and strengthen existing dialogue and cooperation between MSs at the EU level, through and within existing fora and technical working bodies and by continuing work of the Network of Competent Authorities on Pricing and Reimbursement (NCAPR), the Pharmaceutical Committee and the Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) (Council Conclusions 2016).

2. Attitudes on collaboration between national health authorities for pricing and reimbursement

Attitudes are a way of describing differences between people with reference to their different opinions (likes and dislikes). Attitudes are not transient feelings or moods but consistent thoughts that people have about a particular object or intervention (in this case collaboration between national health authorities) and the action they take towards it.

Attitudes consist of 3 aspects: (1) an emotional or evaluative component, (2) a belief or cognitive component (3) an action or behavioural component

Attitudes towards collaboration

Policy Brief 30, "Ensuring access to medicines: how to redesign pricing, reimbursement and procurement?" listed recommended solutions and approached to address barriers and limitations with the current framework for pharmaceutical pricing, reimbursement and procurement. One of the suggested solutions is 'Collaborative approaches'. Collaboration can involve different intensity levels and can involve different actors. Examples include exchange of knowledge and experiences with policies and good practices, technical cooperation in areas such as horizon scanning and HTA, joint price negotiation and procurement. Collaborations could be through bilateral and multilateral collaborations or under the framework of the European Commission (as in the area of marketing authorisation) (Vogler, Paris & Panteli 2018). The authors of Policy Brief 30 consider that the draft legislation "on strengthening HTA collaboration in Europe proposed by the European Commission could be a starting point" (Vogler, Paris & Panteli 2018).

The Council of the European Union in 2016 "recognises that a number of Member States have expressed interest in pursuing voluntary cooperation between two or more Member States in the field of HTA as well as in exploring voluntary cooperation in different areas, for example on issues related to pricing and reimbursement on medicinal products, activities aimed at horizon scanning, the exchange of information and knowledge, the collection and exchange of price data such as EURIPID collaboration, and in some cases by bringing together of facilities and resources as well as instruments for joint price negotiations and the conducting of early dialogue with companies developing new products; all these activities should remain to be voluntary, focused on clear added value, shared interests and objectives" (Council of the European Union 2016).

The Council of the European Union (2016) listed voluntary cooperation could include activities such as joint horizon scanning, pro-active exchange of information between MSs particularly in the pre-launch phase with due respect for existing national rules and frameworks e.g. in relation to business confidentiality; possible strategies on voluntary price negotiations in coalitions of MSs that have interest to do so; reinforcement of existing

cooperation schemes and initiatives to foster agreement on approaches to address unavailability of medicinal products and market failure situations (Council Conclusions 2016).

The current project-based cooperation model for EUnetHTA faced a number of limitations, in particular limited use of joint work in national HTA processes. Low uptake of joint work in national HTA systems is due to legal and administrative hurdles, concerns around quality assurance, timelines and sustainability of work produced in a project setting (Ampelas & Schmitz 2019).

The European Commission proposed that involvement in joint activities other than HTA would be on a purely voluntary basis (Ampelas & Schmitz 2019).

Costs for the horizon scanning initiative (IHSI) will be covered through the solidarity principle: costs shared based on purchase price parity and population. An external party to build infrastructure was to be contracted and a tender was published in March 2019 (Golja 2018).

The National Association of Statutory health Insurance Funds considers that there cannot be alignment because this will interfere with MS responsibility for the organisation of their national health system (Haas & Ermisch 2019).

EURORDIS welcomes mandatory uptake of joint HTA assessments and considers that this is the only guarantee that future cooperation achieves its goals (no duplication, high quality assessment, timely production of reports). Solidarity between MSs is a founding principle of the EU. HTA cooperation on a voluntary basis has its limits (EURORDIS 2018).

EFPIA stress on the need for safeguards in the Proposal to guarantee that there is no duplication of jointly conducted work in the MSs to meet the objectives of the Regulation. Efpia believe the need that the collaborative work must meet high quality standards and stress that he standards need to be specified in the legislation, where there is a clear list of criteria which include that procedural rules and clinical assessment methodology should be in line with agreed best practices, advances in science should be taken into consideration, the best available evidence should be considered, with regards to timelines these should be agreed in guidelines (EFPIA 2018).

EFNA - European Federation of Neurological Associations (Patient associations) called for patient involvement in all HTA activities (joint consultations, early dialogues, scoping, assessments) which is essential to help HTA assessors to determine the relative efficacy and safety of health technologies. Patients consider that submitting comments for HTA assessment as suggested for the HTA proposal was not adequate (EFNA 2018).

EFPIA (2019) expressed their view that in some cases cross-country collaborations may support the objective of increased access to medicines and sustainability of healthcare systems while in some cases national procedures are preferable. EFPIA considered that the implementation of cross-

country collaborations is in its infancy, there is little successful experience of enhanced access through collaborative initiatives: 'Until such evidence exists then national access processes will remain the most efficient tools to guarantee timely access for patients'.

BENELUXA said that sometimes the company does not want it known that it is involved in joint negotiation until the process is finished. For the success of the negotiations some confidentiality is required. BENELUXA try to be as transparent as possible (Kelly, 2019, Pink Sheet). BIOGEN was not keen to engage in joint negotiation with Denmark and Norway over Spinraza (Bruce 2018 Pink Sheet).

The Dutch Minister for Health was reported to say "by joining forces we stand stronger against the power of the pharmaceutical industry and we can also deliver a clearer voice at the European level". Paun C, the reporter from POLITICO was not in agreement and commented 'It hasn't quite worked out, The years since the launch of the pact [BENELUXA] the lack of any concrete deal shows that EU countries will have to play a longer game than initially thought' (Paun 2018 POLITICO).

Ireland decided to put "its eggs in more than one cooperation basket". Ireland is the only country that belongs to two regional groups (Pain, 2018 POLITICO).

Yannis Natsis, Policy Manager of the European Public Health Alliance (EPHA) was quoted by Euractive to say that the collaboration between countries of the Valletta Declaration "Is their response to the 'divide and rule' strategy pharmaceutical companies have been pursuing for years". "With Beneluxa, the Valletta Declaration Group, etc governments are simply getting organised. It is their response to the 'divide and rule' strategy pharmaceutical companies have been pursuing for years and a direct result of the unreasonably high prices drug manufacturers are charging' (Euractive 2018).

2. Attitudes on collaboration between national health authorities for pricing and reimbursement – specific activities

Activity	Attitudes
Horizon scanning	EuroScan international network had 14 member countries in November 2016. Espint et al. considered the gain from cross-border horizon scanning as high (Espin et al. 2016). Horizon scanning is performed in some countries e.g. UK, Denmark, Sweden, Austria and The Netherlands. BENELUXA are starting an International Horizon Scanning Initiative (IHSI), open to all countries. More than 10 countries are interested to participate. There is dialogue with international organisations to access the data (Golja 2018). Pharmaphorum 2019 explained that BENELUXA IHSI 'is the latest in a long list of scenario planning [horizon scanning]activities'. EMA already does it [horizon scanning]; the EUnetHTA collaboration is exploring horizon scanning for the HTA network in the future; EuroScan (a not for profit collaboration) has done it since 1999 and reaches beyond Europe including WHO; individual countries have implemented horizon scanning solutions. The article considers Beneluxa 'late to the horizon scanning party'. The article considers that 'there is an opportunity to learn lessons to get horizon scanning right in IHSI' It was considered that Beneluxa needed to offer something which is 'complementary' for the IHSI to take off (Pharmaphorum 2019). EFPIA (2019) considered that supra-national horizon scanning 'is a valuable complement' to national horizon scanning processes and should aim at reducing duplication by providing national horizon scanning with high-quality information. Industry can play an active role in developing these processes (EFPIA 2019).
Joint scientific consultation / 'early dialogues'/ scientific advice	Joint work in this area will build on the experiences gained with 'early dialogues' under the EUnetHTA (Ampelas & Schmitz 2019; Haas & Ermisch 2019). The scientific advice partnership of EMA and EUnetHTA is very professional and of high quality. Many organisations participate. He result is impressive. The collaboration between ADAPTSMART and HTAs has been positive (ADAPTSMART 2018). EFPIA welcomed the opportunity for pharmaceutical companies to request joint scientific consultation on clinical benefits assessment evidence (in parallel with the EMA process) to discuss data requirements for joint assessment (EFPIA 2018).
Sharing of information and generation of	Espin et al. (2016) considered that there would be challenges to collaboration on joint procurement and recommended that countries start with collaboration in information sharing and knowledge exchange before moving to activities which require more trust and commitment.

evidence and needs assessment	The Commission proposed that joint work will also include the development of common guidance and working documents and cross-cutting activities such as preparation of annual reports and work programmes (Ampelas & Schmitz 2019).
Health technology assessment (REA)	Vogler , Paris and Panteli (2018) considered that 'a more coordinated collaboration on the evaluation of clinical aspects appears feasible, in voluntary cross-country collaboration and also in the EUnetHTA' (Vogler, Paris & Panteli 2018). Espin et al. (2016) considered that it may be easier to harmonise HTA assessment in terms of scientific evidence on effectiveness. The Council of the European Union 2016, supported exchange of HTA methodologies and assessment outcomes through EUnetHTA, while recognising that financial impact and pricing must be addressed separately from HTA, and the applicability of HTA results need to be addressed by national health systems (Council of the European Union 2016). EFPIA, 2019, considered that national assessments create risk of duplication and conflicting outcomes, resulting in potential delay in access to medicines (EFPIA 2019).
Full HTA (with economic evaluation)	Espin et al. considered that context-specific elements such as organisational and economic considerations may be difficult to harmonise and require a country-specific approach. The benefit from collaboration on economic assessment is limited (Espin et al. 2016). Efpia (2019) considered that joint HTA should start with clear criteria to assess whether participating countries have comparable healthcare systems and economies. If a company believes that participating in a cross-country pilot will delay or prevent access for patients then they should retain the right to introduce the medicines through the national procedure (EFPIA 2019).
Pricing policy and price negotiation	Vogler, Paris and Panteli (2018) described an option for a method for the setting a price for medicines for a number of countries: first the countries determine a specific uniform price to be used as a basis and then this is adjusted/ differentiated in accordance with 'the income levels and the ability-to-pay' of the countries concerned. There is no experience with this in Europe. Efpia (2019) believed that joint price negotiations should not aim solely for short-term, financial cost containment goals but should be based on solid legal grounds and offer legal predictability (e.g. confidentiality of net prices and commercially sensitive information) to participating companies. The representative of the Belgian Ministry for Health clarified that the objective of Beneluxa 'is not necessarily to get the lowest possible price but a fair price that reflects the added value of the treatment and a fair return on investment' (Kenny 2019 Pink Sheet).

	An industry representative stressed that collaboration between the industry and country collaborations was 'conditional on there not being trade-off between patient value and time to access'. Companies will not enter into such arrangements if access is restricted' (Bruce 2018 Pink Sheet). Paun from POLITICO reported that Vertex (a small drug maker) was willing to engage with BENELUXA on Orkambi however "Big Pharma has been more reluctant". It was reported that Efpia said that "it supports any initiative that helps drive access to new medicines for patients such as joint assessments of clinical added value, however prices should remain a member state competency based on each individual country's circumstances". Drug price negotiations were considered the most politically sensitive of Beneluxa's efforts (Paun 2018 P0LITICO). Paun from Politico reported that within the Valletta Group there was lack of agreement on the policy to be adopted for the joint price negotiation 'will the price be set for all countries or will there be a range of prices for different members? Will drugmakers have to negotiate with each national authority or with a smaller group representing all countries? These questions came up between the Valletta Declaration and Roche, when it was speaking with this company. Some countries want a price ceiling while smaller countries want a fixed price. Bigger countries want to set a range of prices and have national authorities negotiate them, because they already have the expertise, the official said'' (Paun 2018 POLITICO). Individual MSs and purchasing authorities are 'more or less' not allowed to share the prices they get among themselves (Euractive 2017).
Reimbursement decisions and agreements	The benefits of collaboration on prioritisation and selection of medicines for reimbursement are limited because the budgetary requirements need to relate to the local context (Espin et al. 2016).
Purchasing and contracting and procurement	Although there appear to be benefits in joint procurement, in practice this is challenging and experiences in Europe are limited and only just recent, without enough experience (Espin et al. 2016). Vogler, Paris and Panteli (2018) describe joint procurement as 'collaboration between public purchasers who join forces in negotiation, with the intention of benefitting from greater purchasing power and less information asymmetry. It does not necessarily lead to the same price for all the parties involved'. Under the Joint Procurement Agreement (JPA) there can be joint procurement of vaccines and medicines used for influenza. Pilots for joint procurement under the Beneluxa initiative have started (Vogler, Paris & Panteli (2018). Espin et al. (2016), cite WHO and their four-level classification of regional collaboration for procurement, based on increasing levels of cooperation: informed procurement (countries share information about prices and suppliers); coordinated informed procurement (countries may also undertake joint market research, share supplier performance information and monitor prices;

	Group contracting (jointly negotiating prices and selecting suppliers); central contracting and purchasing (participating countries conduct tenders and award contracts through a central purchaser acting on their behalf). Espin et al. (2016) referred to the WHO model and interpret a 'natural route' of increasing intensity and / or commitment in collaboration for procurement starting with just sharing of information on prices and suppliers, progressing undertaking of joint market research and sharing of supplier performance information, moving joint negotiation and ultimately joint conduct of tenders and award of contracts through a central purchaser working on behalf of the collaboration Characteristics of a cross-border collaboration for procurement included: ownership of the collaboration (e.g. national governmental or organisation specifically created for the purpose); financing mechanisms (models of distributing the economic responsibility and solvency); procurement activities; timeframe of the collaboration (permanent or occasional); range of products or services involved; purchasing mechanisms (Espin et al. 2016). Countries frequently prioritised purchasing and contracting as the main benefit for collaboration in order to improve their market power and negotiating capacity. This potential has been hard to realise to date. Actual initiatives on cross-border collaboration in procurement in Europe are still few and have evolved only recently (Espin et al. 2016). There was an evolution in health technologies and in systems of procurement and thus past experiences of procurement are obsolete and the new conditions require new initiatives (Espin et al. 2016). EFPIA 2019 considered that public joint procurement is complex and should only be used where it can improve access of medicines to patients. Joint procurement should be proportionate to the needs identified by the participating MSs and limited to situations where purchase and supply of products cannot be ensured as efficiently by other means. Public procurement should not be a disincentive for innovation. Company participation in joint procurement should be voluntary in nature (EFPIA 2019).
Post-marketing authorisation studies	
Generation of real world data	Panteli and Edwards (2018) recommended for improvement in coordination and priority-setting across efforts for research and developments, to reflect regional priorities within the EU, based on clinical needs and inequalities with access to essential medicines. The authors also recommended more collaboration and alignment on the requirements for evidence between member states.

3. Perceived impacts (benefits and risks) from collaboration between national health authorities for pricing and reimbursement

Social health impacts: Governance, good administration; access to social protection and health systems; sustainability of health systems; public health

Economic impacts: Costs related to processes; administrative burden; competitiveness; innovation and research; functioning of internal market

Social health impacts	Indicators	Benefits	Risks
Employment			
Governance, participation and good administration	Indicators: i. Impact of collaboration on involvement of different stakeholders in processes ii. the responsibilities of public administrations and other organisations at MS level iii. the uptake of joint outputs (e.g. HTA reports, early dialogues, tools) iv. resource efficiency of processes v. the sustainability of European cooperation (sustainability of processes)	The Council invited MSs to.... where relevant and appropriate, groups of MSs that would like to explore cooperation on a voluntary basis, may make use of international expertise, with full respect of MS's competences (Council of the European Union 2016). The legal proposal for HTA provides a legal and organisational framework for sustainable HTA cooperation. The legal system aims to ensure the production of high quality and timely outputs that are used in national HTA systems (Ampelas & Schmitz 2019). The Commission considered high scientific quality of joint work due to the HTA proposal due to availability of appropriate evidence, pooling of expertise across HTA bodies, selection of HTA bodies with appropriate expertise/ capacity as lead assessors, specialist input by external experts (e.g. therapeutic area expertise of specialised clinicians and patients), rules to ensure conflicts of interest and ensure scientific independence, transparency (publication of joint outputs, procedural rules annual reports etc. The benefits from EUnetHTA: non-duplication; benchmarking against	

		the highest possible quality standards; standardisation of procedures, templates, SOPs, guidelines (Golja 2018). EURORDIS consider that joint HTA reports represent a major progress towards high quality, transparent and timely information (EURORDIS 2019).	
Access to social protection and health systems	Indicator: The potential effect of collaboration on the access to treatments that could be considered as 'innovative'	Voluntary collaboration on procurement of health technologies enables exchange of products in cases of shortages (Espin et al. 2016). Joint procurement was considered to improve the quality of purchased goods, foster innovations and ensure security and availability of supply (Espin et al. 2016). Cross-country collaboration were expected to strengthen the capacity to negotiate and increase the bargaining power. Collaboration is expected to increase access and affordability of medicines through negotiations (Vogler & Suleman 2018). The Commission considered that the proposed regulation on HTA was expected to bring benefits for patients. Patients will benefit from involvement in the HTA process, by providing input on their experience of a particular disease as part of the joint clinical assessment process. Patients will benefit from increased transparency as joint outputs from cooperation will be publicly available (Ampelas & Schmitz 2019). The Commission considered that joint HTA will support timely, evidence-based decision-making at member state level and id therefore expected to improve patient access to innovative health technologies (Ampelas & Schmitz 2019). EURORDIS considered that through joint assessment patients will be better equipped to understand the scientific rational behind the assessment of the added value of health technologies (EURORDIS	

		2018). EURORDIS considered that cooperation on HTA increases fairness, equity, scientific standards and efficiency in the decision-making process (EURORDIS 2018). EFPIA considered that the Proposal on HTA leads to faster patient access to new innovative medicines (EFPIA 2018).	
Sustainability of health systems	Indicators: i. the effect of collaboration on the financing of expensive treatments with little or no added value ii. the negotiating power of MSs in setting prices	Vogler, Paris and Panteli, (2018) considered that Member State collaboration: 'proves to be an effective tool to address a number of barriers such as imbalance in negotiating power, limited transparency and market fragmentation (Vogler, Paris & Panteli 2018). The model of joint procurement is expected to offer good opportunities because it provides large markets (Vogler, Paris & Panteli 2018). Public purchasers have a low bargaining power when purchasing for small populations (either the country is small or the condition is rare) and in such cases there is increased scope for joint procurement (Espin et al. 2016). The most commonly cited reason for joint procurement is the achievement of sustainable prices of medicines through the attainment of economies of scale by the grouping of entities that pool all or some of the functions of purchasing (Espin et al. 2016). Small or lower income countries will more likely from collaboration in procurement, although collaboration may also be of benefit for larger countries (Espin et al. 2016). Collaboration in procurement should be tailored to meet the specific needs of the countries involved, collaboration can help achieve a larger size (Espin et al. 2016).	The trade-offs between the potential benefits and costs of cross-border collaboration depend on the characteristics of the activities, technologies and countries involved. Larger, higher-income countries are likely to get less benefit from pooled procurement if they already reap the benefits from economies of scale (Espin et al. 2016).

		The Council of the European Union 'underlines that health technology assessment is an important tool in achieving sustainable health care systems and to promote innovation that delivers better outcomes for patients and society as a whole and recognises that EU cooperation in line with the Strategy for EU cooperation on HTA and the adopted work programme of EUnetHTA can support the decision-making og Member States, while acknowledging the potential added value of HTA in the context of national health systems (Council of the European Union 2016). Council Conclusions (2017) 'notes that tackling the specific characteristics and challenges arising in the healthcare market for therapeutic innovations, in particular in the field of rare diseases, and the development of personalised medicine, may benefit from voluntary cooperation so as to ensure a balance between access, quality, affordability and sustainability of health systems'. Cooperation between MSs enhances transparency through sharing of information, enables learning through sharing of experience, strengthens bargaining power through voluntary aggregation of demand, ensures access to health technologies through information on products in short supply (Council of the European Union 2017). Efpia considered that the Proposal on HTA leads to synergies in the needs for generation of clinical evidence and assessment by MSs (EFPIA 2018).	

Public health	Overall public health i. Availability of health technologies on the market ii. Access to medicines	Collaboration in public procurement that is aimed to meet the needs of the countries involved is considered to have public health benefits (Espin at al. 2016). The Council Conclusions (2017) considered that strengthening European cooperation in selected areas can bring better outcomes for patients and healthcare professionals, while increasing the efficiency of health systems (Council of the European Union 2017). The Commission considered that the proposed regulation on HTA is expected to bring benefits for EU member states (Ampelas & Schmitz 2019).	
Economic impacts	**Indicators**	**Benefits**	**Risks**
Costs The costs related to the processes	Variability in methods and processes currently employed by national health authorities across the EU; Possible duplication of efforts; Areas for improvement in consistency and transparency in the criteria used for decision making; What clinical and economic evidence is used in processes.	Cross-border collaboration for procurement was cosidered to help agencies to attain a larger operating scale and acquire the advantages of economies of scale (Espin et al. 2016). There is increased size effect and efficiency of procurement planning (Espin et al. 2016). In the treatment of rare diseases and for small countries cross-national collaboration can realise socioeconomic gains (Espin et al. 2016).	The costs of coordinating between partner organisations across countries are high because countries have different regulations, legislation, marketing practices, languages. The different types of national regulations on prices and procurement contracting can hinder collaborative initiatives (Espin et al. 2016).

Administrative burden	Administrative burden derived from processes: overall administrative burden; repeated processes/products across European countries; time needed for process; complexity of processes e.g. HTA assessment processes	The Commission considered that the proposal on HTA will enable HTA bodies to pool resources and expertise resulting in quality and efficiency gains in the preparation of work on the clinical aspects of HTA (Ampelas and Schmitz 2019).	
Competitiveness of EU health technology sector	Competitiveness of SMEs; revenues for the industry; predictability of national systems in Europe	The Commisison considered that the health technology industries wil benefit from more clarity on evidence requirements for HTA across the EU, as a result of consultation with HTA bodies (Ampelas and Schmitz 2019). EFPIA (2019) considered that the HTA proposal presents an opportunity to ensure 'a degree of harmonisation' throughout the EU.	
Innovation and research	Effect of the intervention on: research climate ; innovation in the European market; predictability of the market; reduction in fragmentation	The Commission considered that establishing the requirements for dossiers to be submitted by industry will ensure that HTA bodies have access to relevant clinical evidence for joint clinical assessment (Ampelas & Schmitz 2019).	
International trade innovation and research			
Functioning of the internal market and competition	Fragmentation of the system in Europe; convergence of methodologies; attractiveness of European market for industry	The Commission considered that the proposed regulation on HTA is expected to bring benefits for the health technology industry (Ampelas &Schmitz 2019). EFPIA stressed on the fact that the Proposal on HTA 'clearly states' that one of its core objectives is to remove existing divergences in the internal market for health technologies caused by differences in clinical assessments through harmonisation at the EU level (EFPIA 2018).	
Consumers	The availability of medical technologies for patients	A stakeholder network in the Proposal for HTA will enable stakeholder organisations with an interest in HTA to exchange views with the coordination group on cooperation activities (Ampelas & Schmitz 2019).	
Macroeconomic environment	Overall economic growth; labour market		

4. Motivational Factors which act as barriers (challenges) and factors which act as facilitators (drivers, enablers) for collaboration between national health authorities for pricing and reimbursement

Category of Factors	Factors which act as barriers (challenges)	Factors which act as facilitators, enablers
Social Access to social protection and health systems, sustainable health systems, access to medicines	Espin et al. (2016) pointed out that initiatives aimed at reducing expenditure for Member States mean potential reduction in revenues and profits for suppliers. In contrast EU policies are trying to boost the innovative industry. There is likely to be conflict of interest between different stakeholders. Policies need to be designed to achieve a balance between health and industrial objectives (Espin et al. 2016). EFPIA (2019) considered that any member state collaboration on pricing and reimbursement should lead to broader and/or accelerated access for patients.	The Council of the European Union 'recognises that the pharmaceutical system in the EU and its Member States, which is characterised by a division of competences between Member States and the EU level, can benefit from dialogue and a more holistic approach regarding pharmaceutical policy, by enhancing voluntary cooperation between Member States aimed at greater transparency, to safeguard common interests, ensuring access of patients to safe, effective and affordable medicinal products as well as the sustainability of national health systems (Council of the European Union 2016). The Council of the European Union invited MSs ... to explore possible areas in which such voluntary cooperation can contribute to higher affordability and better access to medicinal products (Council of the European Union 2016). The main objective for cross-country collaborations is to improve affordable and sustainable access to medicines (Vogler and Suleman 2018). EURORDIS believed in collaboration because diseases and patients are the same across the EU. Cooperation is particularly needed where diseases are rare and technologies are complex (EURORDIS 2018).

		A spokesperson for the Minister for Health of Belgium was reported to say that Belgium decided to form BeneLuxA because it 'wanted to break the usual approach for pricing of medicines (and was thus motivated to go for negotiation) after it found that it was going to have to pay a high price for Soliris which was priced at around €18,000 per month per patient. The cost threatened to make it difficult for the Belgian health system to balance its mission to care for individual patients but also for all patients and public health' (O'Donnell 2015, Politico).
Economic External factors arising by an economic factor or by a market event e.g. more intense competition, globalisation, market reaction, competitive advantage	Issues like parallel trade impact on the possibility of setting joint pricing and this needs to be tackled through availability of a legal frame-work (Vogler, Paris & Panteli 2018). Countries that believe that they are able to achieve lower prices and better conditions of supply under confidential price agreements might not want to risk their position of advantage by adopting an approach of procurement that could lead to a single price, which might be higher than the price being paid by the specific country (large high income countries can exert power over negotiations while small countries can benefit from humanitarian or responsible corporate policies (Espin et al. 2016). If one of the pooled countries is a potential parallel exporter, suppliers may be hesitant to grant a low price (Espin et al. 2016). The need for relabeling and repackaging may be a complicating factor for joint procurement (Espin at al. 2016). 'It is very challenging to make the industry adapt to new ways of working which could impact their profit margins' (Espin et al. 2016).	There were differences between payers in large countries such as Germany, France and UK and the smaller ones. There was more collaboration between the smaller countries in pricing negotiations, in assessment and in horizon scanning. 'This multi-country collaboration is a growing and fundamental change in Europe'. Countries have to collaborate more or else they will have to say no to their patients. Collaboration is being driven by economics (ADAPRTSMART 2018). Drug companies are frequently accused of profiting from the current system of pricing of medicines by charging as much as possible in each country, and smaller countries often complain of being disadvantaged in negotiations (O'Donnell 2015 POLITICO). Yannis Natsis, Policy Manager of the European Public Health Alliance (EPHA) was quoted by Euractive to say that the collaboration "With Beneluxa, the

	Respondents considered that the industry had a negative attitude towards the regional cross-border collaboration and compaies were reluctant to get into joint negotiations (Vogler & Suleman 2018).	Valletta Declaration Group, etc governments are simply getting organised. It is their response to the 'divide and rule' strategy pharmaceutical companies have been pursuing for years and a direct result of the unreasonably high prices drug manufacturers are charging' (Euractive 2018). Euractive (2018) reported that the Greek Minister for Health 'stressed that the pharmaceutical industry should understand that the way of negotiating acceptable compensation rates at national and international level was a one-way road as well as an opportunity for quick and guaranteed access to pharmaceutical innovations in large markets'.
Behavioural Trust, ability or willingness to share information, resistance to change, mutual respect, ability to compromise, communication, personal interests	Collaborative efforts, both within as well as between countries, for activities as joint negotiations and procurement, collaboration for horizon scanning, and HTA appear to be promising but require strong commitment from national policy makers (Vogler, Paris & Panteli 2018). There is the need for an 'authority/body' to take over the lead to organise the process of collaboration between countries (Vogler, Paris & Panteli 2018) External reference pricing is considered to have 'undermining effects' (Vogler, Paris & Panteli 2018). Political will, mutual trust among partners and mutual confidence are essential for collaboration. There also needs to be ongoing commitment to honour conditions of procurement agreements. Transparency of prices and sharing of information is important for joint procurement (Espin et al. 2016).	In the Council Conclusions (2017) the Council reiterated that "cooperation between health systems involving Member States" competences should be exclusively Member State driven and voluntary in nature and that such cooperation may require the use of instruments defined by those MSs (Council of the European Union 2017). Respondents from the regional collaborations considered trust, enthusiasm and commitment, highly qualified technical experts, political commitment as facilitating factors for collaboration (Vogler & Suleman 2018). Not all Members within EUnetHTA see the issues in the same way. Some countries are less flexible and experimental than others. Within EUnetHTA there are differences but as a collective they are more apt and willing to find new pathways (ADAPTSMART

	The method for decision making – it is important that efforts to achieve consensus do not result in killing of the price; activities are performed in accordance with national laws and regulations; governing principles are followed e,g, accountability, confidentiality, conflict of interest (Vogler & Suleman 2018). The Beneluxa report that collaboration 'requires flexibility and openness from all parties and the way forward is greater harmonisation within the initiative (Kelly 2019 Pink Sheet).	2018)
Organisational Internal factors related to the form of organisation: supply chain problems, pressure from trading partners, flexibility, development of clear policy and guidelines	It is important to have efficient financial management, continued contracting for joint procurement. Clarity on the management responsibilities for joint procurement and the remuneration for the work done (Espin et al 2016). The level of engagement is different in the various collaborations, some collaborations have a strong Ministerial participation while others rely mainly on technical experts (Vogler & Suleman 2018). The BENELUXA reported the following challenges from their experience: political mandate, legal frameworks (e.g. language issue), synchronisation of national P&R procedures (timelines, HTA outcomes must be identical, decision making), ensuring timeliness, business case for industry, resource planning (Golja 2018). The Valletta Declaration reported the following challenges: the VD is a political and administrative agreement between governments, different procedures and timing of assessments, joint assessments must be harmonised and must start early, each joint outcome has to be implemented in each country in accordance with the respective legal framework, establishing which price is to be jointly negotiated fixed price, maximum price or range of prices, industry is concerned about the possible uncertainty in the implementation of joint outcomes at national levels, need to guarantee confidentiality during the whole process and regarding the final agreed prices (Testori	European Union legislation and policies were considered to support cross-border collaboration (Espin et al. 2016). Cross-country collaborations were in most instances started off through an initiative of one country, in most cases there was a political initiative in one case it was driven bottom up by technical experts (Vogler & Sulemen 2018). Some countries are in more than one collaboration. EURORDIS believes that only a permanent structure can guarantee long-term collaboration and organise the sharing of suitable expertise and methods across all EU HTA agencies (EURORDIS 2018). EURORDIS consider that the objectives of collaboration on HTA are aligned with the development of European Reference Networks (EURORDIS 2018).

	Coggi 2018).	
Contextual History of collaboration	Some MSs have established national HTA systems with significant expertise and capacity and high quality standards and scientific independence while other MSs have more limited resources and capacities for HTA.The Commission claims that EU HTA cooperation aims for 'upwards convergence' ie highest standards of scientific quality, independence and transparency across the EU (Ampelas & Schmitz 2019). Politico reports that in response to the challenge posed to health budgets, in 2014 France and Italy spearheaded a drive among EU MSs to form a common front and create joint purchasing arrangement. The attempt petered out by the end of 2014 in the face of opposition from half a dozen counties, notably the UK and Germany (O'Donnel 2015 Politico).	EU legal framework introduced/strengthened the framework for collaboration through Directive 2014/24/EU on public procurement which covers cross-border joint procurement (particularly Article 39) (Espin et al. 2016). Directive 2011/24 on patient rights and cross-border health care provided a new approach to structured cross-border cooperation between health systems, while respecting Member State competence. Specific areas mentioned include European Reference Networks, rare diseases, e-health and health technology assessment (Espin et al. 2016). Changes in health technology and market behaviour may require different approaches to improve access to health technologies than those applied in the past, through voluntary cooperation (Council of the European Union 2017). Regional collaborations which had experience of long-term collaboration worked well within the collaboration (Vogler & Suleman 2018) EURORDIS consider that after 24 years of joint EU projects on HTA it is time to create a more efficient process with no replication in the 28 MSs (EURORDIS 2018).
Factors related to purpose Concrete attainable goals, shared vision,	Member states in MS collaborations 'must carefully balance the competences of the European Commission and EU Member States and requires continuous commitment by national policy makers' (Vogler, Paris & Panteli 2018).	Increased collaboration between countries in the procurement of health technologies was considered to increase transparency through sharing of information, enable learning cross-country through

unique purpose, membership characteristics, sharing a stake in process and outcome	Joint procurement requires good governance 'that helps curb opportunistic tendencies that could erode the value of the procurement process' (Espin et al. 2016). For cross border collaboration to work there needs to be ownership, equity flexibility, standardisation and gradual development (Espin et al. 2016). Council Conclusions of 2016 The Council of the European Union stresses that it is 'fully Member States' competence and responsibility to decide which medicinal products are reimbursed and at what price and that any voluntary cooperation on pricing and reimbursement between Member States should remain Member State driven' (Council of the European Union 2016). Article 168 of the Treaty on the Functioning of the European Union: Union action, which shall complemet national policies, shall be directed towards improving public health; and the Union shall encourage cooperation between Member States in the field of public health and, if necessary, lend support in their action, and that Union action shall fully respect the responsibility of the Member States for the definiiton of their health policy and for the organisation and delivery of health services and medical care as well as for the allocation of the resources assigned to them' (Council of the European Union 2016). The interviews with participants in regional cross-country collaborations considered identification of products for evaluation or negotiation, the identification of the lead partner in procurement and communication between the different actors within a collaboration; the language for official documents of a collaboration as a challenge (Vogler & Suleman 2018)	the sharing of experiences, strengthen bargaining power and reduce costs for transactions through pooling of capabilities and joint negotiation (Espin et al. 2016) For cross-border collaboration to work there needs to be true political will for countries to work together and overcome common challenges (Espin et al. 2016). The Council of the European Union, 2016, invites Member States to consider further development of exclusively MS driven voluntary cooperation between relevant authorities and payers from MSs, including cooperation **within groups of MSs, that share common interests in relation to pricing and reimbursement of medicinal products,** and to explore ..... (Council of the European Union 2016). Council Conclusions (2017) considers that voluntary cooperation to improve access to health technologies is fully in line with European values and principles (Council of the European Union 2017) The southern member states signing a common declaration "aiming to enhance their cooperation and jointly negotiate with the pharmaceutical industry on drug pricing" (Euractive 2017).

	The data collected for the horizon scanning system of BENELUXA does not prioritise for the countries, the data collected will not be tailored for specific countries (Golja 2018). EFPIA believe that any voluntary MS collaboration on price should be confined to countries of similar economic and health-related needs (EFPIA 2019). The representative of the Ministry for Health of Belgium reported that one of the biggest challenges for the collaboration is 'ensuring effective collaboration while complying with the respective national procedures and legal positions of all countries involved' (Kelly 2019 Pink Sheet). Carmen Paun from Politico reports that the main challenges for BENELUXA were that the partners had significant differences on how decisions are made, what medicines should be paid for through the health systems and the timelines when the decisions should be made. There were also linguistic complications and the group had to start performing assessments in English (Paun 2018 Politico).	
Implementation climate Political and social climate	Collaboration between countries requires appropriate legal provisions and sufficient specific resources and these depend on the level and the set-up of the collaboration (Vogler, Paris & Panteli 2018). A policy for differential pricing will require significant political will to agree on the mechanism and principles for differential pricing including motivation for transparency with regards to differentially set prices (Vogler, Paris & Panteli 2018). Initiatives of joint procurement would require 'strong political will and commitment and mutual trust between purchasing partners in order to succeed' (Espin et al. 2016). Mutual trust and confidence can be built progressively starting with less intensive approaches	Political will and commitment are essential for regional cross-country collaboration (Vogler & Suleman 2018).

	such as sharing of information and progressing to higher commitment. The duration of arrangements influences their effectiveness (Espin et al. 2016). Respondents from the cross-country collaborations considered that 'tangible successes' e.g. the number of successful procurements or joint negotiations or development of a joint horizon scanning instrument are important for politicians to justify initiatives for collaboration. There were mixed positions on indicators for joint collaboration, some considered it was not needed to have hard indicators. Collaborations have high expectations and there are pressures from outside (Vogler & Suleman 2018). The interviews with participants in regional cross-country collaborations considered reluctance of industry to negotiate, communication to the public and lack of concrete results as a challenge (Vogler & Suleman 2018). The National Association of Statutory health Insurance Funds (Germany) considers that there cannot be alignment of HTA because this will interfere with MS responsibility for the organisation of their national health system (Haas & Ermisch 2019). EFPIA (2019), stipulated that collaboration on pricing, reimbursement and access should guarantee confidentiality of pricing and reimbursement agreements. The Belgian representative of BENELUXA stressed on the importance of there being a 'clear political commitment and mandate' from the countries involved (Kelly 2019 Pink Sheet). The Greek Minister for Health emphasised that "The European Commisison must support this voluntary cooperation on the basis of EU law if we really want to talk about a single Europe of citizens and	

	social rights" (Euractive 2018).	
Cultural Difference/similarities in goals and objectives, relationship, capacity to share risks, integration of key processes, flexibility of organisational system, compatibility of organisational culture	There are major challenges with joint procurement because of divergence in the legal, regulatory and organisational procedures within countries (Vogler, Paris & Panteli 2018) The interviews with participants in regional cross-country collaborations considered differences in pricing and reimbursement systems and standardisation of rules, legal barriers as a challenge (Vogler & Suleman 2018).	
Resources / physical Investments, financial resources, funds, staff, expertise, skilled leadership	Cross country collaborations reported that they had no allocated budget and at least 2 to 4 people were involved in collaborative activities on a part-time basis per country. Participants communicated by telephone and most collaborations have set schedules with regular meetings (Vogler & Suleman 2018). The interviews with participants in regional cross-country collaborations considered language, identifying the right people to work in collaboration, resources (particularly time) as a challenge (Vogler & Suleman 2018). Funding, having time from experts and cooperation are essential for cross-country regional cooperations (Vogler & Suleman 2018). Efpia (2019) believe that the collective agreement should impose neither additional market access barriers nor additional price-related measures. There should be no duplication between collective agreement and equivalent steps in participating countries. A representative from Beneluxa reported that joint processes are more 'resource consuming' than national procedures. A lot of time is	Quality assurance is increasingly important in European Countries and small countries find it difficult to afford and attain a high level of expertise and standards required for procurement. As technologies become more complex and evaluation becomes more challenging cooperation for sharing of professional resources becomes more of a driver for collaborative initiatives (Espin et al. 2016). Cross-country collaborations help to ensure rationalisation of procurement and reduce the time and administrative resources required. Collaboration helps to benefit from each other's knowledge and experience (Vogler & Suleman 2018). Structure within which to work, information technology and the use of one language were considered as facilitators for collaboration (Vogler & Suleman 2018) The Commission considers that the legal framework,

	spent preparing each file with the company and within the relevant administration (Kelly 2019 Pink Sheet).	organisational structure and financial support provided by the proposed regulation on HTA will contribute to support upward convergence (Ampelas & Schmitz 2019). It was expected that MSs with advanced HTA systems will play a leading role in the joint scientific work, particularly in the beginning of the cooperation, while MSs with less advanced HTA systems will be able to build up their HTA capacity over time (Ampelas & Schmitz 2019).

5. Recommendations and proposals for action with respect to collaboration between national health authorities for pricing and reimbursement

Recommendations on the following:	Recommendations and considerations for action (possibly consider collaboration for different activities, as applicable)
Supporters/ facilitators of collaboration	Austria started a 'Clearing House' for prices of medicines. A trusted third party collects data of discounted prices from different public purchasers and shares them in an anonymous and aggregated format. This improves transparency of prices while the framework of confidential price negotiations remains. To-date this initiative is applied within Austria but it could be applied intra-country (Vogler, Paris & Panteli 2018). Espin et al. (2016) considered that the EU can contribute cross-border collaboration in procurement by providing support and investing resources either at the initiation stage or for its duration. The Commission can enact or amend legislation to facilitate cross-border initiatives. HTA agencies need to find small and medium sized enterprises or orphan drug manufacturers who are willing to work with payers and HTA agencies to find new business models. Pricing negotiations and money need to be brought into the multi-stakeholder discussions for MAPPs (ADAPTSMART 2018). Companies should be incentivised to move into new models, ideally through the arrangement of pilots (ADAPT SMART 2018). BENELUXA consider that the initiative is still under development and involves the approach of 'learning by doing' (Kelly 2019 Pink Sheet). BENELUXA representative hopes that in the future there will be a larger and more structured collaboration among European countries (Kelly 2019 Pink Sheet).

Information about ongoing cross-country collaborations

In recent years several cross-country collaborations of different formats related to pricing, reimbursement and procurement have formed, and Vogler, Paris and Panteli (2018) expected further cooperative models. The information about these collaborations from various sources was collated in table below (Espin et al. 2016; Vogler, Paris & Panteli 2018; Vogler & Suleman 2018). As the information was from various years and there could have been some progress in the meantime, the final compilation tried to be as updated as possible.

Vogler and Suleman (2018) reported that recently cross-country collaborations were set up in Europe, there was a lack of study on the country collaborations and there was some critical reporting on the collaborations. From the study by Vogler and Suleman (2018) it was concluded that overall there are high expectations from the cross-country collaborations. Respondents from regional cross-country collaborations considered that domestic media were supportive (Vogler and Suleman, 2018). Regional cross-country collaborations had different methods for external communication. Some collaborations had no external communication and some had national press activities. Collaborations were invited to give presentations on their activity; one collaboration had a website and used social media. Communication of the work of the collaboration to the outside world was considered to be a challenge (Vogler and Suleman, 2018). The respondents from the interviews of the regional cross-country collaborations unanimously considered that the collaborations are successful; they considered that it was difficult to measure the results of collaboration so far but considered that they were worth the effort. They considered that collaboration was a good intuitive initiative but it was considered too early to have tangible success. The early benefits of collaboration came from exchange of information and the initiation of some assessments (Vogler & Suleman 2018).

Table: Different initiatives for regional collaboration

Name of collaboration / source of information	Start date	Countries involved	Scope	Activities covered / Achievements
EUnetHTA Sources: Golja (2018); https://www.eunethta.eu/	EUnetHTA collaboration started 2009	81 partners, 29 countries	Increased collaboration, production and usage	Joint HTA production, early dialogues, scientific advice, joint clinical assessment, horizon scanning, post-launch evidence-generation.
Fair and affordable pricing (FAAP) Visegrad Source: Dziurda (2018)	Legal basis MOU on cooperation March2017	Hungary, Lithuania, Poland, Slovak Republic, Chech Republic (observer), Latvia (invited guest)	Pharmaceuticals	Improve and facilitate access to effective and affordable medicines, develop methods and modalities and negotiation. Technical consultation on specific disease areas.

		Similar socio-economic and health related needs and challenges		
Valletta Declaration Sources: Testori-Coggi (2018); Press releases)	Southern European Initiative was started in June 2016 Initiative covers over 30% of EU population. Valletta Declaration signed in May 2017.	Cyprus, Croatia, Greece, Ireland, Italy, Malta, Portugal, Romania, Slovenia, Spain MSs cooperating in full trust, loyalty, solidarity and transparency	Pharmaceuticals, mainly innovative medicines	Information sharing on policies e.g. biosimilars reference price mechanisms, medicines shortages and availability; sharing of information on prices, prioritisation of areas for cooperation, sharing of information and learning from good practices e.g. approaches for the assessment and use of CAR-T cell therapies, horizon scanning, joint assessment and negotiations for candidate products. Discussion on proposal by Italy on their initiative on a draft resolution 'Improving the transparency of markets of drugs, vaccines and other health-related technologies' submitted to the WHO. Discussion on the proposal on the institutional framework to enhance sustainable and effective cooperation on medicines.
FINOSE Source: Stromgren (2018)	launched March 2018, pilot till 2020	Finland, Norway, Sweden Bottom up initiative from agencies Started formally as an MOU		Cooperation on assessment of relative efficacy and applicable parts of economic analysis. Participation in collaboration requires industry to simultaneously submit to the 3 agencies. National decisions. Reaching out to companies, having dialogues, awaiting for applications
Nordic Collaboration Nordic Pharmaceutical Forum Source: Website: Nordic Collaboration, 2019; Sonne (2018)	2015	Denmark, Iceland, Norway, Sweden Stronger northern unity provides strong purchasing power	Innovative medicines	Horizon scanning, information sharing on prices and markets; joint procurement, security of supply, new expensive drugs, manufacturing. The Forum is set up as an operational network by and for practitioners. Driven by concrete collaboration projects. Based on voluntariness and consensus, common responsibility , common funding.
BeNeLuxAI	April 2015	Belgium, Netherlands,	Innovative	HTA, horizon scanning, information sharing on

Source: Website: BENELUXA (2019); Golja (2018); Kenny 2019 Pink Sheet.	Political mandate for collaboration, case driven, voluntary, transparency, consensus-based output, price/ reimbursement decisions are national competence	Luxembourg, Austria (2016), Ireland (2018)	medicines Objectives: earliest possible access to medicines for patients, offering patients a clear insight in the added value of new products, improving the patients' market power, minimise procedural hurdles for the pharma industry Intention to increase transparency within the initiative.	prices and markets, joint negotiation for purchasing to ensure affordability, re-use of HTA reports (countries use parts of HTA reports of other countries). One of the first priorities for BENELUXA is the building of an International Horizon Scanning Initiative (IHSI). They issued an open market consultation and invited all countries (not just EU countries) to participate. BENELUXA are issuing a call for tenders (BENELUXA, 2019). The website reports that pilots on managed entry agreements are ongoing. Many companies involved in these pilots requested discretion until the pilots are finalised. Joint HTA work on 6 assessments so far. In 2017 a pilot was concluded on the pricing and reimbursement of Orkambi. The HTA report was written jointly by Belgium and The Netherlands. The Netherlands and Belgium failed to reach a joint agreement on a price with the company and negotiations were terminated. The authorities at the Netherlands subsequently reached an agreement with the company on their own (Kenny, 2019, Pink Sheet). Positive joint negotiation outcome for Spinraza by BE and NT. The participants analysed the national possibilities and limitations for collaboration and where

				necessary individual countries are changing their national policies and /or legislation. In its report of a presentation given by a representative of BENELUXA it was stressed that the price negotiations within BENELUXA are voluntary. Not all five countries are obliged to participate and if at any stage a company decides that it wants to go to a national procedure it can do so. The five countries were pooling resources, expertise and information to provide' better, faster and sustainable access to innovative therapies without jeopardising their social security system (Kenny, 2019, Pink Sheet).
Baltic Procurement Agreement (Partnership Agreement) *	May 2012	Latvia, Lithuania, Estonia	Pharmaceuticals and medical devices	Centralised joint purchasing (tenders, negotiation, payment and distribution) to reduce expenditure and ensure continuity of access; procurement of vaccines, lending of medicines
Romania and Bulgaria initiative *	June 2015	Romania, Bulgaria	Pharmaceuticals	Joint negotiations in purchasing to get lower pricing and cross border exchange of medicines in short supply

* Not sure whether these collaborations still function

Update on the Proposal for a Regulation on HTA – positions of different stakeholders

a. Report as at the end of the Austrian Presidency (November 2018) (Council of the European Union 2018)

The national Parliaments of 3 MSs raised formal subsidiarity objections on the Proposal. The main concern was how the Proposal, once adopted will influence national decisions on the reimbursement of medicines by national health insurance schemes. A large majority of MSs considered that MSs should have the possibility to carry out national clinical assessments when necessary. Another issue concerned the quality and timely delivery of joint clinical assessments (JCAs) and the structures, procedures and methodologies for achieving these. All delegations agreed that JCA must be at least as good as national clinical assessments and must be available early enough to be used in national decision making. There was overall consensus on the importance of transparency regarding the overall assessment process and the need for strict provisions on conflicts of interest to guarantee an independent assessment process. The proposed governance structure should allow for a MS driven process. Discussions on how MSs were to carry out their own clinical assessments when needed were inconclusive. Several MSs could not agree to the mandatory use of JCAs in their national procedures and considered that JCA could not be legally binding on MSs since HTA is used for Pricing and reimbursement discussions and these are of national competence (Council of the European Union 2018).

b. Attitude of the National Association of Statutory Health Insurance Funds of Germany on the Proposal for a Regulation on HTA (Haas & Ermisch 2019)

The authors considered that the European Commission's proposal intervenes with the existing national systems without ensuring high-quality central assessments and efficient implementation of findings in the MSs, considering specific national contexts. Differences in assessment methods and assessment results of MSs can be attributed to different assessment objectives and health system structure. Value judgements vary in the different countries. Treatment standards vary between MSs. The proposal did not take adequate account of the importance of clinical assessments. Germany considered that current EUnetHTA reports show significant difference to the report from the German agency and these affect key areas that are relevant to the decision in Germany. Germany insisted that the assessment procedure must fulfil the highest transparency requirements.

The National Association of Statutory health Insurance Funds considered that there cannot be alignment because this will interfere with MS responsibility for the organisation of their national health system. Moreover there is no evidence for a legal basis for the 'elimination of obstacles in the Single European Market'. It was recommended that all decisions for organisations responsible for HTA in MSs shall be taken by consensus. HTA organisations of the MSs should take the lead with administrative support from the EC. It is proposed to continue the existing cooperation to extend joint assessment in a step-wise manner, and the National Association of Statutory health Insurance Funds was to continue monitoring and supporting the legislative procedure.

It was considered that during joint scientific consultations different healthcare and assessment systems should be considered in the consultations. The HTA organisations involved in the consultations cannot achieve consensus on every point. The level of flexibility should be retained. Further cooperation on horizon scanning should have a direct added value for the European procedures and for the healthcare systems of the MSs.

In addition to the 3MSs that filed formal subsidiarity objections, the parliaments of 5 other countries also criticised the legal basis of the proposal. Larger MSs rejected the legal obligation regarding the binding use of the clinical assessments, whereas predominantly small countries generally supported the EC's proposal.

c. Position of EURORDIS-Rare Diseases Europe (a network of rare diseases patient organisations)on the Proposal for a Regulation on HTA

EURORDIS called for adoption of the Proposal on HTA (EURORDIS, 2018).

d. Position of EFPIA – European Federation of Pharmaceutical Industry Association, on the Proposal for a Regulation on HTA

EFPIA welcomed the Commission's proposal for a Regulation on HTA. Efpia considered that existing divergences in the internal market can only be addressed if the clinical assessment is effectively used in national processes of HTA. Efpia stressed on the importance of maintaining the original Article 8 of the proposal, i.e. that the joint clinical assessment that is done at European level is 'effectively used' in all the national processes (EFPIA 2018).

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Appendix 6 Data collected from the 'Study on Impact Analysis of Policy Options for Strengthened EU Cooperation on Health Technology Assessment, Final Report' 'the Study'

Summary information on the 'Study on Impact analysis of policy options for strengthened cooperation on health technology assessment, final report' 'the Study' (European Union 2017)

The aims of 'the Study' were:

- To support the Impact Assessment process of the EC and inform this process by generating data and evidence.
- To provide inputs for the baseline scenario as well as for 'the Study' of future policy options (POs) for EU Cooperation on HTA for 2020.
- To provide inputs for analysing the impact of the different cooperation POs for EU cooperation on HTA.
- To utilise the data and information collected to analyse the potential impacts of the different POs.

The method for data collection consisted of the establishment of a baseline scenario through a case study comprising a product sample of health technologies (20 pharmaceuticals). This covered: HTA process in MSs, the costs of performing an HTA for both the developer and the HTA body and the Influence of the regulatory framework on technology developers.

The Impacts of identified Policy Options (POs) on future European cooperation in the field of HTA were analysed through an on-line survey on the economic and social impacts for Public Administrations (HTA bodies), industries, patients and healthcare professionals. Responses were mainly from Public Administrations and Industry. Additional data collection and validation of findings were done through focus group meetings with Public Administrations, industry; interviews with industry and patient representatives and a systematic literature review and desk research.

Multi-criteria analysis was used as an analytical approach for assessing impacts for each stakeholder group. Cost prognosis for implementing and maintaining the investigated POs and business models was performed. An expert panel validated the data obtained and there was peer review by leading experts in the field.

The study was presented as an impact assessment.

a. Updates to the draft Logic Model for the System of Pricing and Reimbursement

Activity	Responder
Activities: Early dialogues Relative effectiveness assessment (REA) Joint Full HTA with economic evaluation	EC
HTA outputs : Common tools and procedures such as a common submission template, an IT system with planned and ongoing assessments, common methodologies, a joint prioritisation process, cooperation on data requirements (including horizon scanning)	EC
The Model There is heterogeneity of the HTA role across countries: variability in methods and processes. Possible duplication of efforts or cases. Consistency and transparency in the criteria used for decision making could be improved.	Authors
Early dialogue and scientific advice are viewed as extremely useful exercises helping to increase transparency. A system aligned to what is done by EMA would be beneficial and simplify development programmes. A few respondents stated the importance of not introducing a parallel system where countries impose additional requirements.	Industry
Assessment and appraisal are different. Assessment is the collection and synthesis of evidence focusing on the traceability/replicability of results. Appraisal is the act of contextualising evidence and formulating recommendations i.e. drafting impact and applicability.	Authors
Scientific work and expertise (i.e. development of joint outputs) would stay with national agencies.	EC Authors

b. Attitudes on collaboration between national health authorities for pricing and reimbursement

Attitude	Responder
The Authors of 'the Study' combined the PO with potential business models	Authors
An implementation mechanism without EC funding was not considered in this study, because intergovernmental cooperation without EU input is strictly the responsibility of the MSs.	Authors
Perceptions and expectations regarding the future cooperation on HTA in Europe differ between stakeholder groups.	Authors
With potential future growth in patient mobility in Europe, as addressed by the Cross-Border Directive, it can be seen advisable to base decision-making on the same evidence.	Authors
'The Study' team covered all impacts (except environment) defined in the EU Better Regulation Guideline. While the economic impacts are primarily relevant for public authorities and / or industry, the social impacts are also relevant for citizens/patients and health professionals.	Authors
Authors focused on the assessment aspect and not on HTA as a provider for inputs that determine pricing and reimbursement decisions, because P&R decisions remain the competence of the MSs.	Authors
HTA bodies had mixed opinions regarding the extent of collaboration: some representatives of HTA bodies prefer loose collaboration, exchange of information and developing common methodologies, while others prefer cross-border assessments. The current situation of the country might influence the perception of cooperation on HTA.	Authors
Relevance of the respective impacts is divergent between the stakeholder groups. The economic impacts were classified higher for the Pharmaceutical industry. Public administration considered a higher impact on the sustainability of health systems.	Authors
In the inception Impact Assessment the EC proposed Policy Options beyond the situation of no further action at EU level (benchmark scenario). The policy options were determined by the EC. The policy options differ regarding the i. Nature of cooperation, as reflected by the type of participation (voluntary V or mandatory M) ii. The uptake of joint outputs (voluntary V or mandatory M)	EC
The PO showed a combination of the outputs, the method of implementation, the financing and the scope (the type of products covered). There are different combinations for the nature of cooperation for the activity for the joint outputs and the uptake of the joint outputs). Baseline: PO 1 If MSs participate voluntarily and uptake of joint outputs is voluntary (V/V) – there will be no EU input and no EU funding Non-legislative: PO 2 (V/M) – project based cooperation – funding by EU and MSs.	EC

Legislative: funding- EU+MS+fees from industry: PO3, PO4 and PO5 PO 3 legislative covering common tools and early dialogue – EU/MS secretariat PO 4- legislative covering common tools, early dialogue and REA- permanent secretariat hosted by an existing EU agency PO 5 - legislative covering common tools, early dialogue and full HTA – permanent secretariat hosted by new EU agency	
There was consensus that EU collaboration on HTA may be possible for generating a REA. Joint work on REA was repeatedly indicated to have the potential to reduce inefficiencies and workload on the pharmaceutical sector.	Industry
No change for non-legislative options and positive effect for legal models for joint work on REA. The industry expects negative effects for option which includes a strictly mandatory and binding HTA process also covering full HTA in Europe. Underlying reasons include that mandatory joint economic evaluations as foreseen in PO5 are perceived as an unrealistic scenario due to country specificities with regard to economic requirements and the fact that pricing and reimbursement decisions remain at national level.	Industry
PO5 red; PO4 dark green; PO3 very light green. POs with mandatory uptake of joint REAs will have positive effect. Industry will benefit from reduction in submissions and better predictability. PO 5 was considered unrealistic.	Industry
There is a 'tension' between regulators who want to promote accelerated access, and reimbursement authorities that are cautious due to evidence uncertainty and resource constraints.	Industry
PO5 dark green, PO4 light green, PO3 very light green POs providing a legislative framework (PO3 upwards) will potentially have a positive effect, increasing up the PO range.	Public administration
Future cooperation in HTA POs with mandatory participation and uptake will increase availability of safe and effective pharmaceuticals and ensure standardised monitoring of health technologies prior to market access.	Patients
Comment: the Authors are of the opinion that countries linked the evidence provided by HTA assessment to pricing and reimbursement decisions to innovation.	Researcher
Any pricing and reimbursement decisions remain purely at national level.	Authors / EC
Different business models of governance (implementation) were considered: No EU input; Project-based cooperation; A permanent secretariat hosted by a MS; A permanent secretariat hosted by the EC; A permanent secretariat hosted by an existing EU agency; A permanent secretariat hosted by a new EU Agency	Authors
Besides the central coordination unit there are 3 main pillars anticipated for the business model: 1. Management Board- defines work programme and defines MS representatives 2. HTA output production – contracted to HTA bodies 3. MS expert committees – MS experts to review and discuss HTA outputs for quality assurance	EC

c. Percieved impacts (benefits and risks) from collaboration between national health authorities for pricing and reimbursement for HTA		
Theme	**Details**	**Responder**
Costs The costs related to the processes (e.g. the HTA process)	Variability in methods and processes currently employed by HTA bodies across the EU Possible duplication of efforts, cases where greater consensus would be needed on HTA processes and methods. Areas for improvement in consistency and transparency in the criteria used for decision making How HTA is currently used in different contexts and what clinical and economic evidence is used in conducting the assessments.	
	Costs reported by industry: A high level of variability in HTA spending and in additional evidence generation. Although a global value dossier is generated for each product, this is usually the main source of input for manufacturer HTA teams and is subject to adaptation based on HTA circumstances prevailing in each setting. There may be heterogeneity in evidence assessment across settings or different needs for data generation. Personnel costs (internal and external) were key expenditure drivers. Focus groups showed that another key driver for HTA costs was (additional) evidence generation. It was mainly in the larger markets that companies perform additional evidence generation studies requested by HTA bodies. Alternatively existing knowledge gaps may be covered by post-marketing studies. There is active engagement in early dialogues (69%) with an average cost of EUR 55,750 per case.	Industry
	Costs reported by HTA bodies Cost differences due to type of assessment performed and the level of integration of HTA bodies with government entities. It appears that the cost for an HTA among 'arms' length bodies' (highest EUR 135,000) is higher than among 'integrated structures' (highest EUR 100,000). The figures for REA (EUR 55,000 / EUR 100,000).	HTA bodies
	Estimated that there will be 90 REAs per year (centrally authorised new substances and indications). In majority of countries HTA bodies do less than 60 HTA reports per year. The majority of HTA reports are industry- based and reviewed by HTA bodies.	Authors
	Staff will be required to cover the work needed/output production. Personnel costs and costs resulting from MS expert committees account for the majority of expected costs.	Authors

	Taking the underlying assumptions into account, with the more legislative and mandatory options, overall savings at EU level for MSs and the industry sector can be expected and savings rise with each successive Poss. However several additional factors that cannot reliably be quantified, but which may have an impact on overall costs/savings may reverse or diminish some of the results. There is a significant increase in costs for establishing a new framework and a potential savings increase. Cost estimates show that industry would benefit from additional savings for full HTA compared to REA only. Options comprising a permanent secretariat and higher joint output lead to substantially larger saving as compared to the project-based cooperation. It has been taken into account that additional evidence generation due to requests by national HTA bodies will be limited when joint REAs are in place, which is a relevant factor for potential savings.	Authors
	Industry respondents expect no major changes with regards to costs for HTA processes except for PO5 where substantial cost increase is feared, particularly for early dialogues, full HTAs and additional data requirements when implementing PO5. Except for PO5, increases and decreases of cost components are expected to level each other out. With regards to PO 4.1 AND 4.2 decrease in costs are expected, due to lower number of dossiers that need to be prepared, especially for mandatory production and mandatory uptake. Possible increases and decreases of cost components would level each other out, meaning that costs on MSs might decrease while costs at EU level increase.	Industry
	Result of cost prognosis for 2020+ indicate that actual savings due to a reduction in duplicated assessments can be achieved for the industry for all Poss. Potential savings are considerably higher in POs that comprise both a mandatory production and mandatory uptake of joint REAs. Options comprising a permanent secretariat and higher joint output lead to substantially larger savings as compared to project-based cooperation.	Authors
	Potential savings are considerably higher in POs that comprise both a mandatory production and mandatory uptake of joint REA's and Joint HTA PO4 and PO5 Options with a permanent secretariat or a new agency are linked to higher joint output as compared to project-based cooperation.	Authors

	Experts do not expect major change in the HTA-related costs irrespective of the future model. Costs are expected to rise for REA and Early Dialogue for Policy Options 4.2 onwards. However some experts have opposing views and expect reduced costs due to decreased duplication of efforts and increases in efficiency (equal distribution of responses towards increase and decrease). The Commission is expected to bear any additional costs for cooperation e.g. personnel costs and costs for MS expert committees. Overall no additional costs are expected.	Public admin
	Options comprising a permanent secretariat and higher joint output lead to substantially larger savings compared to the project-based cooperation. POs providing a legislative framework will potentially have a positive effect on cost evolution for national public administration across MSs.	Authors
Administrative burden	Administrative burden derived from HTA processes was defined in a broader sense and the following indicators were defined: i. overall administrative burden ii. number of HTA submissions for the same product across European countries iii. time needed for an HTA process iv. complexity of HTA assessment processes	
	Duplication in assessment: the same product-indication pair had been assessed at least by 10 HTA bodies in as many countries. Out of 13 bodies, 2 authorities evaluated the same product-indication pair. Three HTA bodies evaluated all new pharmaceuticals applying for marketing authorisation. Some well-developed HTA systems assess all new pharmaceutical products. Others have explicit prioritisation and topic selection processes. The assessment of each product-indication pair is highly influenced by the model of HTA (e.g. clinical benefit assessment vs. Clinical and cost effectiveness) and the overall approach to HTA prevailing in each country (arms' length or integrated approach). A fair amount of duplication is taking place as the evidence considered across settings is by and large the same.	Authors
	Fragmented HTA system requires companies to cater for a range of demands and this might lead to difficulties in submitting reports.	Industry
	The number of evidence-based assessments available for decision-making can be increased with joint outputs because potentially more health technologies can be covered due to single HTA bodies might not have the capacity to assess the same numbers per year. Countries with less mature HTA processes and countries with a low number of professionals working in HTA might especially benefit from joint outputs, in particular from joint REAs. (WHY JOINT REA?)	Public admin
	None of the POs is considered to have a substantial effect on the administrative burden of public administrations across EU MSs and no or little effect on costs for HTA-related outputs. National processes will still remain in some form. Some HTA	Public admin

	bodies expected that closer collaboration would reduce their cost.	
	The expectations of EUnetHTA for evidence generation were considered unrealistic at times.	Industry
	Use/uptake of report should be mandatory by MSs	Industry
	Economic value and socioeconomic impact of products vary substantially across settings.	Industry
	Reducing duplication in submission might lead to decreased administrative burden. No expected change in administrative burden for PO1to 4, steep increase in administrative burden for PO5, mainly because this involves full HTA PO 4.1 and PO4.2 were favoured by the industry as joint REA with mandatory uptake will lead to a reduction in the number of national HTA submissions. More divergent requirements across Europe are expected for PO1 and PO2 and this increases complexity for industry	Industry
	Efficiency gains for HTA bodies when joint assessments are produced, since resources for national assessments can be replaced (references 38, 39) and this is related to a decrease in administrative burden for national assessments. While joint work also requires administrative processes, POs providing a sustainable central organisation have the potential to limit the associated administrative burden by providing administrative support. Time and resources were assessed as critical factors in the framework of establishing more efficient cooperation and outputs (40, 41), thus requiring optimised processes between different stakeholder groups. Time has been identified as an important factor for national uptake and adaptation of joint work at EU level (38)	Literature
	Stronger governance, enabled through a legislative framework as well as establishment of a permanent secretariat, might facilitate a faster assessment of more health technologies as compared to current joint work. Mandatory uptake of joint outputs might make more swift process.	Authors
	The time needed to adapt joint reports for national settings affects the time for the joint HTA process. It is important having clear processes and common methodologies to minimise national adaptations. National adaptation of reports might be less problematic and time-consuming for joint REAs when compared to joint full HTAs. The inclusion of the domains required for the full HTA need more country-specific adaptation.	Authors
	A slight increase in overall administrative burden is expected for the respective POs compared to the status quo.	Public admin
	The number of HTA submissions for the same product across Europe is expected to decline by each PO. A slight increase in complexity of HTA processes is expected from PO2 onwards, particularly for PO5.Complexity increases when trying to reach a common agreement on economic aspects. Although administrative complexity potentially increases from PO 1 to 5, resources for research may be spent more efficiently, which ultimately would lead to a neutral effect. Administrative burden is likely to decrease for less-experienced countries, while it might grow initially for more experienced countries (e.g. Germany and France) because major changes of established systems and resources for information sharing	Public admin

	could be necessary. Most public bodies are legally bound to assess newly authorised pharmaceuticals within 90 days or 180 days after public reimbursement is requested.	
Competitiveness of EU health technology sector	Indicators: i. competitiveness of SMEs ii. revenues for the industry iii. predictability of HTA systems in Europe	
	PO3, PO4 and PO 5 are perceived to increase positive trend in the Predictability of the HTA system competitiveness of SMEs and less on revenues	Public admin
	The predictability of HTA system in Europe has very important impact. Currently the predictability is low due to different requirements regarding: comparators or endpoints. Additional data requirements on top of clinical data relevant for marketing authorisation, these may be harder to fulfil by SMEs due to costs and effort. PO4 a positive effect on the predictability HTA system is expected. PO5 negative effect on predictability of HTA and on competitiveness of SMEs. No major effect on revenues is expected across all POs.	Industry
	Divergent outcomes derived from HTA assessments for the same pharmaceutical and indication were often reported in country comparisons (Nicod, 2016; Kleijnen et al. 2012)	Literature
Innovation and research	Authors assessed effect of the PO on i. research climate ii. innovation in the European market. Predictability of the market, reduction in fragmentation was considered as key factors for a favourable business climate that is meant to facilitate innovation to thrive.	
	Poor predictability, high complexity and high fragmentation constitute barriers to innovation. Harmonisation of evidence requirements, if accompanied by MS acceptability, would facilitate investment decisions. The predictability of the HTA process was agreed to be a key element for investment and resource decisions, particularly for smaller companies. The harmonisation of processes and evidence requirements, would contribute to minimise misunderstandings and enhance the level of predictability of the system. Transparency of evidence requirements, consistency of methods acceptability of indirect comparisons and predictability of outcomes were highlighted as desired characteristics. Industry advocated for inclusion of information on indirect comparisons and secondary endpoints and a clear definition of the comparators.	Industry

	EU HTA with a solid methodology would de-risk the submission process and help eliminate arguments resulting from low quality assessments and data misinterpretation. Greater consistency in HTA assessments would be very beneficial and could be facilitated by early advice and greater clarity on payer expectation. Evidence requirement harmonisation would give the EU a stronger influence on clinical trial development.	
	There is still heterogeneity in the way health technologies are assessed across different countries. However micro-level analysis showed a tendency towards a homogenisation of assessment processes across countries.	Authors
	Poor predictability, high complexity, poor transparency and high fragmentation are barriers to innovation.	Industry
	Expected positive effect on innovation and research for PO 3 and PO4 but negative effect for PO5. Harmonisation of evidence requirements accompanied by MS acceptability would facilitate investment decisions. Less risky environment positively influences investment decisions.	Industry
	The scientific evidence on HTA is the basis for decision-making processes in several countries. The diversity of methodologies applied for producing HTAs across Europe accentuates this (Kleijnen et al. 2015; Barron et al. 2015). The uncertainty surrounding the benefit and value of innovative products as innovative processes, and its wider impact on health systems and patients requires special attention (Henshall et al. 2013). HTA is one approach for valuing innovation when informing relative effectiveness of a health technology and a tool to increase efficiency in health care (OECD 2004; Kanavos et al. 2010). Challenges for innovation and research resulting from cooperation in HTA include to maintain the local context, to ensure compatibility of methodologies, especially for countries with established systems and the introduction of transparent topic selection and prioritisation (Kleijnen et al. 2015; Kalo et al. 2016; Martelli & van den Brink 2014; Lo Scalzo 2014).	Literature
	PO2 to 5 were considered to have increasingly positive effect on innovation and research.	Public admin
	PO3 to PO5 are indicated to promote the research climate and to facilitate innovation to thrive in Europe. A legal framework at EU level will highlight the importance of HTA processes and has the potential to create a more favourable research climate in countries where HTA has low priority.	Authors
International trade innovation and research	An increase in predictability of HTA processes and requirements is expected from the legislative options which were highlighted as a very important factor for research and investment decisions.	Industry
	Neutral for PO 2, 3, and 4 and very negative for PO 5, possibly because PO5is too extensive.	Industry
	International trade is not directly linked to Public Administration.	Authors
Functioning of the internal market and competition	i. fragmentation of the HTA system in Europe ii. convergence of HTA methodologies iii. attractiveness of European market for industry	

	Options with legal obligation are estimated to reduce inefficiencies and workload improving the functionality of the internal market. Positive effects on competitiveness are expected for PO3 and PO4. Industry representatives are of the perception that converged methodologies in economic assessment will not be able to replace national submissions in this field.	Industry
	PO 3, PO4 and PO 5 are increasingly considered to increase the convergence of HTA and the attractiveness of the EU market and international trade and decrease fragmentation.	Public admin
	Current differences in HTA processes and methods (Chamova 2017). Different methodological approaches can lead to varying pathways for pricing and reimbursement decisions, imposing challenges on manufacturers (Martelli & vanden Brink, 2014).	Literature
Consumers and households	The availability of medical technologies for patients	
	All POs improve effect on consumers and households, by increasing the number of health technologies assessed, especially PO 4 and PO5.	Public admin
	Slight positive effect for PO 3 and PO4 and very negative for PO5 (criteria no of health technologies available and no of health technologies assessed)	Industry
	HTA processes and systems differ regarding the capacity to conduct assessments and not all HTA bodies can assess new technologies (Kalo et al. 2016; Kleijnen et al. 2015).	Literature
Macroeconomic environment	Indicators: i. overall economic growth ii. labour market	
	PO3, PO4 and PO5 give an increasing positive trend for the health technology sector.	Public admin
	Positive impact of PO1, neutral for PO 2,,3 and 4 and negative for PO5	Industry
	Macroeconomic environment is influenced by the legal framework	Authors
Employment		
	No change in future employment levels for PO1, PO2 and PO3, small increase employment for PO 4 and PO5	Public admin
	Minimal perceived increase in employment especially PO5	Industry
	Assessment groups require expertise from different disciplines (37)	Literature
Governance, participation and good administration	Indicators: i. How the policy options affect the involvement of different stakeholders in HTA processes ii. The responsibilities of public administrations and other organisations in the field of HTA at MS level iii. The uptake of joint outputs (HTA reports, early dialogues, developed tools)	

	vi. resource efficiency of HTA processes vii. the sustainability of European cooperation in the field of HTA (sustainability of the processes)	
Others	The timeline of performing the assessment across different country or setting	
	Common tools and procedures such as a common submission template, An IT system with planned and ongoing assessments, Common methodologies, A joint prioritisation process, Cooperation on data requirements including Horizon scanning	
	Stricter regulation could be a key element for sustainable, successful collaboration since otherwise the impact of collaboration is limited.	Public admin
	All implementation mechanisms include production of HTA outputs by different HTA bodies and the support provided to the HTA bodies by the central coordination unit. Support includes administrative, scientific/technical, legal and IT support, which differ in extent for different mechanisms. 5 out of 6 mechanisms have a permanent central coordination unit compared to the project-based mechanism oriented on EUnetHTA structures. Permanent central coordination units perform project coordination and for the Management Board, output production and committees.	Authors
	The level of agreement in the recommendations across HTA bodies varies significantly and is affected by HTA body topic selection processes, leading some HTA bodies not to assess all technologies. The level of agreement in HTA recommendations across HTA bodies that assess all technologies is very high k>0.8. This indicates a high level of agreement across HTA bodies in recommendations made i.e. in the same direction of recommendations e.g. accept, accept with criteria or reject. Clinical restrictions in HTA recommendations related to sub-groups of patients (67%) followed by therapeutic pathway restrictions (18%). Economic restrictions are mainly based on information that was publicly available and 64% referred to the introduction of risk-sharing or managed entry agreements.	Authors
	Different national procedures have different impacts on HTA. National methodologies lead to substantial variations in final recommendations/ outcomes showing substantial variation in the way the same product is valued across countries. These differences are also influenced by the therapeutic areas of individual products.	Industry
	Social value judgements (SVJs) aim to interpret key elements related to the impact of treatment on patients and society. SVJs are increasingly being used in HTA recommendations. The baseline study identified and coded 11 main categories	Authors

	across the reports. Three HTA bodies have elicited their SVJs in their guidelines. Other bodies also account for SVJ but not in a consistent manner. All HTA bodies had a strong preference for Phase II trials followed by Phase II trials and other sources of evidence. Not all countries assessed the clinical and cost-effectiveness of each technology and the criteria for assessment varied considerably. In 68% of the cases, the comparator included was the same across HTA bodies.	
	Legislative cooperation can create institutional capacity for HTA cooperation and expertise can be better streamlined. The processes can be set up more efficiently when they are coordinated and facilitated by one permanent institution, since all information is centralised, expertise can be streamlined and overall savings can materialise.	Authors
	Transparent and independent HTA processes require consideration of all stakeholder perspectives to increase efficiency and prevent conflict of interest. Sufficient financial resources are essential to establish a respective mechanism. Besides required investments, stakeholders should draw attention to the potential return on investment different mechanisms offer. The independence of HTA processes must be ensured and the influence of stakeholder groups should be limited and thus HTA should be funded through public funds. Improving transparency of HTA processes Ensure patient involvement, including development of best practice design. Patient involvement in early dialogue. Inclusion of patient – relevant outcomes including well-being Any stronger, more binding collaboration between MSs will reduce duplication, increase the number of outputs and transparency and will thus be beneficial EMA and future HTA cooperative models should work together closely but in an independent and separate way	Patients
	There are clear signals to improve and standardise patient involvement in HTA processes.	Industry & Public admin
	Previous patient involvement in HTA processes is characterised by good intentions on the part of the involved stakeholder groups but successful implementation was limited so far by either the extent or role of involvement. Stronger governance regarding HTA assessment might positively influence patient involvement. Sustainable and transparent long-term cooperation offers the potential to prevent selective assessment in pharmaceuticals and increase accessibility of publicly available information.	Authors
	The quality of the reviewer for EUnetHTA assessments was not always of consistent quality, particularly if the country was less sophisticated on HTA. This led to resistance from larger countries in accepting the assessments.	Industry

	There must be some type of an appeal process.	Industry
	Stakeholder involvement, responsibilities of MSs and uptake of joint outputs are perceived to have a positive trend. PO5 considered negative.	Industry
	A slight positive effect of PO3 and PO 4 is expected; PO1 PO2 and PO5 are expected to have a negative effect mainly due to an expected negative effect regarding the sustainability of HTA cooperation in these options. In PO5 the negative effect is due to the high level of agreement that would be needed in PO5. Scepticism about applicability of joint full HTA across European countries. Overall positive effect for POs including joint work on REA, particularly for positive effects for research, innovation, functioning of the internal market and access to innovative treatments. Industry expects negative effects for PO5. Mandatory joint economic evaluations as foreseen in PO5 are considered as an unrealistic scenario due to country specificities with regard to economic requirements and the fact that pricing and reimbursement decisions remain at national level. Joint work on REA has been indicated to potentially reduce inefficiencies and workload for the industry. Industry stresses on the expected increase of predictability of HTA related processes, which is especially the case for REAs. This related to less administrative burden due to the reduction in multiple submissions for the same product across Europe. Predictability of processes and evidence requirements has been mentioned to be a very important factor, also facilitating innovation drive due to easier investment decisions. Sub-group analysis showed quite similar perceptions for SMEs and larger companies except that SMEs are more positive towards PO1 than large companies.	Industry
	Countries that have no or little HTA related activities will most likely benefit more from joint output and central governance as they have not made major investments in building national HTA systems and are more open to use resources to adapt joint results for national decision-making purposes. This could not be quantified.	Public admin
	Reacting to legislative demands is easier as compared to voluntary demands, emphasising on the value of a legislative frame work.	Public admin
	PO3, PO4 and PO5 are perceived to have positive effect on governance and good administration	Public admin
	No effect from the different POs on the involvement of different stakeholder groups in HTA processes	Public admin
	No policy option is expected to impact on the responsibility of the MSs, showing that none of the POs is seen to interfere with the autonomy of Public Administrations in this area.	Authors
	The assessment of previous collaboration at EU level identified potential for optimisation in the fields of topic selection, priority setting within cooperation and expert involvement with respect to time management (Lo Scalzo et al. 2014) thus impacting resource efficiency of collaboration. When enforcing joint assessments, topic selection processes between stakeholders have been identified as key issues due to diverging national interests (Nachtnebel et al. 2015). Collaboration between stakeholders requires sufficient political support to converge opposing interests (Fronsdal et al. 2012).	Literature

	Studies suggest an inclusion of all relevant stakeholders in assessment processes. Positive developments were achieved in increasing involvement of consumers (including patients and patient advocacy groups) in different steps of assessment processes as reported in a study assessing consumer involvement in HTA activities in INNAHTA agencies (Hailey et al. 2013). However patient involvement in general still varies widely across Europe (Scott & Wale 2017).	
	Strengthening the cooperation on HTA in Europe by introducing a legislative framework can provide positive impulses and support in this context and can be seen as a sign for political support as it aims to enhance a more coordinated cooperation at EU level.	Authors
	Studies suggest an inclusion of all relevant stakeholders in assessment processes. A study assessing consumer involvement showed positive developments were already achieved in increasing involvement of consumers in different steps of the assessment process (Hailey et al. 2013). However the degree and scope in patient involvement still varies widely across Europe (European Patients Forum, 2013) and several points for improvement remain (Scott & Wale 2017).	Literature
	A permanent secretariat might facilitate patient involvement	Authors
	Policy options covering a legislative framework will have positive impact on the sustainability of HTA cooperation by providing a stable framework for joint work.	Authors
	The introduction of MS expert committees, which will organise the cooperation and the active involvement of national HTA bodies in output production.	Authors
	Involvement of patients and patient organisations in HTA processes remains limited so far.	Authors
	Cooperation between MSs would increase the reliability of HTA assessments and safety of new technologies. EU cooperation on HTA is needed also for hospital-based HTA, rehabilitation, disease management programmes, and between pharmaceutical and non-pharmaceutical interventions. Predictability of HTA systems is a key issue. Policy options 1 to 5 might limit innovation initiatives on the one hand, but reduce risks and uncertainty of use resulting from innovative products on the other. Structures PO 1 to PO5 might limit the number of technologies available but the healthcare sector would be more harmonised and uniform, thus supporting availability of safer and more efficient technologies.	Patients
	Patient involvement in HTA varies considerably between countries. Countries with more advanced HTA systems are more engaged to increase patient involvement and include their perspective adequately. Patient involvement in EUnetHTA JA 3 aims to improve patient involvement but faces restriction due to limited financial resources.	Patients
	There are clear signals to improve patient involvement in HTA processes through Europe (Scott & Wale 2017).	Literature
Access to social protection and health systems	Indicator: The potential effect of POs on the access to treatments that could be considered as 'innovative' was surveyed.	

	Positive perceived average for PO3 and PO4, negative for PO5.	Industry
	The POs foresee that appraisal and pricing and reimbursement decisions remain at national level. However even if policy options do not directly affect access to innovative treatments, HTA assessments inform these decisions and thus have an influence. Especially joint REA can provide significant input for decision-making, in particular when limited resources within the country do not allow assessment of all health technologies.	Authors
	Literature indicates that close collaboration between different stakeholders could improve access to and availability of health technologies on the market (Lo Scalzo et al. 2014; Martelli & van den Brink 2014).	Literature
	HTA is a valuable tool to support the use of products with higher additional value as compared to marketed products	Authors
	Positive effect on access to innovative treatments is increasingly expected for PO3, PO4 and PO5. Closer collaboration of HTA systems lead to better selection of products with higher added value.	Public admin
	Mandatory joint REA especially can provide significant input for decision-making across Europe. This would reduce a divergent evidence basis across Europe.	Authors
	Implementation of a life-cycle approach would support evidence generation throughout the whole life-cycle of a health technology, specifically when additional evidence is required. Sufficient funding and investments were necessary to adapt sustainable and transparent HTA processes.	Patients
	Patients would benefit from regulated assessments of health technologies since these would serve as a sound evidence-base for decision-makers and improve the availability of new and safe technologies. Increased regulation and guarantee of assessment processes support quality and safety aspects. Uncertainty surrounding the prescription of (innovative) products would be lower and support HCPs to ensure secure and appropriate use of health technologies. Health risks for patient would be lowered through improving access to assessed innovative health technologies.	Authors
Sustainability of health systems	Indicators: i. The effect of the various POs on the financing of expensive treatments with little or no added value ii. The negotiating power of MSs in setting prices Investing in expensive treatments with little or no added value is questionable, since these resources might provide a higher benefit to patients when used elsewhere.	
	Due to the incomplete nature or the low quality of clinical and economic evidence decision makers need to base their judgements based on considerable uncertainty about the clinical and economic impact of a treatment or accept Incremental Cost effectiveness ratios (ICERs) that are above explicit of implicit national willingness to pay (WTP) thresholds.	Authors
	POs with a legislative framework are more likely to influence the sustainability of health systems than further non-binding cooperation.	Public Admin
	Experience with full HTA at EU level is limited so far. The additional domains for full HTA (economic, organisational, legal, ethical and social) aspects tend to contain many non-transferable issues and need to be adapted at national level.	Industry

	PO 1 has some positive impact on negotiating power of MSs in setting prices, PO2, PO3, PO4 and PO 5 perceived to have no impact sustainability of health care systems and in negotiation power of MSs to set prices.	Industry
	While HTA assessment per se is not decisive for reimbursement or the price that can be achieved for a specific product, several EU countries have linked the evidence provided by HTA assessments to pricing and reimbursement decisions (Kanavos et al. 2010).	Literature
	Even if the proposed POs will not affect the autonomy of MSs in setting prices for pharmaceuticals, a joint REA might provide recognisable evidence at EU level. This can be utilised where there is no structured HTA yet in place, supporting these countries to make more efficient decisions.	Authors
	Studies indicate that a thorough examination of scientific evidence is needed for supporting health policy decision makers, as this can reduce uncertainty in decision-making. Conflicting interests among different stakeholders and potentially biased publications should be identified (Kleijnen et al. 2014; Brown & Calnan, 2013).	Literature
	A small increase in negotiating power of MSs in setting prices was expected with PO4.2 and PO5 due to anticipated stronger standing based on joint output.	Public admin
	Asymmetric information between industry and authorities can cause difficulties for authorities in decision-making processes. The availability of reliable and sufficient information on health technologies is vital and requires corresponding assessment of health technologies (Rummel et al. 2016).	Literature
	A joint perspective on the added value of health technologies has the potential to increase the sustainability of health systems. Stronger cooperation would increase the negotiating power of MSs and thus achieve lower prices for technologies with limited added value. It would be difficult to discontinue the financing of already marketed technologies.	Public admin
	PO3 to PO5 are more likely to positively influence the sustainability of health systems than further non-binding cooperation. Joint output will reduce the financing of new expensive treatments with little or no added value. All types of legal frameworks are enablers of sustainability.	Authors
	All POs are expected to have almost no effect on the financing of expensive treatment with no added value and on the negotiating power of MSs in setting prices. As the POs do not address pricing and reimbursement decisions as these remain the competence of the national authorities.	Industry
Public health	i. Overall public health ii. Availability of health technologies on the market	
	PO5 perceived to have negative impact on public health. Availability of health technologies is expected to be highest with POs 3 and 4.	Industry
	Evidence should be generated in a transparent manner by various stakeholders to avoid misinformation and information withheld (Brown and Calnan 2013) Involvement of different stakeholders appears vital to account for different needs, interests and national structures (Barron et al. 2015; Kalo et al. 2016).	Literature
	The availability of health technologies is expected to be highest for PO 4.1. Increased convergence of HTA methods would	Public admin

	increase the availability of health technologies.	
	The availability of health technologies also depends on other factors : marketing authorisation process, national pricing and reimbursement.	Authors
	Literature shows that the availability and accessibility of health technologies is considered highly important for patients, thus affecting public health. In many European countries, funding for public health research in HTA is limited (Loblova 2016). HTA methods should include other outcomes such as differences in access to healthcare or effects on patients' social environment (Marsh et al. 2016). Accelerated HTA processes would lead to faster patient access in case of favourable assessment (Ciani et al. 2017). HTA results hold the potential to improve restrict or deny patient access to health technologies depending on the assessment results and the role HTA plays in the decision process related to reimbursement. HTA is a tool to limit use of health technologies with no added value.	Literature
	Increased patient empowerment may affect public health positively. Patients would benefit through increased monitoring of health technologies. Mandatory legislative framework offers the opportunity to reduce selective assessments of health technologies and guarantee transparent processes and easier transferability to national systems.	Authors
	Consider that the POs have the objectives to: 1. Ensure better functioning of the internal market 2. Contribute to a high level of human health protection	Authors

4. Motivational factors which act as barriers (challenges) and factors which act as facilitators (motivators, drivers) for collaboration between national health authorities for pricing and reimbursment

Note: These motivational factors were 'indirectly' elicited by the researcher from the feedback given by the responders.

Activity	Category of Factors	+/-	Description	Responder
Early dialogues	economic	+	Currently scientific advice differs widely across agencies and this presents challenges for development programmes. Joint scientific advice or consensus on evidence requirements would simplify development programmes	Industry
	purpose	+	Patient involvement in early dialogues	Patients
REA	resources behaviour purpose	+ + +	Expected increase of predictability of HTA related processes particularly due to different requirements regarding comparators and end-points. Less administrative burden due to reduction in multiple submissions for the same product. Harmonisation of evidence requirements. Transparency of evidence requirements, consistency of methods, acceptability of indirect comparisons and predictability of outcomes are desired characteristics of the industry.	Industry
	purpose	+	Stress on need for legal obligation	Industry
	purpose	+	Reports must be consistent and there must be predictability on how the evidence is looked at and assessed.	Industry
	efficiency	+	HTA assessments should take place in parallel with regulatory approval	Industry
	purpose resources cultural	+	Positive on joint work on REA. This was repeatedly indicated to have the potential to reduce inefficiencies and workload on the pharmaceutical sector. Industry stressed on particularly positive effects for research, innovation, functioning of the internal market and access to innovative treatment, facilitation of innovative drive due to easier investment decisions. Poor predictability, high complexity and high fragmentation constitute barriers to innovation. Solid methodology would de-risk the submission process and eliminate arguments arising from low quality assessments and data misinterpretation.	Industry
	purpose economic	++	Industry considered additional evidence generation as a key driver of HTA costs. Industry expected that cooperation will limit additional requests for evidence and this is considered very positive.	Industry
	purpose	+	Use/uptake of HTA assessment reports should be mandatory.	Industry
	resources	+	The quality of the reviewer for assessment was not always of constant quality and this led to resistance for	Industry

			larger countries to accept the assessments from certain countries	
	cultural	-	Only PO1 has some positive impact on negotiating power of MSs in setting prices. All POs are expected to have almost no effect on the financing of expensive treatment with no added value and on the negotiating power on MSs in setting prices. POs do not address pricing and reimbursement decisions.	Industry
	resources	+	General success factors identified for sustainable joint cooperation included: 1.The use of common tools and templates – facilitating joint work 2.Business models with stronger governance structures – provides timely assessment process 3.Timely assessment processes – important to ensure that uptake can occur at a time when the results are relevant in national settings 4.Cross-country expertise and inputs –ensures quality of assessments performed 5.Mandatory joint output and national uptake of joint outputs 6. A permanent secretariat 7. Reduced duplication as the evidence in different countries is the same 8. Processes can be more efficient when facilitated by one institution 9. guarantee a transparent process 10. mandatory uptake will make transferability to national systems easier	Authors
	behaviour	-	Non-mandatory uptake	Authors
	resources	+	Legislative cooperation can create institutional capacity for HTA cooperation and expertise can be streamlined.	Authors
	social	+	Sustainability and a mandatory nature to HTA cooperation in Europe potentially leads to benefits for patients. An increase in the number of health technologies assessed will increase evidence-based decision making across the EU, especially in MSs where HTA is not well-developed and contributing to a decrease in cross-country inequalities.	Authors
	climate	+	Stronger governance enabled through a legislative framework and the establishment of a permanent secretariat. Legislation can be seen as a sign of political support to cooperation.	Authors
	resources	+	HTA assessments provide input to inform decision making and will positively affect access particularly in countries with limited resources. Joint REA might provide recognisable evidence at EU level supporting countries with no structured HTA in making decisions.	Authors
	purpose	+	HTA is a valuable tool to support the use of products with higher additional value as compared to marketed products	Authors
	purpose	+	Uncertainty surrounding the prescription of innovative products would be lower and this supports HCPs to ensure appropriate use of health technologies.	Authors
	Social purpose	+	Po3 to PO5 are more likely to positively influence the sustainability of health systems than non-binding cooperation. Joint output will reduce the financing of new expensive treatments with little or no added value. Legal systems are enablers to sustainability.	Authors

	resources	+	Provision of a sustainable central organisation limits administrative burden.	Literature
	social purpose	+	The uncertainty surrounding the benefit and value of innovative products and its wider impact on health systems and patients. HTA is a tool for valuing innovation when informing relative effectiveness of a health technology and to increase efficiency in healthcare.	Literature
	culture context	-	A challenge resulting from HTA is to maintain the local context, to ensure compatibility of methodologies for countries will well-established systems and to introduce transparent topic selection	literature
	resources behaviour	+ -	Not all HTA bodies can assess new technologies. Assessment groups require expertise from different disciplines.	Literature
	culture	--	Topic selection processes are a key issue due to divergent national interests (38) Collaboration requires sufficient political support to converge opposing interests (40)	Literature
	resources	+	The number of evidence-based assessments available for decision making can be increased. Countries with less mature HTA processes and countries with a low number of professionals working in HTA might benefit most.	Public admin
	behaviour	+	Increased convergence for HTA	Public admin
	behaviour	+	Increased convergence of HTA methods will increase availability of health technologies	Public admin
	cultural	- _	Complexity increases when trying to reach a common agreement	Public admin
	Cultural	++	Stricter regulation and POs with a legislative framework can be important for sustainable collaboration. Reacting to legislative demands is easier as compared to voluntary demands. POs with a legislative framework are perceived to have a good effect on governance and good administration.	Public admin
	resources	+ /-	Administrative burden is likely to decrease for less-experienced countries while it might grow initially for more experienced countries because major changes could be necessary. Countries that have no or little HTA related activity will benefit more from joint output and central governance as thay have not made major investment and are more likely to adapt joint results for better decision-making.	Public admin
	purpose	-	No impact from involvement of stakeholder groups in the HTA process.	Public admin
	social	+	Positive effects on access to innovative treatments.	Public admin
	social	+	Supports better selection of products with higher added value.	Public admin
	power cultural	+/ -	A small increase in negotiating power of MSs in setting prices due to a stronger standing of joint outputs. A joint perspective on the added value of health technologies has the potential to increase the sustainability of health care systems and increase the negotiating power of MSs.	Public admin
	purpose	++	Coordinated HTA will facilitate consideration of different stakeholders perspectives and patient involvement will consider best practice design. Inclusion of relevant outcomes including well-being.	Patients
	social	++	Cooperation will increase reliability of HTA assessments and the safety of new technologies. Cooperation will reduce risks and uncertainty of use resulting from innovative products, supporting safer technologies.	Patients

	resources	++	HTA should be funded through public funds and not by other stakeholders.	Patients
	purpose	+	Improving transparency of HTA and predictability of HTA processes.	Patients
	purpose	+	Collaboration reduces duplication, number of outputs and transparency.	Patients
	behaviourl	+	Stronger governance will influence patient involvement positively.	Patients
Full HTA	cultural	--	Strongly negative on mandatory joint economic evaluation as in PO5. These are foreseen as unrealistic due to country specificities with regard to economic requirements and the fact that pricing and reimbursement decisions remain at national level. Joint methodologies will not be able to replace national submissions in this field. Experience with full HTA at EU level is limited.	Industry
	economic	-	PO 5 is perceived to have no impact on sustainability of health care systems and negotiating power of MSs to set prices.	Industry
	purpose	+/ -	Increased convergence of HTA. High complexity to reach common agreement especially on economic aspects but resources may be used more efficiently	Public admin

Conclusion of 'the Study on the effect of policy options (authors)

	baseline	Non-legislative	legislative			
Stakeholder group	Baseline scenario (PO1)	Project-based cooperation (PO2)	MS/EU secretariat (PO 3)	Existing EU agency (PO4.1)	Existing EU Agency (PO 4.2)	New EU Agency (PO5)
			Common tools and early dialogues	Joint work on REA Common tools and early dialogues		Full HTA, common tools and early dialogues
Public administration						
Pharma						

Green – positive Red- negative

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