European Commission

Study on impact analysis of Policy Options for strengthened EU cooperation on Health Technology Assessment (HTA)

Final Report

Gesundheit Österreich Forschungs- und Planungs GmbH

LSE The London School of Economics and Political Science

SOGETI

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Abstract

The study's overall aim was to support the Impact Assessment process of the EC and inform this process by generating data and evidence. In doing so, it provides inputs for analysing the impact of the current situation (baseline scenario) as well as potential future policy options (POs) for EU cooperation on Health Technology Assessment (HTA) beyond 2020 and utilises the data and information collected to undertake an Impact Assessment of the different cooperation options. The POs for further cooperation at EU level were proposed by the European Commission (EC) and combined with potential business models by the authors in close cooperation with the EC.

In order to establish the baseline scenario, a case study comprising a product sample of health technologies was analysed, which included 20 Pharmaceuticals, 15 medical devices and five 'other technologies' (including complex health interventions). The study team collected detailed information on the HTA process each technology underwent in the MS. Additionally, the costs of performing a HTA were identified for both the technology developer and the HTA body. Finally, the case study captured the influence of the regulatory framework on technology developers.

In order to analyse impacts of identified POs on future European cooperation in the field of HTA, a survey was performed on the economic and social impacts, complemented by focus groups, a number of interviews and findings from a literature review. A multi-criteria analysis served as an analytical approach for assessing impacts for each stakeholder group. Finally, a cost prognosis was performed to estimate potential costs and savings for implementing and maintaining the investigated POs and business models. An expert panel was involved throughout the study and validated the data obtained.

Study results provide an overview of current HTA practices and processes in Europe including advantages and drawbacks. An analysis of various POs for a future cooperation on HTA across Europe is provided.

Résumé

L'objectif général de l'étude était de soutenir le processus d'évaluation d'impact de la Commission Européenne, notamment par l'apport de données et de preuves. Elle fournit également des informations pour l'analyse de l'impact de la situation actuelle (scénario de base) ainsi que sur les options politiques (OP) potentielles relatives à la coopération sur l'évaluation des technologies de santé (ETS) à l'échelle européenne après 2020 et met à profit les données et les informations recueillies pour mener une évaluation de l'effet des différentes perspectives de coopération. Les OP pour une coopération approfondie au niveau de l'UE ont été proposées par la Commission européenne (CE) et combinées à des modèles commerciaux potentiels par les auteurs en étroite coopération avec la CE.

Afin d'établir le scénario de base, une étude de cas comprenant un échantillon de produits de technologies de santé a été analysée, comprenant notamment 20 produits Pharmaceutiques, 15 dispositifs médicaux et cinq « autres technologies » (notamment des interventions sanitaires complexes). L'équipe d'étude a recueilli des informations détaillées sur les processus d'ETS auxquels chaque technologie a été soumise dans les EM. En outre, les coûts de la réalisation d'une ETS ont été déterminés à la fois pour le développeur de technologie ainsi que pour les organismes d'ETS. Enfin, l'étude de cas a permis de saisir l'influence des cadres réglementaires sur les développeurs de technologies.

Afin d'analyser les impacts des OP identifiées sur la future coopération européenne dans le domaine de l'ETS, une enquête a été réalisée sur les effets économiques et sociaux, soutenue par des groupes de discussion, plusieurs interviews et des conclusions sur de la documentation. Les effets potentiels des options politiques proposées pour les différents groupes d'acteurs ont été étudiés à travers une analyse multicritère (AMC). Enfin, un pronostic des coûts a été effectué pour estimer les coûts de la participation volontaire ou obligatoire à la production conjointe et les économies liées dans la production nationale des OP proposées et les coûts liés aux structures organisationnelles spécifiques/mécanismes de mise en œuvre comprenant des outils communs. Un panel d'experts a été impliqué tout au long de l'étude et a validé les données obtenues.

Les résultats de l'étude donnent un aperçu des pratiques et processus actuels d'ETS à l'échelle Européenne, comprenant les avantages et les inconvénients. Une analyse des différentes OP sur les développements futurs potentiels de la coopération d'ETS en Europe est aussi fournie.

Acknowledgements

We would like to thank all of our colleagues and experts who contributed to this study, which sets out to both capture the current state of play of HTA in Europe and give an outlook on the years beyond 2020.

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Disclaimer

Table of contents

List of tables

List of figures

List of abbreviations

AAZ	Agency for Quality and Accreditation in Health Care and Social Welfare (Croatia)
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spain)
AIFA	L'Agenzia Italiana del Farmaco (Italy)
AIM	International Association of Mutual Benefit Societies
AOTMiT	Agencja Oceny Technologii Medycznych i Taryfikacji (Poland)
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya (Spain)
ASMR	Amélioration du Service Medical Rendu
AT	Austria
CBHC	Cross-Border Health Care
CEESTAHC	Central and Eastern European Society of Technology Assessment in Health Care
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CHAFEA	Consumers, Health, Agriculture and Food Executive Agency
CLL	Chronic Lymphocytic Leukemia
CMA	Conditional Marketing Authorisation
COCIR	European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry
COPD	Chronic Obstructive Pulmonary Disease
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
DE	Germany
DG COMP	Directorate-General Competition
DG ENTR	Directorate-General Enterprise and Industry (now: DG GROW)
DG SANTE	Directorate-General Health and Food Safety
EASA	European Aviation Safety Agency
EC	European Commission
EC	Economic Impacts
ED	Early Dialogue
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFSA	European Food Safety Authority
E.g.	Exempli gratia; for example
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPF	European Patients' Forum
ESIP	European Social Insurance Platform
ESMO	European Society for Medical Oncology
EU	European Union

EUCOPE	European Confederation of Pharmaceutical Entrepreneurs
Eu-LISA	European Agency for the Operational Management of large-scale IT Systems in the Area of Freedom, Security and Justice
EUnetHTA	European network for Health Technology Assessment
EUPHA	The European Public Health Association
EURORDIS	European Organisation for Rare Diseases
FC	Functional Class
Fimea	Finnish Medicines Agency
FinOHTA	Finnish Office for Health Technology Assessment
FR	France
FTE	Full-Time Equivalent
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee, Germany)
GMDN	Global Medical Device Nomenclature
GOEG	Gesundheit Österreich GmbH (Austria)
GO FP	Gesundheit Österreich Forschungs- und Planungs GmbH
GSK	GlaxoSmithKline
HAS	Haute Autorité de Santé (France)
HCC	Chronic Hepatitis C
HEN	Health Evidence Network
HIFU	High-Itensity Focused Ultrasound
HIQA	Health Information and Quality Authority
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HR	Human Resources
HSCT	Haematopoietic Stem-Cell Transplantation
HTA	Health Technology Assessment
HTAi	Health Technology Assessment international
HU	Hungary
ICER	Incremental Cost-Effectiveness Ratio
I.e.	Id est (that is to say)
IE	Ireland
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IMI	Innovative Medicines Initiative
INAHTA	International Network of Agencies for Health Technology Assessment
INAMI	Institut National d'Assurance Maladie Invalidité (Belgium)
INFARMED	National Authority of Medicines and Health Products, I.P. (Portugal)
IPD	Invasive Pneumococcal Disease
IPF	Idiopathic Pulmonary Fibrosis

IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Germany)
ISPOR	International Society for Pharmacoeconomic and Outcomes Research
IT	Information Technology
IT	Italy
IVF	In-Vitro Fertilisation
JA	Joint Action
J & J	Johnson & Johnson
JRC	Joint Research Center
KCE	Belgian Health Care Knowledge Centre
LBI HTA	Ludwig Boltzmann Institute Health Technology Assessment (Austria)
LSE	London School of Economics
MA	Market Authorisation
MAX	Maximum
MCA	Multi-criteria analysis
MedTech	Medical Technologies
MeSH	Medical Subject Heading
MIN	Minimum
MS	Member State
MTA	Multi Technology Assessment
NAATs	Nucleic Acid Amplification Tests
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Service
NICE	National Institute for Health and Care Excellence (UK)
NL	Netherlands
OECD	Organisation for Economic Co-operation and Development
OGYÉI	National Institute of Pharmacy and Nutrition (Hungary)
PAP	Papanicolaou Test
PET	Positron Emission Tomography
PL	Poland
PM	Person Month
PO	Policy Option
POP	Planned and Ongoing Projects
PPP	Purchasing Power Parity
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
REA	(Rapid) Relative Effectiveness Assessment
RRMS	Relapsing-Remitting Multiple Sclerosis
RNA	Ribonucleic Acid

RWE	Real World Evidence
SEED	Shaping European Early Dialogues for Health Technologies Group
SH	Social/Health Impacts
SMC	Scottish Medicines Consortium
SME	Small and Medium-Sized Enterprises
SMR	Service Médical Rendu
SOS	Sinusoidal Obstructive Syndrome
STA	Single Technology Assessment
SVJ	Social Value Judgement
TLV	Dental and Pharmaceutical Benefits Agency
UK	United Kingdom
VMT	Vitreomacular Traction
VOD	Veno-occlusive disease
WHO	World Health Organization
ZiN	Zorginstituut Nederland (the Netherlands)

Glossary

Additional evidence generation

Generation of additional clinical evidence refers to all studies and provision of data in addition to clinical studies performed for marketing authorization within the course of an HTA process.

Administrative data

Administrative data (typically retrospective or real-time, if possible) are collected primarily for reimbursement, but contain some clinical diagnosis and procedure use with detailed information on charges. Claims databases lend themselves to retrospective longitudinal and cross-sectional analyses of clinical and economic outcomes at patient, group, or population level.

Assessment

Assessment relates to the process of HTA when clinical, economic or other evidence is reviewed and described.

Appraisal

Appraisal relates to the process following the assessment phase when recommendations on the use of health technology are given, it includes value judgement.

Business models

The business models presented in this report combine implementation mechanisms with output production (e.g. joint REA). The business models presented are illustrative scenarios. Other combinations of implementation mechanisms and output productions are possible.

Early Dialogue

Early Dialogues are undertaken with the aim of helping Pharmaceutical and MedTech companies understand the evidence and information needs of the HTA organisations and reimbursement bodies in order to improve the quality and adequacy of early evidence generation.

Electronic health records/medical chart reviews

Electronic health records/medical chart reviews, such as the UK General Practice Research Database, contain more detailed, longitudinal information, including disease-specific symptoms at the personal level, and should greatly expand the use of this type of information.

Full HTA

Full HTA not only addresses the medical/therapeutic added value of a new technology (assessment of clinical domain), but also covers the assessment of other aspects such as cost-effectiveness, budget impact, ethical aspects, legal considerations and impact on patients as well as on the health care systems.

Health survey

Health surveys are designed to collect descriptions of health status and well-being, health-care utilization, treatment patterns, and health-care expenditures from patients, providers, or individuals in the general population, which are representative of the target population. Health surveys are methodologically rigorous (for example, relying on complex sample survey designs).

Horizon Scanning

Horizon Scanning is the systematic identification of health technologies that are new, emerging or becoming obsolete and that have the potential to affect health, health services and/or society.

HTA

The EUnetHTA definition for HTA is: a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner.

HTA submission

HTA submission refers to submitting evidence (study or clinical/economic data and studies) to an HTA Body/regulatory body for assessing the value of a health technology.

HTA processes

In the context of this study HTA processes relate to all current and future activities in the area of HTA including all four types of outputs defined in the Policy Options (Common tools, Methodologies and Templates; Early Dialogues; REA, Full HTA).

Internal audit

An internal audit is used to assess operational efficiencies and resource management. It is often compulsory for public bodies to verify cost records and adherence to acceptable cost accounting procedures.

Joint Assessment

A joint assessment is structured information for rapid or full/comprehensive HTAs, which is the output of joint production where two or more countries and/or organisations worked together to prepare shared products or agreed outcomes.

Multiple technology assessment

Multiple technology assessment normally covers more than one technology, or one technology for more than one indication respectively.

Non-clinical domains (see EUnetHTA core model)

Costs and economic evaluation, ethical analysis, organisational aspects, patients and social aspects and legal aspects.

Practical clinical trials

Practical or pragmatic clinical trials (also called 'large simple trials') involve prospective, randomized assignment but are aimed at larger, more diverse real world populations. Practical or pragmatic clinical trials have the important strength of randomization, which minimizes bias in the estimation of treatment effects. These trials are by design larger than conventional randomized controlled trials. For this reason, they are more likely to have sufficient power to capture significant differences in key outcomes of interest, such as hospitalizations.

Predictability

Predictability in the context of this study refers to the harmonization of methodologies, processes and evidence requirements in relation to HTA processes.

Registry data

Registries are prospective, observational cohort studies of patients who have a particular disease and/or are receiving a particular treatment or intervention. They can be used for

understanding natural history, assessing or monitoring real world safety and effectiveness, assessing quality of care and provider performance, and assessing cost-effectiveness.

Relative Effectiveness Assessment (REA)

REA is a specific element of Health Technology Assessment (HTA) that focuses on the clinical benefit of the intervention, whereas HTA is broader and can also include other aspects, such as ethical, cost, and cost-effectiveness considerations.

Single technology assessment

An assessment which covers a single technology for a single indication.

Supplement to randomised controlled trial

To provide additional data alongside standard clinically focused randomized controlled trials, researchers often gather information on variables such as patient-reported outcomes, medical resource use, and costs. Such efforts can add valuable evidence on treatment patterns for common events, such as the doses of drugs used to treat rejection in kidney transplantation.

Uptake

Within the context of this study, up-take concerns using or considering the results and findings of the HTA cooperation, reaching from jointly developed submission templates to full HTA. The subsequent pricing and reimbursement decision remains purely at national level.

Executive Summary

Background

The Member States (MS) and the European Union (EU) have recognised the growing importance of Health Technology Assessment (HTA) for decision- and policy-making for some time. HTA is considered as valuable tool that can contribute to the sustainability of national health systems. Still, the generation of HTA outputs (namely Early Dialogues, Relative Effectiveness Assessment (REA) and, finally, Full HTA reports with economic evaluation) is quite diverse in the EU partly because HTA systems are fragmented.

Cooperation on HTA at EU level commenced in 2009 with the establishment of the EUnetHTA collaboration. Two Joint Actions (JA) were undertaken, the first 2010-2012 (EUnetHTA JA 1) and the second 2012-2015 (EUnetHTA JA 2). The third Joint Action (EUnetHTA JA 3) started in June 2016 with the general objective to increase the use, quality and efficiency of joint HTA work at EU level, to support evidence-based, sustainable and equitable choices in healthcare.

In this context, the question of sustainable cooperation beyond 2020 when the current EUnetHTA Joint Action expires is addressed in line with the 'Better Regulation' agenda of the European Commission (EC), aiming at the design and evaluation of EU policies in a transparent manner, considering both evidence and stakeholder views.

The EC has launched an Impact Assessment initiative ([1]) to identify and assess various Policy Options (POs) on how to continue HTA cooperation at EU level beyond 2020.

Rationale and objective of the study

The study's overall aim is to support the Impact Assessment process of the EC and inform this process by generating relevant data and evidence. In doing so, it provides inputs for analysing the impact of different POs for EU cooperation on HTA beyond 2020 and utilises the data and information collected to analyse the potential impacts of the different POs. Accordingly, the study's specific objectives are:

- To collect data, generate evidence and provide in-depth analysis of **what would happen in the absence of further action at EU level including the associated impacts (baseline scenario)**
- To collect data, generate evidence and provide analysis of the potential impacts of **identified POs for cooperation of the EC**
- To collect relevant literature on HTA, with a specific focus on the EU, to understand the way HTA is used across EU Member States (MS)

While HTA provides input that determines pricing and reimbursement decisions in some countries, the study focuses on the assessment aspect, as in all POs any subsequent appraisal and pricing and reimbursement decision for medical technologies, whether medical devices or Pharmaceuticals, remain the competence of each MS.

A consortium consisting of Gesundheit Österreich Forschungs- und Planungsgesellschaft (Austria), The London School of Economics - LSE Health (UK) and SOGETI (Luxembourg), undertakes this study.

([1]) https://ec.europa.eu/health/technology_assessment/consultations/cooperation_hta_en

Policy Options for Impact Assessment: characteristics and analytical context

The EC has proposed POs for further cooperation at EU level in the Inception Impact Assessment (1), which the authors combined with potential business models.

The POs are defined along several key characteristics extended beyond the benchmark scenario of 'no further action at EU level', including (a) HTA outputs to be covered by the joint cooperation, (b) the proposed nature of the cooperation, (c) different models of governance and (d) funding options for the joint cooperation initiative.

- **Joint HTA outputs to be covered by the cooperation** include a range as follows:
  - Common tools and procedures such as common submission templates, an IT system with planned and ongoing assessments, common methodologies (e.g. EUnetHTA Core Model), a joint prioritisation process, and cooperation on data requirements, including Horizon Scanning
  - Early Dialogues
  - Relative Effectiveness Assessments
  - Joint Full Health Technology Assessments

- **Proposed nature of the cooperation between MS**

POs differ regarding the nature of cooperation, as reflected by the type of participation (voluntary or mandatory) and/or the uptake[2] of joint outputs (voluntary or mandatory):

- Voluntary participation/voluntary uptake (V/V): Cooperation is voluntary and the MS can decide if they wish to participate in the production and uptake of the respective outputs.
- Voluntary participation/mandatory uptake (V/M): The participation in the creation of joint work is voluntary, meaning that MS may decide to opt-in[3] to the joint cooperation. However, once a MS has opted in, the uptake of the joint work into the national setting is mandatory.
- Mandatory participation/mandatory uptake (M/M): Both participation in the production of outputs and uptake of these into the national setting are mandatory for MS.

- **Models of governance for joint EU cooperation**

A variety of governance models for EU cooperation were investigated ranging from loose project-based cooperation to a permanent secretariat within a new EU agency, as follows:

- Project-based cooperation (PO2)
- A permanent secretariat hosted by a MS (PO3)
- A permanent secretariat hosted by the EC (PO4.1)
- A permanent secretariat hosted by an existing EU agency (PO4.2)
- A permanent secretariat hosted by a new EU agency (PO5)

(2) Up-take concerns using or considering the results and findings of the HTA cooperation, reaching from jointly developed submission templates to outcomes in full HTA. The subsequent pricing and reimbursement decision remains purely on national level. Also providers / developers need to adhere to this process.

(3) Opt-in by MS is by output, not by individual products e.g. once a MS has opted in for joint REA, they take part in all joint REAs – but not necessarily as an author.

Across the board, the assumption has been that scientific work and expertise (i.e. the developments of joint outputs) would stay with national agencies. For governance models comprising a permanent secretariat, dedicated MS Committee(s) were foreseen to ensure the quality of joint work and consideration of national agendas. Regardless of the type of cooperation, there are common elements to the governance structure, which are defined by the joint output.

- **Funding options for the joint EU cooperation**

In order to finance the joint cooperation, a combination of several sources is conceivable, although this was not explored in any meaningful depth or detail in the study:

- EU funding, either through a Public Health program or another financial instrument
- Funding by the MS joining the collaboration
- Funding through industry fees

The following table provides an overview for each proposed PO, including the degree of covered outputs, the extent to which cooperation is compulsory and the envisaged implementation/funding mechanism.

Table 1: Overview of Policy Options

		Baseline	Non-legislative	Legislative			
		PO 1	PO 2	PO 3	PO 4 ([4])		PO 5
		No EU action after 2020	Voluntary cooperation through Public Health Programme	Legislation covering common tools and Early Dialogues	Legislation covering Joint work on REA Plus common tools and Early Dialogues		Legislation covering Joint work on Full HTA (including REA) Plus common tools and Early Dialogues
					4.1 REA V/M	4.2 REA M/M	
Outputs	Common tools, including templates, methodology	V/V	V/M	M/M	M/M	M/M	M/M
	Early Dialogue ([5])	V/V	V/M	V/M	V/M	M/M	M/M
	Joint REA ([6])	V/V	V/M	V/V	V/M	M/M	M/M
	Joint Full HTA ([6])	V/V	V/M	V/V	V/V	V/V	V/M
Implementation		No EU input	Project based cooperation	EU/MS secretariat	Existing EU agency	Existing EU agency	New EU agency
Financing		None from EU	EU+MS	EU+MS+fees from industry for Early Dialogues, joint REA and Full HTA			
Scope			All Pharmaceuticals , medical and other technologies	Tools: all Pharmaceuticals , medical technologies, other technologies (phasing in), ED: industry submission	Tools and ED see PO 3. REA: certain categories of Pharmaceuticals (e.g. centrally authorised, high value/budget impact, agreement between MS) and medical technologies (e.g. high risk, high value products) and other technologies (agreement and prioritisation between MS) – phasing in([7])		Tools and ED see PO 3, REA see PO4. For others: ad hoc agreement and prioritisation between MS

Legend. PO: Policy Option; V/V: Voluntary participation/ voluntary uptake; V/M: Voluntary participation/mandatory uptake; M/M: Mandatory participation/mandatory uptake; ED: Early Dialogue; REA: Relative Effectiveness Assessment; MS: Member State; HTA: Health Technology Assessment

([4]) Assuming that 50% of the Member States (MS) participate, a mix of high/low income, large/small MS.
([5]) ED - Early Dialogue: Here mandatory uptake means that the MS cannot repeat an ED that was done at the EU level. Technology providers initiate Early Dialogues.
([6]) Either at time of market or re-assessment.
([7]) A gradual introduction of products during a transitory period that allows to manage the workload while the structures/implementation models are being developed.

Methods

Overall approach

In order to establish the baseline scenario, a case study comprising a product sample of health technologies was analysed, which included 20 Pharmaceuticals, 15 medical devices and five 'other technologies' (including complex health interventions). The study team collected detailed information on the HTA-process each technology underwent in the MS. Additionally, the costs of performing a Health Technology Assessment were identified for both the technology developer and the HTA body. Finally, the case study captured the influence of the regulatory framework on technology developers.

In order to analyse the impacts of identified POs for the EC, a survey was performed on the economic and social impacts of the identified POs, complemented by focus groups, a number of interviews and findings from literature review. The study investigated the following impacts, for which one or more indicators were defined:

The impacts investigated included economic (EC) and social health (SH) criteria:

EC1	Costs	SH1	Employment
EC2	Administrative burden	SH2	Governance, participation and good administration
EC3	Competitiveness of EU health technology sector	SH3	Access to social protection and health systems
EC4	Innovation and research	SH4	Sustainability of health systems
EC5	International trade innovation and research	SH5	Public health
EC6	Functioning of the internal market and competition		
EC7	Consumers and households		
EC8	Macroeconomic environment		

The study also provides a description of the implementation mechanisms (for instance, a joint secretariat) and an estimation of the associated costs.

Data collection

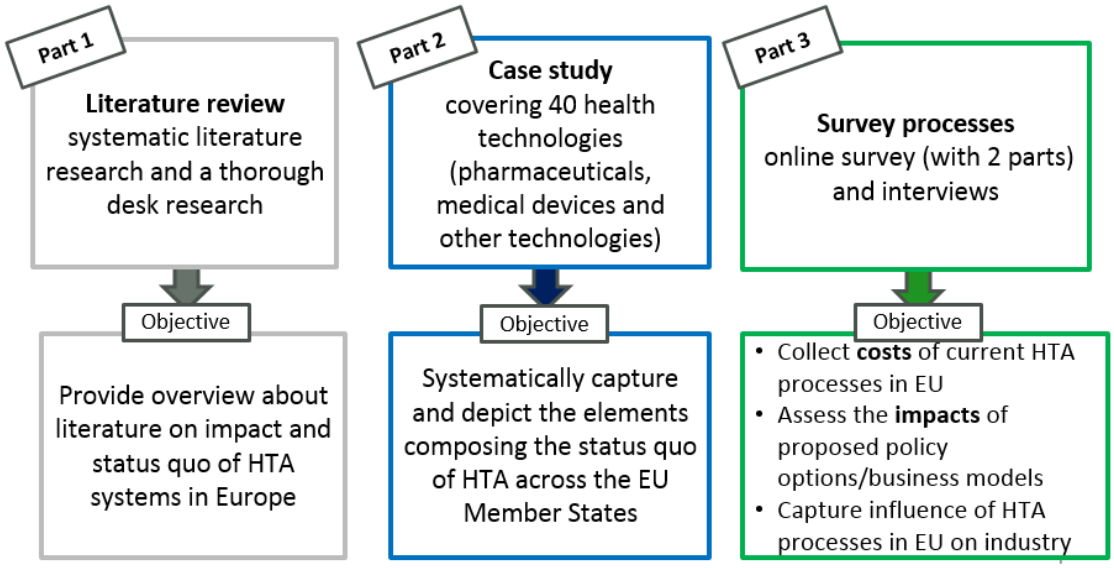
In order to collect a comprehensive data set for analysing the **baseline scenario** and the potential **impacts** of the EC's **identified POs**, a variety of data collection methods was utilised (see Figure 1 on the next page).

Both a **systematic literature review** and desk research were performed to identify relevant literature, which has been used to put in context, verify and complement the findings of the case studies and the survey. The aim was to provide an overview of the status quo and impact of HTA systems across EU MS.

An **online survey** was undertaken targeted at Public Administrations (e.g. HTA bodies), the Pharmaceutical and MedTech Industries as well as Patients and Health Professionals, which yielded responses predominantly from Public Administrations and Industry.

The **case study**, covering 40 health care technologies (20 Pharmaceuticals, 15 medical devices(8) and 5 'other technologies') sought to systematically capture and depict the elements composing the status quo of HTA across EU MS, by adopting a multi-stage, mixed qualitative and quantitative analytical approach.

Figure 1: Overview about streams of activities



Additional data collection and validation of findings included:

- Interviews with industry (Pharmaceutical and medical device) and patient representatives;
- Short surveys/follow-up questions addressed to Public Administrations and Industry aiming to gather more data on costs as well as additional information relevant to interpret the results;
- Use of findings of a further EC study (2) conducted to support the Impact Assessment process;
- Focus group meetings with stakeholders from Public Administrations and both industry sectors (Pharmaceuticals and devices) to discuss the results of the online survey and to gather additional insights and feedback on the results;
- Involvement of an expert group which was set up for the duration of the study; and
- Peer review by leading experts in the field.

Limitations of the Study

The study has several limitations, many of which are linked to the assumptions that were, and had to be, made (e.g. on the future number of joint HTA outputs or IT costs). For some elements (e.g. the current number of ED in Europe) no data was readily available or the granularity of available information was very different among EU countries and HTA bodies. The cost estimates need to be read with caution, taking into account all challenges and limitations, as described in detail in the report.

(8) In this report the word 'devices' is used generically and includes medical devices and associated medical technologies.

With regards to the baseline scenario information on the MedTech sector and 'other technologies' was sometimes scarce compared to Pharmaceuticals, because for the MedTech industry HTA is less common than the Pharmaceutical sector.

Regarding the stakeholder survey, two issues are worth noting: a low response rate from patients and health professionals, as they felt more addressed by the public consultation that was conducted by the EC in parallel; and the level of detail in the questions because the study team had to capture many potential effects of a number of POs as required in the EU 'Better Regulation Guideline' (3). As a consequence, not all EU MS could be covered, but there were respondents from all parts of the EU, including countries with well integrated and less well integrated HTA systems.

Analysis

Case study – Analysis of baseline scenario

We compared and analysed the sample of 40 health technologies to identify the key elements of value assessment of health technologies across different European countries. Although the primary aim of the study is to capture *assessments*, due to the heterogeneity of the HTA role across countries, in some cases *appraisals* were also captured. Thus we identified final HTA decisions, the restrictions put in place in order to include or suggest the inclusion of a technology in the benefits catalogue of each country or setting and how these and the length of the process differed or aligned across countries or settings. Indeed, the systematic analysis identified: (a) the presence of an assessment and the final recommendation made by HTA bodies, capturing possible duplications in assessment; (b) how HTA is currently used in different contexts and what clinical and economic evidence is used in conducting the assessments; (c) the timeline of performing the assessment across different country or setting; (d) the cost related to the HTA process; and (e) perspectives from industry and HTA bodies on methods and processes.

The systematic approach allowed an understanding of the **variability in methods and processes currently employed by different HTA bodies across the EU** and enabled the **identification of possible duplication of efforts or cases where greater consensus would be needed around HTA processes and methods**. It also contributed to identifying areas where **consistency and transparency in the criteria used for decision-making could** be improved.

The systematic analysis of HTA recommendations across MS and for the 40 technologies identified, included the examination and reporting of the following endpoints: (a) Presence of HTA assessments across the sample of technologies; (b) inclusion of clinical and economic evidence; (c) social value judgments; (d) agreement vs. disagreement among HTA bodies in recommendations, through the use of the Kappa score statistic; (e) the direction of HTA recommendations; (f) clinical restrictions in HTA recommendations; (g) economic restrictions in HTA recommendations; (h) HTA timelines relative to MA; (i) baseline HTA costs based on primary data collection (survey) from manufacturers and HTA bodies; and (j) industry views on HTA processes.

Due to the incomplete nature or the low quality of clinical and economic evidence, decision makers need to make judgements based on considerable uncertainty about the clinical and economic impact of a treatment or accept ICERs that are, strictly speaking, above implicit or explicit national willingness to pay (WTP) thresholds. In this context, **social value judgements** (SVJs) aim to interpret key elements related to the impact of the treatment on patients and society. As such, SVJ have increasingly been included in HTA decisions. They have been identified and coded across all HTA reports, and classified into eleven main categories notably: (a) Significant innovation, (b) Life expectancy improvements, (c) Small population, (d) Equality issues, (e) Wider societal benefits, (f)

Impact on quality of life and daily activities, (g) Impact on the family and carers, (h) Unmet need for treatments, (i) Rarity and severity of the disease and, (j) Other considerations, which may be related to the disease or the product in question.

Cost prognosis

One task of the project team was to give input to the EU Impact Assessment regarding the likely evolution of cost for coordinated HTA in the EU. Cost prognosis includes estimates on costs and savings from the implementation of the POs from 2021 onwards, as follows:

- On future **joint outputs** (common tools; Early Dialogues (ED); Joint REA; and Joint Full HTA);
- On **savings** that arise from the reduction in related **national outputs** (diminished by the costs of adaptation of joint outputs to national context);
- On the various proposed **implementation mechanisms and governance structures** (project-based cooperation, MS secretariat, EU secretariat located at EC level, integration of such a secretariat into an existing EU agency, founding a new EU agency).

Costs of implementation mechanisms include potential one-time investment costs (if estimable) and operating costs. **Several sources,** including published and unpublished studies, (validated) data from the study survey and baseline scenario as well as additional information provided by stakeholders and EC services were the basis of the cost prognosis. If cost data and/or information were not available, the team made justified assumptions to derive estimates. Considering cost evolution for output and some other parameters, **sensitivity analyses** aimed to investigate related uncertainties. Potential funding mechanisms for POs and business models were not part of the prognosis.

Assumptions on the future number of joint outputs were made for the Pharmaceutical and MedTech sectors separately and are outlined in detail in the full report; the same applies for the expected opt-in rates of MS for the voluntary POs and the expected overlaps between joint and national outputs (indicating potential savings). An **implementation mechanism without EC funding was not considered in this study, because intergovernmental cooperation without EU input is strictly the responsibility of the MS**. Detailed assumptions regarding the establishment of a permanent secretariat were made, addressing the general structure and personnel requirements, including the establishment of three MS expert committees responsible for quality assurance and consideration of national agendas. Underlying assumptions were based on literature or other sources, if available.

The main limitations of this approach were as follows: We could not incorporate ED fully within the calculations due to a lack of data. Further cost impacts like system change costs at country level could not be quantified on an aggregate level and are, therefore, depicted in a descriptive way. Current HTA outputs are heterogeneous across Europe and data sources for current costs and quantities of outputs at MS level show many gaps and uncertainties. At national level, there may be an uptake of joint output (and related savings or costs) for other purposes than reimbursement decisions. Finally, it was not possible to quantify the long-term overall impact of centrally organised mandatory HTA outputs on national HTA systems, e.g. in terms of transparency, standardisation or methodological quality.

Assessment of Policy Options

Potential impacts of the proposed POs on the different stakeholder groups were assessed by **multi-criteria analysis (MCA)**. These findings were validated by focus groups, follow-up discussion and literature. The MCA approach captures multiple criteria, permits differentiation between stakeholder groups (i.e. Public Administrations, the Pharmaceutical Industry, and the MedTech industry) and allows differences or similarities between the stakeholder groups to be shown.

Identification of relevant criteria for assessing economic and social/health impacts took place in collaboration with DG SANTE and were based on the impacts stated in the EC's Better Regulation Guideline (3, 4). For each impact one or more indicators were defined, such as Research and Innovation in the European market, the fragmentation of HTA systems in Europe, the number of health technologies assessed or available, and sustainability or resource efficiency in HTA processes in Europe. A consultation with the expert group set up for this study was performed in order to validate the relevance of the identified impacts and indicators and to identify potential missing impacts/indicators.

The direction (positive or negative) and the extent (scale from -100 to +100, i.e. increase or decrease) for each impact was surveyed and represented an important source for analysis and an attempt to quantify estimates. Additional to the effect of the respective POs on the impacts, the MCA included an assessment of the importance or relevance of the impacts for different stakeholder groups. In order to capture variability within stakeholder groups in the analysis of survey results, additional sub-group analyses were performed, e.g. separate analysis for different company sizes and a comparison of responses of companies with and without experience in the field of HTA. Different data plausibility checks were performed to investigate the reliability and robustness of survey data as well as the response behaviour of stakeholder groups.

Additional information collected through literature, stakeholder focus groups, stakeholder interviews and information derived through the analysis of the baseline scenario and the cost prognosis supplemented the survey results. Results were depicted separately for each stakeholder group. To strengthen the stakeholder group of patients and consumers, an additional follow-up targeted further information collection to depict the stakeholder groups' perspective adequately. Follow-up consisted of interviews with consumer and patient organisations at EU level.

The main limitation of this approach was that the different levels of detail in the evidence across the different HTA bodies, the number of functional differences across HTA bodies in Europe and their different levels of transparency (e.g. not all assessments are in the public domain or were shared with the study team) may have affected our analysis.

Results

Analysis of baseline scenario – Case study approach

The baseline scenario analysed forty technologies (**20 Pharmaceutical products, 15 medical technologies (predominantly devices) and five 'other technologies'** (e.g. HPV vaccination) in detail to capture critical aspects of HTA processes in the MS. The main objective was to provide clarity on HTA models, processes and outcomes in the MS through comparative analysis of HTA recommendations across the selection made.

HTA across the sample of technologies: In the Pharmaceutical products sample, evidence showed that the same product-indication pair had been assessed at least by 10 HTA bodies in as many countries. An average across the sample of 13 out of 24 bodies assessed the same product-indication pair. This is confirmed by HTA bodies such as HAS (France), G-BA (Germany) and AIFA (Italy) due to their topic selection process – evaluating all new Pharmaceuticals applying for MA (Marketing Authorization) – and the high level of agreement among other HTA bodies such as TLV (Sweden) and NICE (England) or INFARMED (Portugal).

Clearly, not all HTA bodies assess all Pharmaceutical products. Some well-developed HTA systems assess all new Pharmaceutical products. Others have explicit prioritisation and topic selection processes, which (a) results in a proportion of all new product-indication pairs being assessed in a given year, (b) results in a very small number of technologies being assessed, or (c) only results in simply performing HTA referencing. Additionally, the assessment of each product-indication pair carried out 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 (i.e. arms' length or integrated approach).

The **situation in HTA for medical technologies and 'Other Technologies' is less developed and established across EU MS**. The sample shows that the number of HTAs per product-indication pair was lower than in Pharmaceuticals. On average, one medical technology or one 'Other Technology' was evaluated by six HTA bodies, with at least four countries evaluating the same medical technology.

Inclusion of clinical and economic evidence. In terms of clinical evidence across the entire Pharmaceutical sample, all HTA bodies had a clear preference for **phase III clinical trials,** followed by phase II trials and other sources of evidence. The most commonly used trial comparators were placebo/current standard of care. Across the **medical technologies** sample, a clear preference is shown for **RCT trials** (28%) followed by observational studies (17%) and safety studies (19%). The most commonly used trial comparator was the current standard of care. Finally, in the 'Other Technologies' sample on average 6 clinical studies showed a general preference for literature reviews (89%), which include different aspects of public health programmes and not just the clinical and cost effectiveness of technologies.

There is a clear difference in preferences among HTA bodies for the type of evidence required for Pharmaceuticals compared to medical technologies and 'other technologies'. This is partly driven by what is feasible in the context of either medical technologies or 'other technologies' and highlighted by the high proportion of retrospective studies and safety studies (in the medical devices sample) and literature reviews (in the 'other technologies' sample).

In terms of **economic assessment**, not all countries assessed the clinical and cost effectiveness of each study technology, and the criteria for assessment varied considerably. In the Pharmaceuticals sample, eight countries considered an economic evaluation in their assessment and, on average, 1.5 economic studies were considered for each Pharmaceutical product/indication pair. Findings showed that, in general, a cost-utility

analysis was considered across all study Pharmaceuticals (in 85% of cases), followed by budget impact analysis (43% of cases). Only in a limited number of cases (6%) was a cost-minimization analysis performed. The most commonly used trial comparators were a direct comparator (86%). **Across studied countries, in 68% of the cases, the comparator included was the same across HTA bodies**. In the medical technologies sample, eight countries considered economic evaluation, with an average number of 2.5 studies per technology considered. Looking at the type of economic analysis, the trend was confirmed with mostly cost-utility studies (67%), followed by cost comparisons (21%). In the 'other technologies' sample, seven countries considered economic evaluation with 73% accounting for cost utility analysis, followed by 45% of a budget impact analysis.

Social value judgments. Social value judgments (SVJs) are increasingly used in informing HTA recommendations. Across the selected HTA bodies, only three have elicited/revealed their social value judgments in their guidelines: NICE in the context of end-of life (EoL) criteria, SMC with the so-called 'disease modifiers' and TLV with the 'human dignity, needs and solidarity' principle. Other HTA bodies also account for these values, but not in a consistent manner. Considering specific trends across different health technologies, the highest number of SVJs was identified in the Pharmaceuticals sample (n=304) followed by the medical devices sample (n=67) and the 'other Technologies' sample (n=4).

Agreement vs. disagreement among HTA bodies in recommendations. In the Pharmaceutical sample, 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 to not assess all technologies. However, the level of agreement in HTA recommendations across HTA bodies that assess all technologies is very high (as indicated by the kappa score, $k>0.8$). 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).

This trend is not confirmed for the medical technologies or the 'other technologies' samples. The number of assessments of the former is lower and fragmented across the sample illustrated by a poor K score ($k<0.20$). Equally, in the 'other technologies' sample, the level of agreement is generally poor with 64% of the HTA bodies achieving a poor level of agreement ($k<0.2$) and 36% achieving an agreement between fair ($0.21<kj<0.4$) to very good ($0.81<k<1$).

Direction of HTA recommendations. Seventy six percent (76%) of the technologies received a positive recommendation with or without restrictions. Breaking down this figure: 62% were positive with restrictions whereas the remaining were positive without restrictions. Across the sample of Pharmaceuticals and medical technologies this trend was confirmed with 81% and 64% respectively receiving a positive recommendation, of which 63% and 59% respectively received a positive recommendation with restrictions. Across the 'other technologies' sample, most recommendations were positive with restrictions (66%).

Clinical restrictions in HTA recommendations. Across the entire sample, the most common type of restriction was **clinical** (56% of all cases). In the Pharmaceutical sample, the most common clinical restrictions were related to sub-groups of patients (67%) followed by therapeutic pathway restrictions (18%). For **Pharmaceuticals and medical technologies, common restriction types were specialist prescribing and setting restrictions**. The first relates to a health technology that can be prescribed only by a specialised physician, whereas setting restrictions refer to a condition on the location where the treatment can be prescribed or offered. In the **medical technologies sample, the most common clinical restrictions were patient sub-groups (67%)** followed by therapeutic pathway restrictions (32%). In the 'other technologies' sample, the most common clinical restrictions were related to a technology-specific

feature, i.e. a recommendation made for one technology over another (58%), followed by programme design, i.e. a recommendation made regarding various features of the programme in order to improve the clinical performance of the entire programme (34%).

Economic restrictions in HTA recommendations. Economic restrictions were mainly present in the Pharmaceuticals sample and based on information that was publicly available. **Of all economic restrictions, 64% referred to the introduction of a risk-sharing or a Managed Entry Agreement** in reimbursing the product, and 14% requested a further price negotiation. In the medical technologies sample, only five economic restrictions were identified with main focus on the use of special price negotiations with the regulatory agency responsible for reimbursement decisions.

HTA timelines relative to MA. There is often a significant time lag between marketing authorisation (MA) and publication of a HTA recommendation. This time lag is not uniform and differs by country or HTA body and by type of technology. On average, the longest time between MA and HTA recommendation in the Pharmaceutical sample was found to be 21.6 months, while the shortest was 9 months. However, it should be acknowledged that this difference might be related to factors such as willingness to submit a report or delays in HTA submission by the relevant company, the different selection criteria in the choice of technologies to assess and the different role of the HTA body. In the medical technology sample, looking at the average time lag between the CE mark and the submission of an HTA, the timing is much longer, approximately 60 months, although caution is required due to the scarcity of publicly available data on CE mark dates (an indication being the certificates, but these are usually not published). Importantly, across HTA bodies, **on average the time lag between assessments was three years**. In the 'other technologies' sample and similarly to medical technologies, there was significant time difference between assessments for the same technology across HTA bodies; in the case of colorectal cancer screening, for example, the programme was evaluated in 2006 in one jurisdiction and in 2016 again in two other jurisdictions.

Baseline HTA costs based on primary data collection (survey) from manufacturers and HTA bodies. Survey results revealed significant differences between the Pharmaceutical and the MedTech industries. For the Pharmaceutical sector, the results indicate a high variability in HTA spending (between EUR 73 000 to EUR 1 700 000 per HTA submission), and in additional evidence generation (between EUR 50 000 to EUR 20 000 000). The diversity in the figures reported may reflect the heterogeneity in evidence assessment across settings or the different needs for data generation and does not provide a definitive picture of average spending across products or manufacturers. 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 the HTA circumstances prevailing in each setting. HTA submission figures of the MedTech industry revealed a range of EUR 1 000 to EUR 3 400 000 while additional evidence generation in the context of HTA submission ranged from EUR 17 000 to EUR 12 800 000. MedTech industry representatives argued that the current number of medical device assessments across countries differs considerably. Therefore constructing an average based on the above ranges would not be reliable.

In terms of the **composition of the cost components**, in both, the Pharmaceutical and the MedTech industry, personnel costs (internal and external) were the key expenditure drivers. However, focus group discussion showed that another key driver for HTA-related 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.

Evidence on **Early Dialogue indicates a completely different level of engagement between Pharmaceutical and MedTEch industry**. The former actively engages in early dialogue (69% of responses) with an average cost of EUR 55 750 per case, the

latter showing a much lower level of engagement (28% of responses) and a lower level of spending (around EUR 21 700) per case. In focus group discussion, MedTech industry representatives confirmed that they do not engage routinely in ED for medical devices.

In terms of the *costs reported by HTA bodies*, cost differences are highly influenced by factors such as the type of HTA process in place, the type of assessment performed and the level of integration of HTA bodies with government entities. In general, it appears that the cost of performing a Single Technology Assessment (STA) among 'arms' length bodies' is higher than among 'integrated' structures (the highest reported figure for STA was EUR 135 000 for the former vs. EUR 100 000 for the latter), while the maximum reported figure for REA was EUR 55 000 for arms' length bodies and EUR 100 000 for integrated structures. However, as the data received in some cases contain missing values, these estimates should be interpreted with caution.

Industry views on HTA processes. Overall, interviews across the Pharmaceutical and MedTech industries showed that the 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. However, it is important to highlight that these differences are also influenced by the therapeutic areas of individual products.

Manufacturers highlighted that the current fragmented HTA system across Europe requires companies to cater to a diversified range of demands. Our analysis confirms that this might lead to difficulties in submitting reports or multiple re-submissions to the same HTA bodies.

There is consensus across the Pharmaceuticals industry respondents that EU collaboration on HTA may be possible for generating a REA. By contrast, MedTech respondents highlighted the heterogeneity and diversity of the medical device/technology market in comparison with Pharmaceuticals. MedTech representatives highlighted that HTA currently plays a minor role for medical devices and related technologies in most settings (due to the extremely fragmented market access of medical devices), and therefore the current impact of HTA on their business is low.

The predictability of the HTA process was agreed to be a key element for investment and resource decisions, particularly for smaller companies. It was commonly stated that, **the harmonization of processes and evidence requirements, would contribute to minimize misunderstandings and enhance the level of predictability in the system.**

Transparency of evidence requirements, consistency of methods, acceptability of indirect comparisons and predictability of outcomes have been highlighted by several companies as desirable characteristics. Specifically, interviewees from the Pharmaceutical industry, advocated for a better summary and inclusion of information on important issues such as indirect comparisons and secondary endpoints and a clear definition of the appropriate comparators. By contrast, MedTech interviewees suggested that, while long RCTs may be desirable from an evidence standpoint, they may not always be appropriate, feasible or sufficient for medical devices and related technologies, advocating for a lighter touch approach to HTA in this sector because of its peculiarities, the fact that innovations typically come from smaller-sized companies and the innovation cycle is significantly shorter compared to Pharmaceuticals.

Early Dialogue and scientific advice are viewed as extremely useful exercises helping to increase transparency from an industry perspective, suggesting that a system aligned with what is currently done with EMA would be beneficial and simplify development programmes. However, a few respondents stated the importance of not introducing a parallel system where countries impose additional requirements.

Finally, manufacturers highlighted a number of issues relating to **innovation**: poor predictability, high complexity and high fragmentation constitute barriers to health innovation. 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. **We understood that harmonisation of evidence requirements, if accompanied by MS acceptability, would facilitate investment decisions for technology providers**. Additionally, an 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 expectations. Finally, **evidence requirement harmonisation would give the EU a stronger influence on clinical trial development.**

Summarising the findings confirmed that 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**.

Cost prognosis

The cost prognosis addressed two issues:

1. The estimate of the costs of voluntary or mandatory **joint outputs** and related **savings in national outputs** of the proposed POs; and

2. The costs related to **specific organisational structures/implementation mechanisms, including common tools.**

An implementation mechanism without EU funding was not considered in this study because intergovernmental cooperation without EU input is the sole responsibility of the MS. All types of implementation mechanisms include production of HTA outputs by different HTA bodies and the support provided to the HTA bodies by the central coordination unit. The support includes administrative, scientific/technical, legal and IT support, which differ in extent for different mechanisms. The main differentiation criteria between implementation mechanisms is the establishment of a permanent central coordination unit (5 out of 6 mechanisms) compared to the project-based mechanism oriented on EUnetHTA structures.

Besides the central coordination unit, there are three main pillars anticipated for the business models:

- Management Board (defines work programme and consists of MS representatives)
- HTA output production (contracted to HTA bodies)
- MS expert committees (comprised of MS experts to review and discuss HTA outputs for quality assurance).

Permanent central coordination units perform project coordination and overall support for the respective Work Packages of output production, the Management Board and the Committees. The business models combine predictions of joint outputs, organisational/implementation mechanisms, are the basis for further developments and represent illustrative scenarios. Other combinations of POs with business models than the ones analysed in more detail are possible as well (e.g. a new agency already for PO 4.1). The presented combinations are considered the most plausible ones.

Cost prognosis was based on **several sources:**

- Information obtained from the study by Julia Chamova (2)
- Information provided from EUnetHTA members

- Data gathered through the baseline survey
- An additional follow-up on costs via a short survey distributed by e-mail
- Focus group input by Public Administrations, the Pharmaceutical Industry and the MedTech industry
- Other sources, e.g. EC Services or Agencies (explicitly stated if applicable)

Two models were proposed with one distinctive factor: the **basic model** covers 65 jointly produced REAs, 40 on Pharmaceuticals and 25 on medical technologies, and the **advanced model** with 115 joint REAS in total, 90 on Pharmaceuticals and 25 on medical devices. Assessment of both models included adaptation of implementation mechanisms, specifically human resources, according to the anticipated joint output.

Estimated output production is relevant for the period until structures and processes are well-established. After adaptation, i.e. an increase from 65 REAs to 115 REAs (90 on Pharmaceuticals, 25 on medical technologies) ([9]), covering all centrally authorised new substances and indications, could be considered. Accordingly, more staff will be needed to handle this expanded output production. Therefore, the number of staff would increase for POs 4.1, 4.2 and 5 (Table 17 of main study). A sensitivity analysis was performed to account for related uncertainties.

Basic assumptions on the cost elements included a categorization of MS by annual HTA output volume or HTA reports mainly produced by HTA bodies or produced by industry and reviewed by HTA bodies. Within the majority of countries, HTA bodies produce less than 60 HTA reports on Pharmaceuticals and less than 50 HTA reports on medical devices. The majority of HTA reports are industry-based and reviewed by HTA bodies.

Regarding the implementation mechanisms, personnel costs and costs resulting from MS expert committees account for the majority of expected costs. Estimates of personnel costs were based on EU staff regulations, indexed to MS if applicable, and EC expert fees. Overall estimates on implementation mechanisms increase by twofold from PO2 to PO5. Moreover, costs for the basic model and the advanced model differ significantly for PO4.1, PO4.2 and PO5 due to increased output production.

Calculations also show that, taking the underlying assumptions into account, **especially with PO 4.1, 4.2 and 5** – i.e. the more 'legislative' and mandatory options – **overall savings at EU level for MS and the industry sector can be expected,** and that savings rise with each successive POs. However, several additional factors that cannot reliably be quantified, but which may have an impact on overall costs/savings and may reverse or diminish some of the results, have to be considered additionally. Examples are costs related to implementing the mandatory uptake of joint output within national procedures, laws and regulations but on the other hand also potential additional savings related to a reduced number of national ED or reduction in additional evidence generation requested by HTA bodies.

Concluding, calculations show on the one hand, a significant increase in costs for establishing a new framework from PO2 to PO5, but on the other hand a potential savings increase from PO2 to PO5.

([9]) Based on EMA annual reports 2015 & 2016.

Overall assessment of POs

We investigated, guided by the Better Regulation Guidelines ([5]), a number of impacts in order to establish a comprehensive picture of how the different POs and business models would affect different stakeholder groups.

The analysis of impacts focused on three main stakeholder groups, i.e. **Public Administration**, **Pharmaceutical Industry** and **MedTech Industry**, as these provided the most input. We also analysed the impact on patient groups and health professionals, whenever information was available ([10]).

An overview of the results per stakeholder group for each impact category, from Economic Criteria (EC) to Social and Health Impacts (SH), are described in detail in chapter 7.3 of the study. In sum, the survey results and the focus group discussion showed that the perceived effects of the POs as well as the **perceptions and expectations regarding the future cooperation on HTA in Europe differ between the stakeholder groups** in a number of ways.

Information collected indicates that **Public Administration does not expect any major effects with regard to HTA-related processes for PO1 and PO2**. But, with POs covering a legislative framework (PO3-PO5), positive effects are expected by Public Administration, which are amplified with each output that is covered by the legislative framework. This is confirmed by our assessment as **POs with a legislative framework (PO3 to PO5) are more likely to positively influence the sustainability of health systems** than further non-binding cooperation.

This increase in positive effects with stronger requirements and central governance relates to the expectation that the uptake of joint outputs will increase with each of these subsequent POs. **Stricter regulation could be a key element for sustainable, successful collaboration, since otherwise the impact of the cooperation is limited.** Moreover, it was expected **that 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 the fact that 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.**

None of the POs is considered to have a substantial effect on the administrative burden of Public Administrations across EU MS and no or only little effect on costs for HTA-related outputs were indicated in the online survey. This relates to the fact that national processes will still remain in some form. However, some HTA bodies voiced the expectation that indeed a closer collaboration would reduce their cost. This is confirmed by our cost calculations, which indicate potential savings across MS, especially from PO4.1 onwards.

For the **Pharmaceutical Industry,** results indicate no changes for PO1 and PO2 **while positive effects of POs including joint work on REA at EU level, namely PO3 and PO4, are stated.** These POs are estimated to reduce inefficiencies and workload for the Pharmaceutical sector, improving the functionality of the internal market. Moreover, an increase in predictability of HTA processes and requirements is expected by the Pharmaceutical Industry, which was highlighted to be a very important factor for research and investment decisions.

([10]) These both groups hardly contributed to the survey, so findings were derived from other sources a/o indirectly.

The Pharmaceutical Industry **expects negative effects for PO5,** which includes a strictly mandatory and binding HTA process also covering Full HTA in Europe. Underlying reasons for this were indicated during the interviews as well as in comments to the survey and in the focus group with Pharmaceutical company representatives: mandatory joint economic evaluations as foreseen in PO 5 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. Instead, **joint work on REA was repeatedly indicated to have the potential to reduce inefficiencies and workload for the Pharmaceutical sector.**

With regard to costs for HTA processes, respondents from the Pharmaceutical sector expect no major changes with the exception of PO5, where a substantial cost increase is feared. Based on focus group discussions this relates to the fact that possible increases and decreases of cost components would level each other out, meaning that costs on MS level might decreases while at the same time costs on EU level increases.

Still, the results of our cost prognosis for 2020+ indicate that **actual savings due to a reduction in duplicated assessments can be achieved** for the Pharmaceutical Industry across the EU for all POs. Potential savings are considerably higher in POs that comprise both a mandatory production and mandatory uptake of joint REAs (PO4.2 and PO5). Options comprising a permanent secretariat and higher joint output lead to substantially larger savings as compared to the project-based cooperation (EUR 3.7 million in PO2 versus more than EUR 60 million in PO4.2).

For MedTech, our analysis yielded a different picture: MedTech industry representatives indicated a negative effect for all POs except for PO 2. This negative assessment is related to the peculiarity of the medical devices market. Whereas Pharmaceutical products have a well-established pathway from Marketing Authorization to HTA evaluation and an established HTA process in a large number of EU MS, MedTech companies follow heterogeneous rules or processes regarding the evaluation of their products. Moreover, the market for medical devices is intrinsically different from that of Pharmaceuticals with a higher level of competition from market entry onwards. While HTA has been largely developed for Pharmaceuticals, there appears to be a need for adaptation and development of established HTA processes for the MedTech sector as well.

The **negative assessment of POs covering a legislative framework** links to the expectation of MedTech industry that this will function as a driver for an upsurge of HTA activities in MS. This point was perceived as a very important element of unpredictable change and additional burden for the MedTech industry, as HTA activities have not played a major role in the medical technologies' market access path until now. Related uncertainty was seen to subsequently influence the attractiveness of the European market and potential delays in first revenues are feared due to the likelihood of longer processes. Another key impact is the expected decrease in competitiveness and innovation. According to focus group discussions and the interviews, this is due to the perceived unpredictable change in the market access path of medical technologies, also attributed to the two new EU Regulations on medical devices. Potential new administrative barriers, which are typically the most burdensome for the first movers (innovators) are thus expected. A further important aspect is the expected increase in costs, driven by additional evidence generation. Study findings indicate that this impact seems to be overestimated by the MedTech industry. One identified reason for this is that the actual level of experience with HTA for the respondents from this sector is considerably lower than for the respondents from the Pharmaceutical Industry.

Our **cost calculations did not confirm the expectation of cost increase** for MedTech industry. On the contrary, findings indicate that the MedTech industry might also benefit from the 'tighter' POs under consideration when it comes to costs (aggregated across Europe). Potential savings are especially noticeable for POs with a legislative framework (PO4.1, 4.2 and 5).

In summary, POs with a legislative framework entail some negative effects for the MedTech industry in the sense of additional burden (from their perspective), especially if joint REAs are covered. However, for PO3 only a slight negative effect is expected and in the long-run, the development of joint common tools and templates could lead to clearer HTA requirements, which may subsequently facilitate HTA processes for MedTech industry.

Finally, patient groups call for improved transparency in this field, which is considered to strengthen the quality and safety of technology. Strengthening HTA of Medical Technologies inherits potential positive effects for patients because better evidence for decision-making is available. Ultimately, therefore, we expect positive effects regarding the safety of medical devices.

The following table gives a concise overview of the potential effects of the POs – aggregated across all investigated impacts – for each stakeholder group. Green colours indicate positive and red colours negative perceptions based on the judgment of the study team, considering all collected evidence and information regarding the different stakeholder groups and combining all retrieved information.

Table 2: Conclusion - Effect of Policy Options

Stakeholder group	Baseline scenario (PO1)	Project-based co-operation (PO 2)	MS/EU secretariat (PO 3)	Existing EU agency (PO4.1)	Existing EU agency (PO 4.2)	New EU agency (PO 5)
Public Administration						
Pharma						
MedTech						

Overall, the perceived effects of the POs and the perceptions and expectations regarding the future cooperation on HTA in Europe differ between the stakeholder groups in a number of ways.

For Public Administration, POs providing a legislative framework for HTA cooperation in Europe (PO3 onwards) will potentially have a positive effect, gradually increasing as we move along the PO range. The predictability of the HTA system in Europe is expected to considerably increase for PO3 and the positive effect is amplified with each of the subsequent Policy Options.

For the Pharmaceutical Industry POs with mandatory uptake of joint REAs will have a positive effect, while PO5 is considered as unrealistic by representatives of the industry. While this position could be endorsed in general by the study team, our analysis shows also cost savings for PO5 in the long run.

For the MedTech Industry, a voluntary project-based cooperation (PO2) is favoured, since this will not entail a **legislative framework which is perceived as additional burden for the industry with negative effects**. This relates to the fact that HTA is not as common and related methods are not as developed for the MedTech sector as compared to the Pharmaceutical sector.

Based on our analysis, a successful and sustainable future HTA system at EU level needs to respect the peculiarities of the MedTech industry. One solution might be that the same PO and business model(s) shall not apply to both sectors. A starting point for the MedTech sector could be the development and **mandatory use of common tools because further development of methods will help provide a clearer picture of requirements related to HTA processes**. Moreover, the voluntary conduct of joint REA could be envisaged simultaneously, as this could provide significant input for decision-making across the EU. This would also contribute to (a) the reduction of a divergent evidence base across EU MS for medical technologies and (b) public health and patient safety.

Key findings

- Overall, the vast majority of clinical evidence considered by HTA bodies in the case of Pharmaceuticals comes from phase III clinical trials and less so from phase II trials. The latter are increasingly used in those cases where the production of evidence from phase III trials is challenging, or in those circumstances where the likely clinical benefit is considered significant and the treatment would merit conditional marketing authorisation (CMA). Only a fraction of the clinical evidence is considered related to other types of clinical evidence (extension trials or observational studies). It is thus reasonable to suggest that there is a **fair amount of duplication taking place as the evidence considered across settings is by and large the same**.

- There is a clear difference in the preferences of HTA bodies for the type of evidence required for Pharmaceuticals compared with medical devices/technologies and 'other technologies'; this is partly driven by what is feasible in the context of either medical devices or 'other technologies' and is highlighted by the high proportion of retrospective studies and safety studies (in the medical devices sample) and literature reviews (in the 'other technologies' sample).

- In terms of economic evidence, although there are both similarities and differences across MS in terms of preferences in approach, modelling or models, one issue worth noting was that across MS, and for those MS pursuing economic evaluation, in **68% of all cases, the comparator was the same across HTA bodies.**

- From an industry perspective, harmonisation of evidence requirements, if accompanied by MS acceptability, would facilitate easier investment decisions. Additionally, an 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 beneficial, and could be facilitated by early advice and greater clarity on payer expectations. Finally, harmonisation of evidence requirements would give the EU a stronger influence on clinical trial development.

- **The Pharmaceutical Industry is in favour of options covering mandatory uptake of joint REAs.** Due to the currently fragmented HTA systems, they will benefit from a reduction in submissions and better predictability across the EU. It might be necessary to relocate staff to a central level, but the number of staff is expected to remain stable.

- **Both the MedTech and the Pharmaceutical Industry perceive Full HTA at EU level as not meaningful, despite cost estimates showing that industry in general could benefit from additional savings compared to REA only.** That, however, very much depends on the nature of topics that are chosen for coverage under Full HTA. Experience with Full HTA at EU level so far is limited. The additional domains of Full HTA (economic, organizational, legal, ethical and social aspects) tend to contain many 'non-transferable' issues; to that end, they need to be substantially

adapted at national level. These points may explain in part the perceived scepticism on the industry side.

- **The MedTech industry sees the most challenges when introducing a legislative framework for future cooperation in HTA at EU level.** Currently, the MedTech industry faces lower regulations regarding market access for their products due to the significant heterogeneity of products, pointing out the great fragmentation within the sector. Two recently established regulations on medical devices at EU level aim to better govern the heterogeneous market. Because the MedTech industry has little experience with HTA processes, they expect a massive burden on procedures and processes and slower market access for their products.

- **Synergies for Public Administration can be expected since potentially more assessments will be available for decision-making.** One HTA body might not have the capacity to conduct all assessments decision-makers would need in their country. Additionally, with potential future growth in patient mobility in Europe, as addressed by the Cross-Border Healthcare Directive, it can be seen as advisable to base decision-making on the same evidence.

- **General success factors identified for sustainable joint cooperation include (1) the use of common tools and templates, (2) business models with stronger governance structures (3) timely assessment processes (4) cross-country expertise and inputs and (5) mandatory national uptake of joint outputs** ([11]), **all of which are inter-related**. The latter applies in the Pharmaceutical sector only. Using common tools and templates facilitates joint work while sufficient institutional capacity and strong governance form the basis to provide timely assessment processes. Timely assessment is important to ensure that uptake can occur at a time when the results are relevant in national settings. Adequate expert input is needed to ensure the quality of assessments performed, thus increasing efficiency of process for all stakeholder groups. Finally, mandatory uptake of results is important and ensures that the purpose of joint work is met. These factors will be relevant for setting up future cooperation on HTA, although the peculiarities of the MedTech sector may need to be taken into account and success factors may be more relevant for HTA in Pharmaceuticals.

- **Legislative cooperation can create institutional capacity for HTA cooperation and expertise can be better streamlined**. Our study findings suggest that processes can be set up more efficiently when they are coordinated and facilitated by one permanent institution, since all relevant information is centralised, expertise can be streamlined and overall savings can materialise.

- **Potential savings are considerably higher in POs that comprise both a mandatory production and mandatory uptake of joint REAs and Joint HTA (PO4.2 and PO5)**. Options comprising a permanent secretariat or a new Agency, which is linked to higher joint output, lead to substantially higher savings in the long run as compared to project-based cooperation (in total nearly EUR 4 million across all countries in PO2 versus around EUR 70 million with PO4.2 and EUR 77 million with PO5). Regarding the results of the cost prognosis, there are uncertainties in data collection, as is clearly outlined in the corresponding sectors of our study.

([11]) Up-take concerns using or considering the results and findings of the HTA cooperation, reaching from jointly developed submission templates to outcomes in full HTA. The subsequent pricing and reimbursement decision remains purely on national level.

- **Improved 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 the evidence-base for decision-making across the EU, especially in MS where HTA is not well-developed, thus also contributing to a decrease in cross-country inequalities.

- From a **patient perspective,** future EU cooperation in HTA POs with mandatory participation and uptake **will increase availability of safe and effective Pharmaceuticals and medical technologies and ensure standardised monitoring of health technologies prior to market access**. Transparent and independent HTA processes require consideration of all relevant stakeholder perspectives to increase efficiency and prevent conflict of interest. Sufficient financial resources are vital to establish a respective mechanism. Besides required investments, stakeholders should draw their attention to the potential return on investment different mechanisms offer.

- Previous patient involvement in HTA processes is characterised by good intentions on the part of involved stakeholder groups, but successful implementation was limited so far by either the extent or the role of involvement. There are clear signals both from Public Administration and the Pharmaceutical Industry **to improve and standardise patient involvement in HTA processes. Stronger governance regarding HTA assessment might positively influence patient involvement**. Overall, sustainable and transparent long-term cooperation in the field of HTA offers the potential to prevent selective assessment of Pharmaceuticals, reduce availability of health technologies with little or no added value and improve the accessibility of publicly available information.

Sommaire

Contexte

Les États membres (EM) et l'Union européenne (UE) ont saisi l'importance croissante des systèmes d'évaluation des technologies de santé (ETS) dans les processus de prise de décision et d'élaboration de politiques depuis quelque temps maintenant. L'ETS est unanimement reconnu comme un outil précieux, qui peut contribuer à la durabilité des systèmes de santé nationaux. Pourtant, la production de résultats d'ETS (notamment les Dialogues préliminaires, Évaluations de l'efficacité relative (EER) et Rapports définitifs sur l'ETS avec évaluation économique) reste du moins éparse et diverse en Europe, car les systèmes d'ETS sont partiellement fragmentés dans l'Union.

La coopération sur l'ETS à l'échelle européenne a commencé en 2009, avec la création du Réseau européen pour l'évaluation des technologies de la santé (EUnetHTA). Deux actions communes (AC) ont été lancées; la première en 2010–2012 (EUnetHTA JA 1), et la seconde en 2012–2015 (EUnetHTA JA 2). Une troisième action commune (EUnetH-TA JA 3) a démarré en juin 2016 avec pour objectif général d'accroître l'utilisation, la qualité et l'efficacité des travaux communs sur l'ETS à l'échelle européenne, afin de permettre des choix durables, équitables et fondés sur des faits dans les domaines des soins et technologies de santé, mais également pour garantir une réutilisation des rapports et activités nationales ou régionales relatives à l'ETS.

Dans ce contexte, nous aborderons la question d'une coopération durable après 2020, lorsque l'action commune EUnetHTA actuelle aura pris fin, en accord avec l'agenda « Mieux légiférer » de la Commission européenne (CE) visant l'élaboration et l'évaluation de politiques européennes de manière transparente, en prenant en compte à la fois les faits et le point de vue des acteurs concernés.

La CE a déployé une initiative d'évaluation d'impact ([12]) afin d'identifier et de mesurer diverses options politiques (OP) concernant la poursuite de la coopération sur l'ETS à l'échelle européenne après 2020.

Motif et objectif de l'étude

L'objectif général de cette étude est de soutenir les processus d'évaluation d'impact de la CE, notamment par l'apport de données et de preuves pertinentes. Elle fournit également des informations pour l'analyse de l'impact de différentes OP relatives à la coopération sur l'ETS à l'échelle européenne après 2020, et met à profit les données recueillies pour mener une évaluation de l'effet des différentes OP. Ainsi, les objectifs spécifiques de l'étude sont:

- Recueillir des données, apporter des preuves et fournir une analyse approfondie des événements qui pourraient survenir en l'absence d'action prolongée à l'échelle européenne et des conséquences afférentes (scénario de base);
- Recueillir des données, apporter des preuves et fournir une analyse sur l'impact potentiel des OP identifiées pour la coopération avec la CE;
- Rassembler les documents pertinents sur l'ETS, avec une attention particulière pour l'Union européenne, afin de comprendre leur mode de fonctionnement dans les EM de l'UE.

([12]) *https://ec.europa.eu/health/technology_assessment/consultations/cooperation_hta_en*

Bien que l'ETS fournisse des informations qui permettent de déterminer les pratiques de tarification et de remboursement dans certains pays, l'étude se concentre sur l'évaluation de toutes les OP, ainsi que des décisions en matière de tarification et de remboursement liées aux technologies médicales, pour déterminer si les dispositifs ou produits Pharmaceutiques relèvent de la compétence de chaque État membre.

Cette étude a été réalisée par un consortium composé de Gesundheit Österreich Forschungs- und Planungsgesellschaft (Autriche), de l'université London School of Economics - LSE Health (Royaume-Uni) and de SOGETI (Luxembourg).

Options politiques pour l'évaluation de l'impact: caractéristiques et contexte analytique

La CE a proposé des OP pour la poursuite de la coopération sur l'évaluation de l'impact à l'échelle européenne, que les auteurs ont combinées avec de potentiels modèles de gestion.

Les OP sont définies selon différentes caractéristiques clés allant au-delà du scénario de base (« aucune action supplémentaire à l'échelle européenne »), comprenant (a) des résultats d'ETS devant être traités par l'action commune, (b) la nature proposée de la coopération, (c) différents modèles de gouvernance et (d) plusieurs options de financement pour l'initiative d'action commune.

- **Les résultats d'ETS devant être traités par l'action commune** comprennent les éléments suivants:
  - Procédures et outils uniformes tels qu'un modèle de présentation de référence, un système informatique avec des évaluations planifiées et en temps réel, des méthodologies communes (par exemple, EUnetHTA Core Model), un processus de définition des priorités commun et une coopération sur les exigences en matière de données, y compris l'exploration de l'horizon.
  - Dialogues préliminaires
  - Évaluations de l'efficacité relative
  - Évaluations communes des technologies de santé

- **Nature proposée de la coopération entre les États membres**

  Les OP diffèrent selon la nature de la coopération, comme cela se reflète dans le type de participation (volontaire ou obligatoire) et/ou d'assimilation des résultats communs (volontaire ou obligatoire):
  - Participation volontaire et assimilation volontaire (V/V): La coopération se déroule sur une base volontaire, et les EM peuvent décider de participer à la production des résultats respectifs, ainsi que de les assimiler, ou pas.
  - Participation volontaire et assimilation obligatoire (V/O): La participation à la création de travaux communs est volontaire, aussi les EM peuvent décider de prendre part ([13]) à l'action commune ou non. Cependant, une fois qu'un État membre s'est engagé dans une initiative commune, l'assimilation des travaux à l'échelle nationale est obligatoire.

([13]) http://ec.europa.eu/smart-regulation/roadmaps/docs/2016_sante_144_health_technology_assessments_en.pdf

- Participation obligatoire et assimilation obligatoire (O/O): Les EM ont l'obligation de participer à la production de résultats et d'assimiler ces derniers dans le contexte national

- **Modèles de gouvernance pour la coopération européenne**

L'étude a examiné une variété de modèles de gouvernance pour la coopération européenne, allant d'une coopération flexible fondée sur des projets à la création d'un secrétariat permanent au sein d'une agence européenne, comme présenté ci-dessous.

- Coopération sur base de projets (OP 2)
- Secrétariat permanent hébergé par un État membre (OP 3)
- Secrétariat permanent hébergé par la CE (OP 4.1)
- Secrétariat permanent hébergé par une agence européenne existante (OP 4.2)
- Secrétariat permanent hébergé par une nouvelle agence européenne (OP 5)

De manière générale, nous avons supposé que les travaux scientifiques et les expertises (c.-à-d. les développements de résultats communs) resteraient au sein des agences nationales. En ce qui concerne les modèles de gouvernance composés d'un secrétariat permanent, la création d'un ou de plusieurs Comités serait nécessaire. Dans tous les types de coopération se retrouvent des éléments communs à la structure de gouvernance, qui sont définis par les résultats communs.

- **Options de financement pour la coopération européenne**

Plusieurs sources de financement de l'action commune sont envisageables, mais n'ont pas été étudiées en détail dans l'étude:

- Financement européen, soit par un programme de santé publique soit par un autre instrument financier
- Financement par les États membres prenant part à la coopération
- Financement par les taxes imposées aux industries

Le tableau suivant présente un aperçu de chaque option politique, avec l'étendue de résultats couverte, le type de participation à l'action commune et les mécanismes de mise en œuvre/financement envisagés.

Tableau 3: Aperçu des options politiques

		Scénario de base	Non législatif	Législatif			
		OP 1	OP 2	OP 3	OP 4[14]		OP 5
		Aucune action européenne après 2020	Coopération volontaire à travers le programme de santé publique	Législation visant les outils communs et les dialogues préliminaires	Législation visant les travaux communs sur l'EER ainsi que les outils communs et les dialogues préliminaires		Législation visant les travaux communs sur l'ETS (comprenant une EER) ainsi que les outils communs et les dialogues préliminaires
					4.1 EER V/O	4.2 EER O/O	
Résultats	Outils communs, y compris modèles et méthodologie	V/V	V/O	O/O	O/O	O/O	O/O
	Dialogue préliminaire([15])	V/V	V/O	V/O	V/O	O/O	O/O
	EER commune([16])	V/V	V/O	V/V	V/O	O/O	O/O
	ETS commune complète([6])	V/V	V/V	V/V	V/V	V/V	V/O
Mise en œuvre		Aucune participation de l'UE	Coopération fondée sur des projets	Secrétariat UE/EM	Agence européenne existante	Agence européenne existante	Nouvelle agence européenne
Financement		Aucun de l'UE	UE + EM	UE + EM + taxes sur les industries pour les dialogues préliminaires, l'EER commune et l'ETS complète			
Portée			Tous les médicaments, technologies médicales et autres dispositifs	Outils: tous les médicaments, autres technologies (introduction progressive), DP: présentation à l'industrie	Outils et DP, voir OP 3. EER: certaines catégories de médicaments (par exemple, médicaments autorisés par procédure centralisée, fort impact sur la valeur/le budget, accord entre EM), certaines catégories de technologies médicales (par exemple, produits à haut risque et haute valeur) et d'autres systèmes (accord et définition des priorités entre EM) – introduction progressive ([17])		Outils et DP, voir OP 3; EER, voir OP 4 Pour les autres: accord ad hoc et définition des priorités entre EM

OP: option politique; V/V: participation volontaire/assimilation volontaire; V/O /: participation volontaire/assimilation obligatoire; O/O: participation obligatoire/assimilation obligatoire; DP: dialogue préliminaire; EER: évaluation de l'efficacité relative; EM: États membres; ETS: évaluation des technologies de santé

([14]) À supposer que 50% des États membres participent à l'action, un mélange de revenus élevés/faibles et de grands/petits États membres.
([15]) DP: dialogue préliminaire Dans ce cas, l'assimilation obligatoire implique l'impossibilité pour les États membres de répéter un dialogue préliminaire qui s'est déroulé à l'échelle nationale. Les fournisseurs de technologie lancent les dialogues préliminaires.
([16]) Soit au moment de la commercialisation soit à la réévaluation
([17]) Une introduction progressive des produits au cours d'une période de transition qui permet de gérer la charge de travail pendant que les structures/les modèles de mise en œuvre sont développés.

Méthodes

Approche générale

Afin d'établir le scénario de base, nous avons mené une étude de cas sur des échantillons de produits de technologie de santé, dont 20 produits Pharmaceutiques, 15 dispositifs médicaux et 5 « autres technologies » (notamment des interventions complexes). L'équipe de l'étude a recueilli des informations détaillées sur les processus d'ETS auxquels chaque technologie a été soumise dans les EM. En outre, elle a déterminé les coûts de la réalisation d'une ETS pour les deux parties concernées, les développeurs de technologies et les organismes d'ETS. Enfin, l'étude a permis de saisir l'influence des cadres réglementaires sur les développeurs de technologies.

Afin d'analyser l'impact des OP de la CE, l'équipe a également réalisé une enquête sur les effets économiques et sociaux des OP identifiées, soutenue par des groupes de discussion, un certain nombre d'entrevues et des conclusions sur de la documentation. L'étude visait les effets suivants, pour lesquels nous avons défini un ou plusieurs indicateurs:

Les effets étudiés comprenaient des critères économiques (CE) et de santé sociale (SS):

CE1	coûts	SS1	emploi
CE2	charge administrative	SS2	gouvernance, participation et bonne administration
CE3	compétitivité du secteur européen des technologies de santé	SS3	accès aux systèmes de protection sociale et de santé
CE4	innovation et recherche	SS4	durabilité des systèmes de santé
CE5	innovation et recherche dans le commerce international	SS5	santé publique
CE6	fonctionnement du marché interne et de la concurrence		
CE7	consommateurs et ménages		
CE8	environnement macroéconomique		

L'étude fournit également une description des mécanismes de mise en œuvre (notamment un secrétariat commun) et une estimation des coûts afférents.

Recueil de données

Afin de rassembler une large base de données pour l'analyse du **scénario de base** et de l'**impact** potentiel des **OP** de la CE identifiées, l'équipe a employé différentes méthodes de recueil des données, comme le montre l'image 1 sur la page suivante.

Nous avons réalisé une **recherche documentaire systématique** afin d'identifier les textes pertinents, qui nous ont permis d'établir le contexte, de vérifier et de compléter les résultats des études de cas et de l'enquête. Le but était de fournir un aperçu du statu quo et de l'impact des systèmes d'ETS dans les EM de l'UE.

L'équipe a mené une **enquête en ligne** visant les administrations publiques (comme les organismes d'ETS), l'industrie Pharmaceutique et des technologies médicales, ainsi que

les patients et les professionnels de santé, ce qui a engendré des réponses principalement des administrations publiques et des industries.

L'**étude de cas**, couvrant 40 technologies de santé (20 produits Pharmaceutiques, 15 dispositifs médicaux et 5 « autres technologies »), a systématiquement tenté de saisir et de décrire les éléments composant le statu quo de l'ETS dans les EM de l'UE, en adoptant une approche analytique multiniveau qualitative et quantitative.

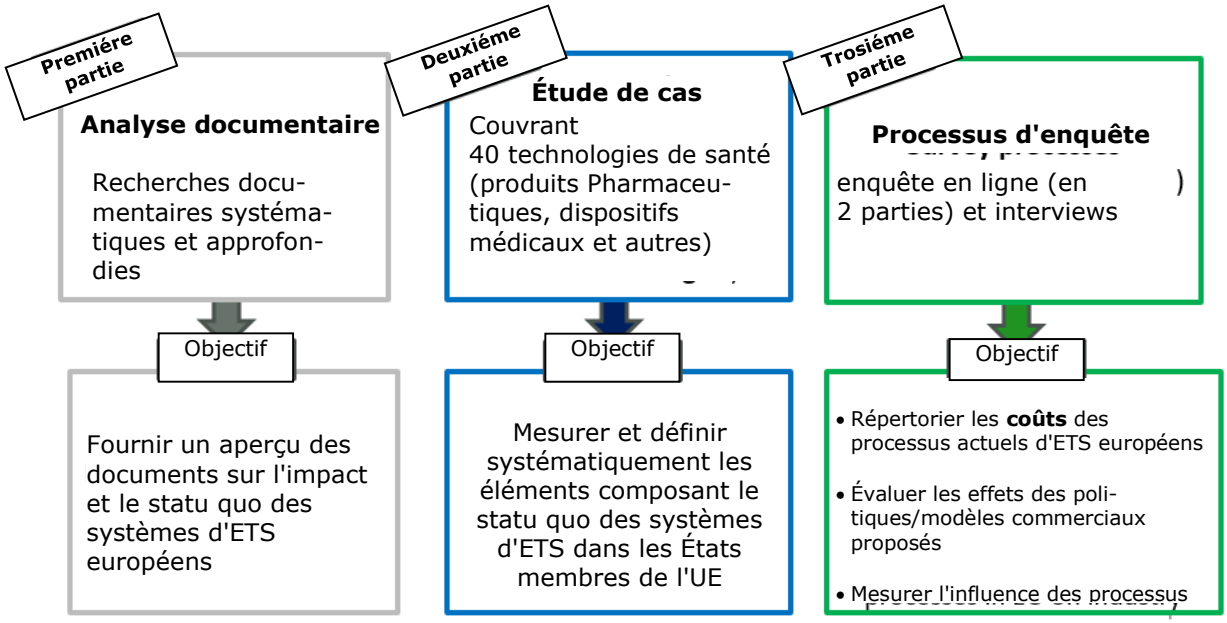


Schéma 2: Aperçu des flux d'activité

Les travaux supplémentaires de recueil de données et de validation des résultats comprenaient:

- des entrevues avec des représentants de l'industrie (produits Pharmaceutiques et dispositifs médicaux) et des patients;
- de courtes enquêtes et questions complémentaires destinées à recueillir davantage de données sur les coûts et d'informations utiles à l'interprétation des résultats;
- l'utilisation des résultats dans une étude supplémentaire de la CE2 menée en parallèle;
- des réunions de groupes de discussion rassemblant des acteurs des administrations publiques et des secteurs industriels (Pharmaceutiques et dispositifs médicaux) afin de débattre des résultats de l'enquête en ligne et mettre en commun les suggestions et commentaires de chacun;
- l'implication d'un groupe d'experts mis en place pour la durée de l'étude; et
- un examen par des pairs avec des experts leaders dans le secteur.

Limites de l'étude

L'étude s'est vue imposer différentes limites, dont la plupart sont liées aux hypothèses qui ont été avancées ou qui devaient l'être (par exemple, sur le futur montant de production commune ou coûts informatiques). En outre, aucune donnée sur des éléments simples, tel que le nombre actuel de discussions préliminaires en Europe, n'était facilement accessible, ou la granularité des informations disponibles différait significativement d'un État membre et d'un organisme d'ETS à l'autre. L'estimation des coûts doit notamment être appréhendée avec précaution, considérant tous les défis et limitations décrits en détail dans le rapport.

Les informations de base sur le secteur des technologies médicales et des autres technologies étaient parfois éparses comparé à l'industrie Pharmaceutique, notamment en raison du manque d'expérience du secteur technologique avec l'ETS.

L'enquête sur les acteurs a rencontré deux problèmes notables: un faible niveau de réponse de la part des patients et professionnels de santé, car ils se sentaient moins affectés par la concertation publique qui se déroulait en parallèle; et le niveau de détail des questions, car l'équipe de l'étude devait analyser de nombreux effets potentiels d'un certain nombre d'OP, comme le veulent les lignes directrices européennes sur le programme « Mieux légiférer »26. Par conséquent, l'étude n'a pas pu couvrir tous les EM de l'UE, mais a rassemblé des réponses de toutes les régions d'Europe y compris de pays dotés de systèmes d'ETS solidement intégrés comme d'autres avec des systèmes moins assimilés.

Analyse

Étude de cas: analyse du scénario de base

Nous avons analysé et comparé un échantillon de 40 technologies de santé pour déterminer les éléments clés qui composent les estimations de valeur de ces technologies dans les différents pays européens. Bien que le but principal de l'étude fût d'obtenir des *évaluations,* étant donné l'hétérogénéité des rôles de l'ETS entre les pays, certaines *estimations* ont également été enregistrées. Nous avons ainsi pu identifier les décisions d'ETS définitives, les restrictions mises en place afin d'inclure et de suggérer l'inclusion d'un produit spécifique dans le catalogue de bénéfices de chaque pays, et la façon dont ces processus, et leur durée, différaient ou s'alignaient dans les différents contextes. Ainsi, l'analyse systématique a permis d'identifier: (a) la présence d'évaluation et la décision finale rendue par l'organisme d'ETS, en rassemblant les cas de répétition; (b) l'utilisation actuelle de l'ETS dans les différents contextes, ainsi que les informations cliniques et économiques utilisées au cours de l'évaluation; (c) le délai de mise en œuvre des processus dans différents contextes nationaux; (d) les coûts liés aux processus d'ETS; et (e) les perspectives de l'industrie et des organismes d'ETS sur les méthodes et procédées.

Cette approche systématique permettrait de comprendre la **variabilité des méthodes et processus actuellement utilisés par les différents organismes d'ETS en UE**, ainsi que d'**identifier les répétitions possibles des efforts ou situations où un consensus plus large pourrait être nécessaire autour des procédures et méthodes d'ETS**. Il serait aussi plus aisé de déterminer les domaines où l'**uniformité et la transparence des critères utilisés pour la prise de décision** pourraient être améliorées.

Par l'analyse systématique des recommandations d'ETS dans les différents EM pour les 40 technologies identifiées et la synthèse des preuves réunies, nous avons identifié un certain nombre de paramètres: (a) ETS sur l'échantillon de technologies; (b) soumissions des preuves cliniques et économiques; (c) jugements de valeurs sociales; (d) accords/désaccords sur les recommandations entre organismes d'ETS, malgré l'utilisation

de statistiques kappa; (e) orientation des recommandations d'ETS; (f) restrictions cliniques aux recommandations d'ETS; (g) restrictions économiques aux recommandations d'ETS; (h) délais d'ETS relatifs à l'autorisation de mise sur le marché; (i) prévision de base des coûts d'ETS fondée sur le recueil de données initial (enquête) visant les fabricants et les organismes d'ETS; et (j) perspective de l'industrie sur les processus d'ETS.

En raison de la nature incomplète ou de la faible qualité des preuves cliniques et économiques, les responsables doivent émettre des jugements fondés sur un faible de taux de certitude ou accepter des rapports coûts-efficacité différentiels qui sont au-dessus du seuil de consentement à payer (SCP) des ménages. Dans ce contexte, les **jugements de valeurs sociales** (JVS) visent à interpréter les éléments clés liés à l'impact d'un traitement sur les patients et la société. Ainsi, ces jugements de valeurs sont de plus en plus souvent inclus dans les décisions d'ETS. Ces jugements ont été identifiés et codifiés dans tous les rapports d'ETS, mais également classés en onze catégories principales: (a) innovation significative; (b) augmentation de l'espérance de vie; (c) faible population; (d) enjeux relatifs à l'égalité; (e) avantages sociaux plus larges; (f) impact sur la qualité de vie et les activités quotidiennes; (g) impact sur les familles et la carrière; (h) besoins de traitement non satisfaits; (i) rareté et gravité de la maladie; et (j) les autres considérations qui peuvent être liées à la maladie ou le produit en question.

Pronostic des coûts

L'une des tâches de l'équipe du projet consistait à fournir des informations sur les évaluations d'impact européennes concernant l'évolution probable des coûts de coordination d'ETS en Europe. Ce pronostic comprend une estimation des coûts et économies à prévoir dès la mise en œuvre des options politiques pour 2021 et au-delà:

- sur la prochaine **production conjointe** (outils communs, dialogues préliminaires (DP), EER commune, ETS complète conjointe)
- sur les **économies** réalisées à partir de la diminution de la **production nationale** (réduite par les coûts d'adaptation de la production commune au contexte national)
- divers **mécanismes de mise en œuvre et structures de gouvernance** (coopération fondée sur des projets, secrétariat EM, secrétariat UE hébergé par la Commission, intégration d'un tel secrétariat dans une agence européenne existante, création d'une nouvelle agence européenne).

Les coûts des mécanismes de mise en œuvre comprennent des frais liés aux potentiels investissements ponctuels (si mesurables) et charges opérationnelles. Le pronostic des coûts se fonde sur **différentes sources**, notamment des études publiées ou non, des données (vérifiées) issues de l'enquête, le scénario de base, ainsi que des informations recueillies auprès des acteurs concernés et des services de la Commission européenne. Lorsqu'aucune donnée/information sur les coûts n'était disponible, l'équipe a émis des hypothèses justifiées pour obtenir une estimation. Au vu de l'évolution des coûts de production et certains autres paramètres, l'équipe a réalisé des **analyses de sensibilité** destinées à étudier les incertitudes liées. Le mécanisme de financement potentiel pour les options politiques et les modèles de gestion n'ont pas été pris en compte dans ce pronostic.

Nous avons émis des *hypothèses* concernant le futur montant de production commune pour le secteur Pharmaceutique et des dispositifs médicaux séparément, et ces hypothèses sont décrites en détail dans le rapport complet. Il en va de même pour les prévisions de taux d'assimilation volontaire des options politiques par les États membres et la corrélation attendue entre la production nationale et conjointe (dénotant des

économies potentielles). L'**étude n'a pas envisagé de mécanisme de mise en œuvre sans financement par la Commission européenne, car la coopération intergouvernementale sans apport de l'UE relève strictement de la responsabilité des États membres.** Plus particulièrement, la création d'un secrétariat permanent comprend des hypothèses détaillées sur les exigences en matière de structure et d'effectif, notamment pour la création de trois Comités d'experts au sein des États membres. Les hypothèses sous-jacentes étaient fondées sur des textes ou d'autres sources, lorsque disponibles.

Principales restrictions: Nous n'avons pas pu incorporer les dialogues préliminaires entièrement dans nos calculs en raison d'un manque de données. Les autres impacts sur les coûts, tels que les frais de changement de système à l'échelle nationale, n'ont pas pu être mesurés à un niveau global, et sont ainsi présentés de manière descriptive. À l'heure actuelle, les recherches sur l'ETS sont hétérogènes en Europe, et les sources de données pour les coûts et quantités de production actuels à l'échelle nationale montrent de grandes lacunes et incertitudes. L'on pourrait assister à une plus grande adhésion à la production commune (ainsi qu'aux économies et coûts liés) au niveau national à d'autres fins que les décisions de remboursement. En outre, il ne fut pas possible de mesurer l'impact global à long terme des résultats d'ETS obligatoire et organisée de manière centralisée sur les systèmes d'ETS nationaux, par exemple, en matière de transparence, normalisation ou qualité méthodologique.

Évaluation des options politiques

Les effets potentiels des options politiques proposées pour les différents groupes d'acteurs ont été étudiés à travers une **analyse multicritère (AMC)**. Les résultats ont ensuite été vérifiés par des groupes de discussion, des réunions complémentaires et des documents. L'approche AMC se concentre sur plusieurs critères, permet une différenciation entre les groupes d'acteurs (c.-à-d. les administrations publiques, l'industrie Pharmaceutique et le secteur des technologies médicales) et met en évidence les disparités ou similarités entre ces groupes.

L'identification des critères pertinents pour l'évaluation de l'impact économique et social/sur la santé a été réalisée en collaboration avec la DG SANTÉ et s'est fondée sur les effets mentionnés dans les lignes directrices de la Commission européenne pour le programme « Mieux Légiférer »3, 4. Chaque effet contient un ou plusieurs indicateurs, tels que la recherche et l'innovation sur le marché européen, la fragmentation des systèmes d'ETS en Europe, le nombre de technologies de santé évaluées ou disponibles, ainsi que la durabilité ou l'efficacité d'utilisation des ressources dans les processus d'ETS en Europe. De plus, le groupe d'experts a été impliqué dans le processus d'élaboration des effets et des indicateurs. L'objectif spécifique de la réalisation d'une consultation d'experts concernait la validation de la pertinence des effets et indicateurs identifiés, ainsi que le potentiel et l'identification des possibles effets et indicateurs manquants.

L'orientation (positive ou négative) et la portée (de -100 à +100, diminution ou augmentation) de chaque effet ont fait l'objet d'une enquête, qui a fourni une importante source d'analyse et une tentative de quantification des estimations. Outre les effets supplémentaires de chaque OP sur les impacts, l'AMC comprend une évaluation de l'importance ou la pertinence des impacts pour les différents groupes d'acteurs. Afin de saisir la variabilité au sein de chaque groupe d'acteurs dans l'analyse des résultats de l'enquête, des études complémentaires sur des sous-groupes ont été réalisées, notamment une analyse séparée pour des entreprises de différentes tailles et une comparaison des réponses des sociétés avec et sans expérience dans le domaine de l'ETS. Les données ont été soumises à différents contrôles de plausibilité pour évaluer la fiabilité et la solidité des données de l'enquête ainsi que le comportement de réponse des groupes d'acteurs.

Aux résultats de l'enquête viennent s'ajouter le pronostic des coûts ainsi que des informations supplémentaires recueillies à partir de documents, de groups de discussion composés d'acteurs concernés, d'entrevues avec les acteurs et de renseignements dérivés de l'analyse du scénario de base. Les résultats sont détaillés séparément pour chaque groupe d'acteurs. Afin de renforcer le groupe des patients et consommateurs, nous avons réuni des informations supplémentaires via des discussions de suivi pour décrire les perspectives des groupes de manière adéquate. Ces discussions prenaient la forme d'entrevues avec nos organisations de consommateurs et patients au niveau de l'UE.

Les principales restrictions de cette approche ont mis en évidence que les différents niveaux de détail dans les informations des organismes d'ETS, le nombre de disparités fonctionnelles entre les organismes d'ETS européens et le degré variable de transparence (par exemple, toutes les évaluations ne relèvent pas du domaine public ou n'ont pas été partagées avec l'équipe de l'étude) ont affecté notre analyse.

Résultats

Analyse du scénario de base: étude de cas

Le scénario de base a étudié 40 technologies (**20 produits Pharmaceutiques, 15 dispositifs médicaux (principalement des appareils) et 5 « autres technologies** » (comme la vaccination anti-VPH) pour permettre de comprendre les aspects fondamentaux des processus d'ETS dans les EM. L'objectif principal visait à apporter de la clarté sur les modèles, processus et résultats d'ETS dans les EM par le biais d'une analyse comparative sur les recommandations d'ETS au sein de la sélection effectuée.

ETS de l'échantillon de technologies. Dans l'échantillon de produits Pharmaceutiques, les résultats ont monté que la même paire produit-indication a été évaluée par au moins 10 agences dans plusieurs pays. En moyenne, 13 agences sur les 24 étudiées ont évalué la même paire produit-indication. Ce phénomène se confirme dans des organismes d'ETS tels que HAS (France), G-BA (Allemagne) et AIFA (Italie), en raison de leur processus de sélection (évaluant tous les nouveaux produits Pharmaceutiques demandant une autorisation de mise sur le marché) et du degré élevé de consensus entre les organismes d'ETS tels que TLV (Suède), NICE (Royaume-Uni) et INFARMED (Portugal).

Manifestement, les organismes d'ETS n'évaluent pas tous l'ensemble des produits Pharmaceutiques. Certains systèmes d'ETS bien développés évaluent tous les nouveaux produits Pharmaceutiques. D'autres suivent des processus explicites de définition de priorité et de sélection des sujets, ce qui permet uniquement (a) l'évaluation d'une proportion de toutes les nouvelles paires produit-indication à une année donnée et (b) d'un très faible nombre de technologies, tandis que (c) d'autres se contentent de référencement à l'ETS. En outre, l'évaluation de chaque pair produit-indication effectuée a été fortement influencée par le modèle d'ETS (par exemple, évaluation des bénéfices cliniques c/ efficacité clinique et rentabilité) et l'approche globale d'ETS prévalant dans chaque pays (c.-à-d. approche autonome ou intégrée).

L'**ETS est bien moins développé et établie dans les EM de l'UE en ce qui concerne les technologies médicaux et les « autres technologies »**. L'échantillon montre que le nombre d'ETS réalisées par paire de produit-indication était inférieur que dans l'industrie Pharmaceutique. En moyenne, une technologie médicale ou une « autre technologie » ont été évalués par 6 agences d'ETS, avec au moins 4 pays étudiant la même technologie médical.

Soumission des preuves cliniques et économiques En termes de preuves cliniques, dans l'ensemble d'échantillons de produits Pharmaceutiques, tous les organismes d'ETS

montrent une préférence claire pour les **essais cliniques de phase III**, suivis par les essais de phase II et d'autres sources de fondement. Les comparateurs les plus souvent utilisés étaient les placébos/traitements standards actuels. Dans l'échantillon de **technologies médicales**, il apparaît une claire préférence pour les **essais contrôlés randomisés** (28%), suivis par les études rétrospectives (22%) et les études de sécurité. Le comparateur le plus souvent utilisé était le traitement standard actuel. Cependant, un nombre considérable d'essais envisagés dans cet échantillon n'étaient pas contrôlés. Enfin, dans l'échantillon des « autres technologies », une moyenne de 6 études cliniques a montré une préférence pour l'analyse documentaire (89%), qui comprend différents aspects de programmes de santé publique et non uniquement les avantages cliniques et la rentabilité des technologies.

Une nette différence de préférence apparaît chez les organismes d'ETS dans les types de preuves requises pour les produits Pharmaceutiques, comparé aux technologies médicales et aux « autres technologies ». Ce phénomène est en partie lié aux possibilités dans le contexte des technologies médicales ou des « autres technologies », et mis en avant par la forte proportion d'études rétrospectives et de sécurité (dans l'échantillon des dispositifs médicaux), ainsi que d'analyses documentaires (dans l'échantillon des « autres technologies »).

En matière d'**évaluation économique**, tous les pays n'ont pas analysé les avantages cliniques et la rentabilité de chaque étude technologique, et les critères d'évaluation variaient considérablement. Dans l'échantillon Pharmaceutique, 8 pays ont envisagé une évaluation économique dans leur étude et, en moyenne, 1,5 étude économique fut considérée pour chaque paire de produit Pharmaceutique-indication. Les résultats ont montré qu'en général, une analyse coût-utilité a été envisagée pour tous les types de médicaments à l'étude (dans 85% des cas), suivie par une évaluation de l'impact budgétaire (43% de cas). Une analyse de minimisation des coûts n'a été envisagée que dans un nombre limité de cas (6%). Les comparateurs les plus souvent utilisés était un comparateur direct (86%). **Parmi les pays étudiés, dans 68% des cas, le comparateur utilisé était identique à celui des organismes d'ETS.** Dans l'échantillon des technologies médicales, 8 pays ont envisagé une évaluation économique, avec une moyenne de 2,5 études par technologie considérée. En ce qui concerne le type d'analyses économiques, la tendance a confirmé la prépondérance des études coût-utilité (67%), suivies par les comparaisons de coûts (21%). Dans l'échantillon des « autres technologies », 7 pays ont envisagé une évaluation économique, dont 73% concernaient l'analyse coût-utilité et 45%, l'analyse de l'impact budgétaire.

Jugements de valeurs sociales Les jugements de valeurs sociales (JVS) occupent une place croissante dans les informations sur les recommandations d'ETS. Parmi les organismes d'ETS sélectionnés, seuls trois ont défini/révélé leurs jugements de valeurs sociales dans leurs lignes directrices: NICE, dans le contexte des critères de fin de vie; SMC, avec les « modificateurs de maladie »; et TLV, avec le principe: « la dignité humaine repose sur la solidarité ». D'autres organismes d'ETS prennent en considération des valeurs, mais pas de manière cohérente. Étant donné les tendances spécifiques parmi les différentes technologies de santé, le plus grand nombre de JVS fut identifié dans l'échantillon Pharmaceutique (n=304), suivi par celui des dispositifs médicaux (n=67) et les « autres technologies » (n=4).

Accords et désaccords dans les recommandations des organismes d'ETS Dans l'échantillon Pharmaceutique, le degré de consensus dans les recommandations varie significativement entre organismes d'ETS et est lié au fait que tous les organismes n'évaluent pas l'ensemble des technologies. Toutefois, les organismes d'ETS qui évaluent toutes les technologies enregistrent un très haut degré de consensus (comme le montre la note kappa, $k>0,8$). Ceci démontre un haut degré de consensus entre les organismes d'ETS dans leurs recommandations, c.-à-d. une même orientation des recommandations dans tous les organismes (par exemple: accepté, accepté avec critères ou rejeté).

En revanche, cette tendance ne se confirme pas dans les échantillons des technologies médicales et des « autres technologies ». Le nombre d'évaluations est plus faible pour les « autres technologies », et l'échantillon est plus fragmenté, comme le montre la faible note kappa (k<0.2). Le degré de consensus est généralement faible dans cet échantillon, avec 64% des organismes d'ETS enregistrant une mauvaise note kappa (k<.02) et 36%, un degré de consensus allant du raisonnable (0.21<ki<0.4) au très élevé (0.81<k<1).

Orientation des recommandations d'ETS Dans l'étude de cas, **soixante-six pourcent (66%) des technologies ont fait l'objet de recommandations positives, avec ou sans restrictions.** Si l'on détaille ce chiffre: 62% des recommandations étaient positives avec des restrictions et les autres (n=75), positives et sans restrictions. Cette tendance se confirme dans les échantillons des médicaments et des technologies médicales, avec respectivement 81 et 64% recevant une recommandation positive, et respectivement 63% et 59% faisant l'objet d'une recommandation positive sans restriction. Dans l'échantillon des « autres technologies », la plupart des recommandations étaient positives et sans restrictions (66%).

Restrictions cliniques aux recommandations d'ETS Dans l'ensemble des échantillons, la restriction la plus récurrente était d'ordre **clinique** (56% des cas). Pour l'échantillon Pharmaceutique, les restrictions cliniques les plus communes étaient liées aux sous-groupes de patients (67%), suivies par les restrictions concernant le parcours thérapeutique (18%). Les **produits Pharmaceutiques et les technologies médicales sont le plus souvent concernés par des restrictions prescrites et liées aux professionnels spécialistes et au contexte.** La première restriction se rapporte aux technologies de santé qui peuvent uniquement être prescrites par un médecin spécialiste, et la seconde, au contexte de l'endroit où le traitement peut être prescrit ou prodigué. Dans l'**échantillon des technologies médicales, les restrictions cliniques les plus communes étaient liées aux sous-groupes de patients (67%),** suivies par les restrictions concernant le parcours thérapeutique (32%). Dans l'échantillon des « autres technologies », les restrictions les plus courantes concernaient les caractéristiques spécifiques des technologies (58%), c.-à-d. les recommandations émises pour une technologie comparée à une autre, suivies par la conception du programme (34%), c.-à-d. les recommandations liées aux différentes caractéristiques d'un programme afin d'améliorer les performances cliniques du programme entier.

Restrictions économiques aux recommandations d'ETS Les restrictions économiques concernaient principalement l'échantillon des produits Pharmaceutiques et sont fondées sur les informations accessibles au public. **64% des restrictions économiques concernaient l'introduction d'un accord de partage des risques ou d'accords de participation gérée au remboursement** des produits, et 14% exigeaient une négociation de prix complémentaire. Nous avons identifié seulement 5 restrictions économiques dans l'échantillon des technologies médicales, avec une attention particulière sur l'utilisation de négociations de prix spéciales avec l'agence de réglementation compétente pour les décisions de remboursement.

Délais d'ETS relatifs à l'autorisation de mise sur le marché L'on constate souvent un délai significatif entre l'obtention d'une autorisation de mise sur le marché (AMM) et la publication de recommandations d'ETS. Ce délai n'est pas uniforme et varie selon le pays ou l'organisme d'ETS et le type de technologies. En moyenne, le délai le plus long entre les AMM et les recommandations de l'ETS en ce qui concerne l'échantillon Pharmaceutique a été enregistré à 21,6 mois, et le plus court, à 9 mois. Cependant, il convient de reconnaître que cette différence pourrait être liée à des facteurs tels que la volonté de soumettre un rapport ou des retards dans la soumission de l'ETS par l'entreprise concernée, les différents critères de sélection dans le choix des technologies à évaluer et le rôle différent de l'organisme d'ETS. Dans l'échantillon des technologies médicales, le délai moyen entre le marquage CE et la réalisation d'une ETS est bien plus important,

environ 60 mois, bien qu'il faille traiter ce chiffre avec précaution en raison de la rareté des données accessibles au public sur les dates de marquage CE (une indication faisant office de certificat, mais n'étant généralement pas publiée). Notamment, nous avons identifié, parmi les organismes d'ETS, **un délai moyen entre évaluations de trois ans**. Dans l'échantillon des « autres technologies » comme dans celui des technologies médicales, l'on remarque un délai significatif entre plusieurs évaluations d'une même technologie parmi les organismes d'ETS. Dans l'exemple du dépistage du cancer colorectal, le programme a été évalué en 2006 dans une juridiction, puis à nouveau en 2016 dans deux autres juridictions.

Estimation de base des coûts d'ETS fondée sur le recueil de données initial (enquête) visant les fabricants et les organismes d'ETS Les résultats de l'enquête ont révélé d'importantes différences entre l'industrie Pharmaceutique et le secteur des technologies médicales. Dans le secteur Pharmaceutique, les résultats indiquent une forte variabilité dans les dépenses d'ETS (entre 73 000 euro et 1 700 000 euro par soumission d'ETS) et dans la production de preuves supplémentaires (entre 50 000 euro et 20 000 000 euro). La diversité des chiffres mentionnés pourrait refléter hétérogénéité des évaluations de résultats entre les différents contextes ou besoins de production de données, et ne permet pas de dresser le tableau définitif des dépenses moyennes parmi les produits ou fabricants. Bien qu'un rapport de valeur global ait été élaboré pour chaque produit, ce dernier est souvent la principale source d'information pour les équipes d'ETS des fabricants, et il est sujet à adaptation selon les conditions d'ETS prévalentes dans chaque contexte. Dans l'*industrie des technologies médicales*, les chiffres de soumissions d'ETS révèlent une fourchette de 1 000 euro à 3 400 000 euro, et la production de preuves supplémentaires, 17 000 euro à 12 800 000 euro. Les représentants du secteur des technologies médicales ont avancé que le nombre actuel d'évaluations de dispositifs médicaux variait considérablement selon les pays. Ainsi, il ne serait pas raisonnable de définir une moyenne fondée sur les fourchettes présentées ci-dessus.

En ce qui concerne la **composition des éléments de coûts**, dans le secteur Pharmaceutique comme dans celui des technologies médicales, les coûts d'effectifs (internes et externes) sont les principales composantes qui motivent les dépenses. Cependant, les groupes de discussion ont permis de mettre en lumière un autre facteur clé de coûts liés à l'ETS: la production de preuves (supplémentaires). Ce sont principalement les plus importants marchés qui voient le plus d'entreprises réaliser des études de production de preuves supplémentaires exigées par des organismes d'ETS. En outre, les lacunes de connaissances actuelles pourraient être comblées par des études post-commercialisation.

Les preuves issues du **dialogue préliminaire suggèrent un niveau d'implication complètement différent entre l'industrie Pharmaceutique et celle des technologies médicales**. Le secteur des technologies médicales s'est activement impliqué dans le dialogue préliminaire (69% des réponses), avec un coût moyen de 55 750 euro par dossier, tandis que celui des produits Pharmaceutiques a fait preuve d'un engagement et de dépenses plus faibles (28% des réponses et environ 21 700 euro) par dossier. Au cours des groupes de discussion, les représentants de l'industrie des technologies médicales ont reconnu ne pas s'impliquer régulièrement dans le dialogue préliminaire concernant les dispositifs médicaux.

En ce qui concerne les *coûts notifiés par les organismes d'ETS*, les différences de dépenses sont fortement influencées par des facteurs tels que le type de processus d'ETS en place, le genre d'évaluation réalisée et le degré d'intégration des organismes d'ETS dans les agences gouvernementales. De manière générale, il semble que les coûts de réalisation d'une évaluation de technologie unique (ETU) soient supérieurs parmi les organismes autonomes que chez les structures intégrées (les frais d'ETU les plus élevés rapportés étaient de 135 000 euro pour les agences autonomes et de 100 000 euro pour celles intégrées). En ce qui concerne l'évaluation d'efficacité relative (EER), les maxi-

mums rapportés étaient de 55 000 euro pour les premiers types d'organismes, et de 100 000 euro pour les derniers. Toutefois, puisque les données recueillies comportaient, dans certains cas, des valeurs manquantes, ces estimations devraient être interprétées avec précaution.

Perspective de l'industrie sur les processus d'ETS De manière générale, les entrevues réalisées dans l'industrie Pharmaceutique et celle des dispositifs médicaux ont démontré que les diverses procédures nationales avaient un impact différent sur l'évaluation des technologies de santé. Les méthodologies nationales entraînent d'importantes variations dans les recommandations/résultats, indiquant une différence significative sur la manière dont un même produit est perçu dans plusieurs pays. Cependant, il est important de souligner que ces différences sont également influencées par les domaines thérapeutiques de chaque produit.

Les fabricants ont mis en avant le fait que la fragmentation des systèmes actuels d'ETS en Europe imposait aux entreprises de répondre à un éventail diversifié de demandes. Notre analyse confirme que ce phénomène pourrait entraîner des difficultés dans la soumission ou la resoumission de rapports aux mêmes organismes d'ETS.

Il existe un consensus entre les représentants de l'industrie Pharmaceutique interrogés, selon lequel une collaboration à l'échelle européenne sur l'ETS serait possible pour réaliser des EER. En revanche, les représentants des technologies médicales ont mis en avant l'hétérogénéité et la diversité du marché des technologies/dispositifs médicaux, comparé à l'industrie Pharmaceutique. Ces derniers ont également insisté sur le faible rôle actuel de l'ETS sur les dispositifs médicaux et les technologies connexes dans la plupart des contextes, en raison de l'accès extrêmement fragmenté à ce marché. Ainsi, l'impact actuel de l'ETS sur leur activité est très bas.

La prévisibilité des processus d'ETS est apparue comme un élément clé dans les décisions d'investissement et d'utilisation des ressources, notamment pour les petites entreprises. Tout le monde s'est accordé sur la nécessité d'**harmonisation des processus et exigences en matière de preuves pour garantir une large compréhension et améliorer le niveau de prévisibilité dans le système.**

Plusieurs entreprises ont mis en avant la transparence des exigences en matière de preuves, l'uniformité des méthodes, la recevabilité des comparaisons indirectes et la prévisibilité des résultats parmi les caractéristiques désirables. Notamment, les représentants de l'industrie Pharmaceutique interrogés ont recommandé une meilleure synthèse et inclusion des informations sur des sujets importants tels que les comparaisons indirectes et les évaluations secondaires, ainsi qu'une définition claire des comparateurs appropriés. En revanche, les représentants du secteur des dispositifs médicaux ont suggéré que, bien que les essais contrôlés randomisés à long terme soient désirables du point de vue des preuves, ils peuvent ne pas toujours être appropriés, réalisables ou suffisants dans le domaine des dispositifs médicaux et les technologies connexes. Ces derniers recommandent une approche plus modérée de l'ETS dans le secteur, en raison de ses spécificités et du fait que les innovations sont généralement issues des petites entreprises, avec un cycle d'innovation plus court comparé à l'industrie Pharmaceutique.

Les dialogues préliminaires et les avis scientifiques sont considérés comme des tâches très utiles à l'amélioration de la transparence, de la perspective de l'industrie, suggérant qu'un système aligné sur les pratiques actuelles de l'Agence européenne des médicaments (EMA) serait bénéfique et simplifierait les programmes de développement. Cependant, peu de représentants interrogés ont mentionné l'importance de la non-introduction d'un système parallèle dans les pays imposant des exigences supplémentaires.

Enfin, les fabricants ont mis en avant un certain nombre de problèmes liés à l'**innovation**: la faible prévisibilité, la haute complexité et la forte fragmentation constituent des

barrières à l'innovation dans le domaine de la santé. Il existe une certaine « tension » entre les organes de réglementation qui souhaitent promouvoir un accès accéléré et les autorités de remboursement qui restent prudentes à cause de l'incertitude des preuves. **Nous avons compris que l'harmonisation des exigences en matière de preuves, si elle est accompagnée d'une acceptation par les EM, faciliterait les décisions d'investissement des fournisseurs de technologies.** En outre, un système d'ETS européen comprenant une solide méthodologie réduirait le risque dans les processus de soumission et aiderait à éliminer les débats liés à la faible qualité des évaluations et des interprétations de données. Une plus grande uniformité des évaluations d'ETS serait véritablement bénéfique, et pourrait être facilitée par un recueil d'avis préliminaire ainsi qu'une plus grande transparence sur les attentes des payeurs. Enfin, **l'harmonisation des exigences en matière de preuves offrirait une influence plus importante à l'UE sur le développement d'essais cliniques**.

La synthèse des résultats a confirmé l'hétérogénéité des évaluations de technologies de santé selon les différents pays. Pourtant, une analyse de niveau micro a démontré une **tendance à l'homogénéisation des processus d'évaluation dans les EM**.

Pronostic des coûts

Le pronostic des coûts s'est intéressé à deux sujets:

1. l'estimation des coûts de la participation volontaire ou obligatoire à la **production conjointe** et les **économies liées dans la production nationale** des OP proposées.
2. Les coûts liés aux structures organisationnelles spécifiques/mécanismes de mise en œuvre comprenant des outils communs.

L'étude n'a pas envisagé de mécanisme de mise en œuvre sans financement par l'UE, car la coopération intergouvernementale sans apport de l'UE relève de l'unique responsabilité des EM. Tous les types de mécanismes de mise en œuvre comprennent la production de résultats d'ETS par différents organismes d'ETS et une unité de coordination centrale pour soutenir les organismes d'ETS. Ce soutien serait d'ordre administratif, scientifique/technique, juridique et informatique, dans une étendue différente selon le mécanisme. Le principal critère de différenciation des mécanismes de mise en œuvre repose sur l'établissement d'une unité centrale de coordination permanente (5 mécanismes sur 6), comparé au mécanisme sur base de projets orienté sur les structures du réseau EUnetHTA.

Outre l'unité de coordination centrale, trois autres piliers principaux sont prévus pour les modèles de gestion:

- Conseil d'administration (composé de représentants des EM et qui définit le programme de travail)
- Production de résultats d'ETS (contractée auprès des organismes d'ETS)
- Comités des EM (composés de spécialistes qui analyseront et débattront des résultats d'ETS)

L'unité de coordination centrale permanente assurerait la coordination des projets et apporterait un soutien global aux modules de travail respectifs, au conseil d'administration et aux comités.

Représentant des scénarios illustratifs, les modèles de gestion allient des prévisions de résultats conjoints et de mécanismes organisationnels/de mise en œuvre, et jette les fondements pour les futurs développements. D'autres combinaisons OP et de modèles de gestion que celles analysées plus en détail sont également possibles (par exemple, la création d'une nouvelle agence pour l'OP 4.1). Les combinaisons présentées sont

considérées comme les plus plausibles. Le pronostic des coûts se fonde sur **plusieurs sources:**

- Les informations issues de l'étude de J. Chamova([2]);
- Les informations fournies par les membres du réseau EUnetHTA;
- Les données recueillies dans l'enquête de base;
- Un débat complémentaire sur les coûts par l'intermédiaire d'un questionnaire envoyé par e-mail;
- Les informations issues des groupes de discussions composés de représentants d'administrations publiques, de l'industrie Pharmaceutique et du secteur des technologies médicales; et,
- D'autres sources, par exemple, services de la Commission ou d'agences européennes (explicitement mentionnées le cas échéant).

Deux modèles furent proposés, avec un seul élément distinctif: le **modèle de base**, qui couvre 65 EER réalisées conjointement, 40 sur des médicaments et 25 sur des technologies médicales; et le **modèle avancé**, avec 115 EER conjointes au total, 90 sur des médicaments et 25 sur des dispositifs médicaux. L'évaluation des deux modèles comprenait l'adaptation des mécanismes de mise en œuvre, notamment des ressources humaines, selon les résultats conjoints anticipés.

La production commune estimée se montre pertinente pour les périodes, jusqu'à ce que les structures et processus soient bien installés. À l'issue de l'adaptation, c.-à-d. l'augmentation de 65 EER à 115 EER (90([18]) sur des médicaments et 25 sur des technologies médicales), il était envisageable de couvrir toutes les nouvelles substances et indications autorisées par procédure centralisée. Ainsi, plus d'effectif sera nécessaire pour assurer cette croissance de production de résultats. Le nombre d'effectifs nécessaire augmenterait donc pour les OP 4.1, 4.2 et 5 (tableau 17 l'étude principale). Une analyse de sensibilité a été réalisée pour représenter les incertitudes liées.

Les hypothèses de base concernant les éléments de coûts comprenaient une classification des EM selon le volume de leurs résultats annuels d'ETS ou de rapports d'ETS émis principalement par les organismes d'ETS, ou par l'industrie et revus par les organismes. Dans la plupart des États, les organismes d'ETS produisent moins de 60 rapports d'ETS sur les produits Pharmaceutiques et moins de 50 sur les dispositifs médicaux. La majorité des rapports d'ETS sont issus de l'industrie et revus par des organismes d'ETS.

En ce qui concerne les mécanismes de mise en œuvre, ce sont les coûts d'effectifs et les coûts liés aux comités d'experts des EM qui représentent la majorité des dépenses attendues. Les estimations des coûts d'effectifs sont fondées sur les réglementations européennes en matière de personnel, indexés sur les EM le cas échéant, et sur les frais d'experts de la Commission. Les estimations globales sur les mécanismes de mise en œuvre de l'OP 5 sont deux fois supérieures à l'OP 2. En outre, les coûts du modèle de base et du modèle avancé diffèrent significativement de l'OP 4.1 à l'OP 4.2 et l'OP 5 en raison de l'augmentation de la production commune.

Les chiffres montrent également que, **notamment pour les OP 4.1, 4.2 et 5** – c.-à-d. les options à l'aspect plus « législatif » et obligatoire – l**es EM et l'industrie peuvent s'attendre à réaliser des économies à l'échelle européenne**, si l'on prend en compte les hypothèses sous-jacentes, et que ces économies augmenteront avec les OP ultérieures. Toutefois, plusieurs autres facteurs, qui ne peuvent être mesurés avec

([18]) Selon les rapports annuels de l'EMA de 2015 et 2016

fiabilité, mais pourraient influencer les coûts/économies généraux, et ainsi inverser ou diminuer certains résultats, doivent également être considérés. Par exemple, les coûts liés à la mise en œuvre d'une assimilation obligatoire des résultats au sein des procédures, législations et réglementations nationales, ainsi que les potentielles économies supplémentaires dégagées grâce à la réduction du nombre de dialogues préliminaires à l'échelle nationale ou du montant de production de preuves supplémentaires exigé par les organismes d'ETS.

En conclusion, les chiffres montrent d'un côté une augmentation significative des coûts d'établissement d'un nouveau cadre de l'OP 2 à l'OP 5, et de l'autre un potentiel accroissement d'économies de l'OP 2 à l'OP 5.

Évaluation globale des options politiques

Nous avons étudié, à la lumière des lignes directrices « Mieux légiférer » (5), un certain nombre d'effets afin d'établir un aperçu complet de l'impact qu'auraient les différentes OP et modèles de gestion proposés sur les divers groupes d'acteurs.

L'analyse de l'impact s'est concentrée sur trois principaux groupes d'acteurs: l'**administration publique**, l'**industrie Pharmaceutique** et le **secteur des technologies médicales**, car ce sont ces groupes qui ont fourni le plus d'informations. Les auteurs ont également analysé l'impact sur les groupes des patients et professionnels de santé, lorsque des informations étaient disponibles[19].

Un aperçu des résultats par groupe d'acteurs pour chaque catégorie d'impact (des critères économiques (EC) aux effets sociaux et sur la santé (SS) est présenté en détail dans le chapitre 7.3 de l'étude. En résumé, les résultats de l'enquête et du groupe de discussion ont montré que les effets perçus des OP ainsi que les **perceptions et attentes en ce qui concerne la future coopération européenne sur l'ETS diffèrent selon le groupe d'acteurs** dans plusieurs aspects.

Les informations rassemblées indiquent que l'**administration publique ne s'attend à aucun impact significatif en ce qui concerne les processus liés à l'ETS pour les OP 1 et 2**. Cependant, avec les OP comprenant un cadre législatif (OP 3–OP 5), l'administration publique perçoit des effets positifs, qui sont amplifiés par chaque résultat couvert par le cadre. Ce phénomène se confirme dans notre évaluation, étant donné que les **OP comprenant un cadre législatif (OP 3 à OP 5) sont plus susceptibles d'avoir une influence positive sur la durabilité des systèmes de santé** que la poursuite d'une coopération non contraignante.

Cette augmentation d'effets positifs avec des exigences plus strictes et un système de gouvernance centralisé se rapporte à l'hypothèse d'une augmentation de l'assimilation des résultats conjoints avec chacune des OP suivantes. **Des réglementations plus strictes pourraient former un élément clé pour une collaboration durable et fructueuse, car sans elles, l'impact sur la coopération resterait limité.** En outre, nous avons estimé **que le nombre d'évaluations fondées sur des preuves disponibles pour les prises de décision pouvait être augmenté** avec les résultats conjoints, puisque davantage de technologies pourraient être couvertes en raison du fait d'un unique organisme d'ETS pourrait ne pas disposer des capacités nécessaires pour analyser le même nombre d'évaluations chaque année. Les **pays dotés de processus**

(19) Les deux groupes n'ont apporté que très peu de réponses à l'enquête, aussi les résultats ont-ils été dérivés d'autres sources et/ou de manière indirecte.

d'ETS moins matures pourraient particulièrement profiter de la production commune, notamment grâce aux **ETS conjointes**.

Aucune OP n'est jugée avoir un impact significatif sur la charge administrative ou les administrations publiques sur les EM de l'UE, et aucun sinon peu d'effets sur les coûts de résultats liés à l'ETS n'ont été indiqués dans l'enquête en ligne. Ce phénomène est inhérent au fait que les processus nationaux devraient perdurer d'une quelconque façon. Toutefois, certains organismes d'ETS s'attendent à une collaboration plus étroite qui réduirait leurs coûts. Cette hypothèse se confirme dans nos calculs de coûts, qui indiquent de potentielles économies parmi les EM, notamment pour l'OP 4.1 et les suivantes.

Dans l'**industrie Pharmaceutique**, les preuves n'indiquent aucun changement entre l'OP 1 et l'OP 2, **tandis qu'elles suggèrent des effets positifs des OP comprenant des travaux d'ETS conjoints au niveau de l'UE, les OP 3 et 4**. Ces OP devraient permettre de diminuer les facteurs d'inefficacité, d'améliorer le fonctionnement du marché intérieur et d'augmenter la charge de travail du secteur Pharmaceutique. Nous attendons également un accroissement de la prévisibilité dans le secteur Pharmaceutique, un facteur également considéré très important dans les entrevues avec les représentants de l'industrie et dans les réponses apportées à l'enquête, puisqu'elle facilite également l'innovation à travers des décisions d'investissement facilitées.

L'industrie Pharmaceutique **prévoit des effets négatifs dans l'OP 5**, qui comprend des processus d'ETS strictement obligatoires et contraignants, couvrant également une ETS complète en Europe. Les raisons sous-jacentes de ce phénomène ont été identifiées au cours des entrevues, dans les réponses à l'enquête et lors des groupes de discussion réalisés avec les représentants des entreprises Pharmaceutiques: les évaluations économiques conjointes obligatoires, telles qu'établies dans l'OP 5, sont considérées comme un scénario irréaliste en raison des spécificités de chaque pays en ce qui concerne les exigences économiques, mais également à cause de la stagnation des décisions de tarification et de remboursement à l'échelle nationale. **Il est apparu à plusieurs reprises que les travaux d'ETS communs**, notamment, **ont le potentiel de réduire les facteurs d'inefficacité et la charge de travail du secteur Pharmaceutique.**

En ce qui concerne les coûts liés aux processus d'ETS, les représentants de l'industrie Pharmaceutique interrogés n'envisagent aucun changement important, à l'exception de l'OP 5, qui fait peser un risque d'augmentation significative des dépenses. Cette hypothèse est liée au fait que les augmentations et diminutions potentielles des facteurs de coûts s'annuleraient mutuellement, selon les débats réalisés en groupes de discussion.

Néanmoins, les résultats de notre pronostic des coûts pour 2021 et au-delà montrent **les économies réelles que l'industrie Pharmaceutique pourrait réaliser** dans toute l'UE grâce à la réduction des duplications d'évaluations, et ce pour toutes les OP. Les économies potentielles augmentent considérablement dans les OP qui comprennent une production et une assimilation obligatoires des ETS conjointes (OP 4.2 et OP 5). Les options qui prévoient un secrétariat permanent et une production conjointe plus élevée entraîneraient des économiques largement plus importantes, en comparaison avec une coopération fondée sur des projets (3,7 millions d'euros dans l'OP 2 contre plus de 60 millions d'euros dans l'OP 4.2).

Pour le secteur des technologies médicales, notre analyse dresse un tableau différent: Les représentants de l'industrie des technologies médicales ont indiqués un effet négatif pour toutes les OP, à l'exception de l'OP 2. Cette évaluation négative est liée à la particularité du marché des dispositifs médicaux. Alors que les produits Pharmaceutiques peuvent profiter d'un parcours bien établi, de l'autorisation de mise sur le marché jusqu'à l'évaluation ETS, ainsi que de processus d'ETS matures dans un grand nombre d'EM de l'UE, les technologies médicales et les « autres technologies » doivent

suivre des règles et processus d'évaluation hétérogènes de leurs produits. En outre, le marché des dispositifs médicaux est intrinsèquement différent de celui des produits Pharmaceutiques, qui connaît un niveau élevé de concurrence dès l'entrée sur le marché. Bien que l'ETS soit largement développée dans l'industrie Pharmaceutique, elle semble souffrir d'un besoin d'adaptation et de développement de processus matures dans le secteur des dispositifs médicaux.

L'**évaluation négative des OP dotées d'un cadre législatif** est liée au fait que, selon l'industrie, ces options devraient entraîner une recrudescence des activités d'ETS dans les EM. Ce phénomène a été perçu comme un élément décisif de changements imprévisibles et de charge supplémentaire pour l'industrie des technologies médicales, étant donné que les travaux d'ETS ne jouent pas un rôle important dans le parcours d'accès au marché à l'heure actuelle. L'industrie voit cette incertitude comme un élément qui influencera ultérieurement l'attrait du marché européen et redoute des délais dans les premiers revenus en raison des processus potentiellement plus longs. Un autre élément clé repose sur la diminution attendue de la compétitivité et de l'innovation. Selon les groupes de discussion et les entrevues, cet élément est lié au changement imprévisible perçu dans le parcours d'accès au marché des technologies médicales, qui serait attribuable aux deux nouvelles réglementations européennes sur les dispositifs médicaux132. L'industrie prévoit ainsi la possibilité de nouvelles barrières administratives, qui constituent généralement la charge la plus lourde pour les précurseurs (ou innovateurs). Un aspect tout aussi important est l'augmentation attendue des coûts, entraînée par la production de preuves supplémentaires. Selon les résultats de l'étude, cet impact semble être surestimé par l'industrie des technologies médicales; l'une des raisons identifiées étant que le niveau actuel d'expérience en ETS des représentants des technologies médicales interrogés est largement inférieur à ceux du secteur des produits Pharmaceutiques. En outre, l'analyse de base montre une tendance à l'alignement des procédures et comparateurs utilisés.

Par ailleurs, nos **calculs de coûts n'ont pas confirmé l'hypothèse d'une augmentation des dépenses** dans l'industrie des technologies médicales. Au contraire, les résultats suggèrent que ce secteur pourrait également tirer profit des OP plus « strictes » proposées en ce qui concerne les coûts (agrégés entre les EM). Des économies potentielles notables sont à prévoir dans les OP dotées d'un cadre législatif (OP 4.1, 4.2 et 5).

En résumé, les OP dotées d'un cadre législatif impliquent certains effets négatifs pour l'industrie des technologies médicales sous la forme d'une charge supplémentaire (selon leur perspective), notamment lorsque des ETS conjointes sont concernées. Cependant, pour les OP 3, seul un léger impact négatif est à prévoir, et sur le long terme, le développement d'outils et de modèles communs permettra l'établissement d'exigences d'ETS plus claires qui, *in fine*, faciliteront également les processus d'ETS dans l'industrie des technologies médicales. Les groupes de patients ont également manifesté leur besoin d'une meilleure transparence dans ce secteur, qu'ils perçoivent comme un moyen de renforcer la qualité et la sécurité des technologies.

Le renforcement des processus d'ETS pour les technologies médicales entraînerait de potentiels effets positifs sur les patients, grâce aux meilleures preuves à disposition pour les prises de décision. Nous prévoyons donc, *in fine*, des effets positifs sur la sécurité des dispositifs médicaux.

Le tableau suivant présente un bref aperçu de l'impact potentiel des OP, agrégé entre tous les effets étudiés, pour chaque groupe d'acteurs. Le vert indique une perception positive et le rouge, une négative, selon les jugements de l'équipe de l'étude, qui a pris en compte toutes les preuves et informations réunies sur les différents groupes d'acteurs et compilé tous ces renseignements.

Tableau 4: Conclusion: effets des options politiques

Groupe d'acteurs	Scénario de base (OP 1)	Coopération fondée sur des projets (OP 2)	Secrétariat hébergé par EM/UE (OP 3)	Agence européenne existante (OP 4.1)	Agence européenne existante (OP 4.2)	Nouvelle agence européenne (OP 5)
Administration publique						
Pharma						
MedTech						

De manière générale, les effets perçus des OP ainsi que les perceptions et attentes en ce qui concerne la future coopération européenne sur l'ETS diffèrent selon le groupe d'acteurs dans plusieurs aspects.

Les OP dotées d'un cadre législatif pour la coopération européenne sur l'ETS (OP 3 et suivantes) peuvent avoir des effets positifs sur l'**administration publique**. La prévisibilité des systèmes d'ETS en Europe devrait augmenter considérablement pour l'OP 3, et les effets positifs sont amplifiés avec chaque option ultérieure.

Les OP comprenant une assimilation obligatoire des résultats d'ETS conjointes auront un effet positif sur l'**industrie Pharmaceutique**, l'OP 5 étant considérée comme la moins plausible par les représentants du secteur. Cette position pourrait être approuvée par l'équipe d'étude dans l'attente que nos analyses indiquent également des économies à long terme pour l'OP 5.

Une coopération volontaire fondée sur des projets (OP 2) serait favorable au secteur des **technologies médicales**, puisqu'elle ne comprendrait aucun **cadre législatif, qui est perçu comme une charge supplémentaire pour l'industrie aux effets négatifs**. Ce phénomène est lié au fait que l'ETS n'est pas encore très répandue dans le secteur, et les méthodes liées ne sont pas suffisamment matures dans l'industrie des dispositifs médicaux, en comparaison avec celui des produits Pharmaceutiques.

Selon notre analyse, il est nécessaire de prendre en considération les particularités de l'industrie des technologies médicales afin de développer un système d'ETS durable et efficace. Une solution consisterait à appliquer différentes OP et modèles de gestion aux deux secteurs. Dans le secteur des technologies médicales, un bon point de départ serait la création et l'**utilisation obligatoire d'outils communs, alors que le développement de méthodes supplémentaires aiderait à dresser un tableau clair des exigences liées aux processus d'ETS**. Par ailleurs, la réalisation volontaire d'EER conjointes pourrait être envisagée en parallèle, puis qu'elles fourniraient d'importantes informations, utiles aux prises de décision dans toute l'UE. Ces études contribueraient également à (a) réduire la base de preuves divergentes dans tous les EM de l'UE pour les technologies médicales, mais également à (b) renforcer la santé publique et la sécurité des patients.

Principaux résultats

- De manière générale, la vaste majorité des preuves cliniques étudiées par les organismes d'ETS concernent principalement les produits Pharmaceutiques soumis à un essai clinique de phase III, et dans une moindre mesure ceux soumis à un essai de phase II. Ces derniers connaissent une utilisation croissante dans les cas où la production de preuves issues d'essais de phase III est compliquée, où lorsque le bénéfice clinique est jugé important et que le traitement nécessiterait une autorisation de mise sur le marché conditionnelle (AMMC). Seule une portion des preuves cliniques ont été examinées en relation avec d'autres types de preuves cliniques (essais prolongés ou études par observation). Il est donc raisonnable d'avancer l'existence d'**un certain**

montant de duplications à l'heure actuelle étant donné que la preuve considérée dans tous les paramètres est en général la même.

- L'on constate une différence claire de préférences parmi les organismes d'ETS envers le type de preuves exigées pour les produits Pharmaceutiques, en comparaison avec les technologies médicales et les « autres technologies ». Ce phénomène est en partie lié aux possibilités dans le contexte des dispositifs médicaux ou des « autres technologies », et mis en avant par la forte proportion d'études rétrospectives et de sécurité (dans l'échantillon des dispositifs médicaux), ainsi que d'analyses documentaires (dans l'échantillon des « autres technologies »).

- En ce qui concerne les preuves économiques, bien que des similarités et disparités se retrouvent parmi les différents EM en matière de préférence d'approche, de gestion ou de mise en œuvre, il est important de noter que, parmi les pays étudiés et pour ceux qui réalisent des évaluations économiques, **le comparateur était identique dans 68% des organismes d'ETS**.

- L'harmonisation des exigences en matière de preuves, si elle est accompagnée d'une acceptation par les EM, faciliterait les décisions d'investissement. En outre, un système d'ETS européen comprenant une solide méthodologie réduirait le risque dans les processus de soumission et aiderait à éliminer les débats liés à la faible qualité des évaluations et des interprétations de données. Une plus grande uniformité des évaluations d'ETS serait véritablement bénéfique, et pourrait être facilitée par un recueil d'avis préliminaire ainsi qu'une plus grande transparence sur les attentes des payeurs. Enfin, l'harmonisation des exigences en matière de preuves offrirait une influence plus importante à l'UE sur le développement d'essais cliniques.

- **L'industrie Pharmaceutique se montre favorable aux options comprenant une assimilation obligatoire des résultats d'ETS conjointes**. En raison du système d'ETS actuellement fragmenté, le secteur profitera d'une réduction des soumissions et d'une meilleure prévisibilité dans toute l'UE. Il pourrait être nécessaire de relocaliser les effectifs vers une structure centralisée, mais leur nombre devrait rester stable.

- **L'industrie des technologies médicales comme celle des produits Pharmaceutiques ne saisissent pas importance d'une ETS complète à l'échelle européenne, bien que notre estimation des coûts indique que le secteur profiterait d'économies supplémentaires, en comparaison avec l'EER seule.** Cependant, cela dépend fortement de la nature des sujets sélectionnés pour une ETS complète. L'expérience en ETS complète dans toute l'UE est encore limitée à l'heure actuelle. Les domaines complémentaires de l'ETS complète (économique, organisationnel, juridique, étique et social) comprennent souvent de nombreux sujets « non transférables », et doivent donc être substantiellement adaptés à l'échelle nationale. Ces éléments pourraient en partie expliquer les scepticismes de l'industrie.

- **Le secteur des technologies médicales envisage plus de défis lorsque la future coopération sur l'ETS à l'échelle européenne comprend un cadre législatif**. À l'heure actuelle, l'industrie des dispositifs médicaux se heurte à un nombre inférieur de réglementations concernant l'accès au marché des produits, en raison de l'hétérogénéité significative des produits et de la fragmentation du secteur. Deux réglementations européennes récentes sur les dispositifs médicaux visent à améliorer la gestion de ce marché hétérogène. Étant donné que le secteur des dispositifs médicaux ne profite que d'une expérience limitée avec les processus d'ETS, elle prévoit une importante charge sur les procédures et processus, ainsi qu'un accès au marché ralenti.

- **L'on peut prévoir différentes synergies dans l'administration publique, puisque davantage d'évaluations seront potentiellement disponibles (si la coopération est fructueuse) pour les prises de décision**. Un seul organisme

d'ETS pourrait ne pas disposer des capacités nécessaires pour réaliser toutes les évaluations dont les dirigeants auraient besoin à l'échelle nationale. En outre, avec la croissance attendue de la mobilité des patients en Europe à l'avenir, comme prévu par la directive sur les soins transfrontaliers, des prises de décisions plus harmonieuses et fondées sur les mêmes preuves seraient souhaitables.

- **Les facteurs de réussite généraux identifiés pour la poursuite d'une coopération durable comprennent: (1) l'utilisation d'outils et de modèles communs, (2) des modèles de gestion avec une structure de gouvernance renforcée, (3) des processus d'évaluation opportuns, (4) une expertise et des informations transfrontalières, et (5) l'assimilation obligatoire des résultats à l'échelle nationale**(11) (ce dernier point uniquement dans le secteur Pharmaceutique), qui sont liés: L'utilisation d'outils et modèles communs facilite la réalisation de travaux conjoints avec la capacité institutionnelle suffisante, tandis qu'une solide gouvernance est fondamentale pour assurer des processus d'évaluation opportuns. La réalisation des évaluations en temps opportun est cruciale pour garantir une assimilation au moment ou les résultats sont pertinents pour le contexte national. Des avis d'experts adéquats sont nécessaires pour assurer la qualité des évaluations réalisées, ce qui augmentera l'efficacité des processus pour tous les groupes d'acteurs. Enfin, l'assimilation obligatoire des résultats est pertinente pour garantir le succès des objectifs des travaux conjoints. Ces facteurs se montreront pertinents pour la mise en place de la future coopération sur l'ETS, bien qu'il faille prendre en considération les spécificités du secteur des technologies médicales, et le fait que les facteurs de succès pourraient être mieux adaptés à l'industrie Pharmaceutique.

- **Une collaboration législative pourrait notamment créer la capacité institutionnelle nécessaire pour cette coopération, et les expertises pourraient être rassemblées.** Par ailleurs, les résultats de notre étude montrent que les processus peuvent être mis en place de manière plus efficace lorsqu'ils sont coordonnés et facilités par une institution permanente, puisque toutes les informations pertinentes sont centralisées, dégageant ainsi des économies globales.

- **Les économies potentielles augmentent considérablement dans les OP qui comprennent une production et une assimilation obligatoires des EER et ETS conjointes (OP 4.2 et OP 5)**. Les options qui prévoient un secrétariat permanent ou une nouvelle agence, impliquant une production conjointe plus élevée, entraîneraient des économiques largement plus importantes sur le long terme, en comparaison avec une coopération fondée sur des projets (environ 4 millions d'euros pour tous les pays dans l'OP 2, 70 millions dans l'OP 4.2 et 77 millions dans l'OP 5). En ce qui concerne les résultats du pronostic des coûts, il convient de noter certaines incertitudes dans le recueil de données, qui sont clairement indiquées dans les secteurs correspondants de notre étude.

- **Une durabilité accrue et une nature obligatoire renforcée de la coopération sur l'ETS en Europe pourraient entraîner des bénéfices pour les patients:** une augmentation du nombre de technologies évaluées accroîtrait la base de preuves pour les prises de décision dans toute l'UE, notamment dans les EM ou l'ETS n'est pas encore bien développée, contribuant ainsi à une diminution des inégalités transfrontalières.

- De la **perspective des patients**, la future coopération européenne sur l'ETS, avec des OP comprenant une participation et une assimilation obligatoires, **augmenterait la disponibilité de médicaments et de technologies médicales sûrs et efficaces, et garantirait un contrôle normalisé des technologies de santé avant la mise sur le marché**. Des processus d'ETS transparents et autonomes exigent la prise en considération de la perspective de tous les acteurs concernés afin d'améliorer l'efficacité et de prévenir les conflits d'intérêts. Des ressources financières suffisantes

sont indispensables pour établir les mécanismes respectifs. Outre les investissements requis, les acteurs devraient porter leur attention sur le potentiel retour sur investissement des différents mécanismes.

- La participation antérieure des patients aux processus d'ETS est caractérisée par de bonnes intentions de la part des groupes d'acteurs impliqués, mais les applications fructueuses sont encore limitées, soit par l'étendue ou l'objectif de la participation. L'administration publique et l'industrie Pharmaceutique émettent des signaux clairs indiquant un besoin d'**amélioration et d'uniformisation de l'implication des patients dans les processus d'ETS**. De manière générale, une coopération à long terme transparente dans le domaine de l'ETS offre le potentiel de prévenir les évaluations sélectives des médicaments, de réduire la disponibilité des technologies de santé avec peu ou pas de valeur et d'augmenter la disponibilité d'informations accessibles au public.

1 Introduction

The European Commission (EC) is exploring options for a new and sustainable mechanism for Health Technology Assessment (HTA) in Europe after 2020.

As part of that pursuit, the Directorate General for Health and Food Safety (DG SANTE) of the EC launched a new initiative, which addresses the question of whether and how to continue HTA cooperation at EU level beyond 2020, when the current EUnetHTA Joint Action 3 (JA3) ends.

The initiative commenced in summer 2016 with an **Impact Assessment process** (1) to support the initiative on strengthening the EU cooperation on Health Technology Assessment. This was resulting in the launch of a Public consultation (6) by EC between 21 October 2016 and 13 January 2017 ([20]). The consultation showed that 87% of **responding citizens and stakeholders supported an EU cooperation beyond 2020** (6).

In the context of this process, the EC commissioned the consortium of Sogeti, the Austrian Public Health Institute, Gesundheit Österreich Forschungs und Planungsgesellschaft GmbH (GÖ FP) and the London School of Economics and Political Science (LSE Health) to conduct an impact analysis of Policy Options (POs) for strengthened EU cooperation on HTA to **support the preparation of the Impact Assessment and the formulation of the EC initiative with data and evidence**.

The so-called 'baseline scenario', which takes into account both national and EU policies and practices currently in place, and reflects possible developments until 2020 is the defined starting point of the study.

This final report is the deliverable for Specific Contract N° CHAFEA/2016/Health/16 under Framework Contract N° CHAFEA/2013/Health/01 for Health reports (Lot 1) for the 'Study on impact analysis of POs for strengthened EU cooperation on HTA'.

In parallel, the EC commissioned two further studies to support the Impact Assessment process, notably (1) a mapping of HTA national organisations, programmes and processes in the EU and Norway, undertaken by Julia Chamova (2) and a mapping of HTA methodologies in the EU, undertaken by Finn Børlum Kristensen (7). This report cross-references these two studies.

([20]) http://ec.europa.eu/health/technology_assessment/consultations/cooperation_hta_en.htm

2 Background and context

This study aims to provide input to the above mentioned Impact Assessment process and analyses the likely impact of the identified Policy Options for strengthened EU cooperation on HTA.

The specific objectives of the study are to:

- Gather data and generate evidence on and provide an in-depth analysis of the baseline scenario including its impacts on different stakeholders;
- Collect data and generate evidence on and provide an in-depth analysis of the potential impacts of identified options for future HTA collaboration and
- Collect relevant literature on HTA, focusing on the European context.

There are several definitions of HTA, but within the Europe Union, HTA is defined as 'a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner´.

The aim of the study is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value (8). In doing so there are several steps and in the context of this study, it is important to highlight the difference between Assessment and Appraisal. 'Assessment' is defined as the collection and synthesis of evidence focusing on the traceability/replicability of results, whereas 'Appraisal' is the act of contextualizing evidence and formulating recommendations, i.e. defining impact and applicability (8, 9).

The study focuses on the 'Assessment' aspect, and stresses that any subsequent pricing and reimbursement decision for medical technologies, devices or Pharmaceuticals remains purely at national level, as stated in the Inception Impact Assessment in relation to the initiative on strengthening of EU HTA cooperation.

Over the past few decades, the diffusion of HTA has increased and its application has become more common across health systems in Europe. By now, public HTA bodies have been established in most Member States (MS) of the European Union (EU) and the European Economic Area (EEA), providing evidence-based information for both decision- and policy-making (10).

Organisations conducting HTAs have become institutionalized elements of the respective health system in which they operate thereby providing information on the (clinical and cost-) effectiveness of health care interventions but also on promising technologies, which could lead to innovation in health care delivery (11). This process does not have the same speed in all MS, resulting in some countries having more advanced HTA systems while others are still in the initial phase of establishing HTA systems (12).

At EU level, the value of HTA and the fact that joint work could facilitate the implementation of HTA processes and reduce redundancies regarding the assessment of technologies has been recognized. Already in the 1980, the Health Services Research Committee of the EC began to assign contracts for economic appraisals and mechanisms for the regulation of expensive health technologies in different countries. Between 1993 and 2002, three projects were funded by the EC to support collaboration on HTA between MS (13). Subsequently, project reports were provided in the course of a political process on cross-border health care and the need for a sustainable European network for HTA was identified (14). In 2004, the EC and Council of Minsters requested the establishment of a sustainable European network on HTA. This was initiated in 2005 when a group of 35 organisations started the EUnetHTA project, which explored possibilities and key challenges for an enhanced transnational collaboration for the following years and thus examined the HTA-process regarding its political links (14, 15).

In 2009, the EUnetHTA collaboration was founded and two Joint Actions were undertaken between both 2010 and 2012 (EUnetHTA Joint Action 1) and 2012 and 2015 (EUnetHTA Joint Action 2). During the Joint Actions, the joint work conducted was organised in several work streams, focusing mainly on the development of common methodologies and the creation of common IT Tools. Moreover, one purpose of the Joint Action was to reduce duplication of work between national agencies (16, 17).

The third Joint Action (EUnetHTA JA3) started in June 2016, includes 81 partners and will run for 48 months. The general objective is to increase the use, quality and efficiency of joint HTA work at EU level to support evidence-based, sustainable and equitable choices in healthcare and health technologies and to ensure re-use in regional and national HTA reports and activities, in order notably to avoid duplication of assessments. Another overarching objective is to develop a general strategy, principles and a proposal for a scientific and technical mechanism of permanent sustainable European Collaboration on HTA in the light of the Directive 2011/24/EU on the application of patients' rights in cross-border healthcare (CBHC) (18).

Key outputs created by the two previous Joint Actions are (1) the HTA Core Model, which provides a methodological framework for shared production and sharing of HTA information to enable the conduct of high quality HTA evidence in a structured format; (2) guidelines for rapid relative effectiveness assessment (REA), which address issues on the endpoints used for REA in Pharmaceuticals, the choice of the most appropriate comparator(s) as well as direct and indirect comparison(s); and (3) guidelines addressing the level of evidence such as internal validity.

A tool established during the Joint Actions is the 'Planned and Ongoing Projects' (POP) Database, which aims to facilitate the collaboration among European HTA bodies and to reduce the duplication of work by providing an overview of ongoing or recently published projects of participants. Within the first two Joint Actions, members of EUnetHTA undertook a total of 20 joint assessments of Pharmaceuticals and medical technologies including REA and Full HTAs (19).

Additionally, the Health Technology Assessment Network was established based on Directive 2011/24/EU on patients' rights in *cross-border healthcare* (18), stipulating the support of cooperation between national authorities or designated national bodies responsible for HTA by the European Union (16). It is a voluntary network, which supports the cooperation between national authorities on HTA and focuses on strategic aspects of the European cooperation on HTA. All MS participate in this network (16), which set up a strategy for EU Cooperation on HTA that will be implemented by JA3 (20).

While there have been several positive developments in HTA at EU level, there are several shortcomings in the current state of the art. Until now, the inclusion of joint work in HTA processes at national level has remained limited (also leading to the production of a reflection paper addressing the re-use of joint work in a national setting, which was published by the HTA network, aiming to provide concrete recommendations to increase the uptake of joint work) (21).

One reason for this could be that participation in EUnetHTA and the uptake of joint work within the MS is strictly voluntary. There are some variations regarding the procedural frameworks and administrative capacities between MS because their HTA Bodies are embedded in different institutional settings. As HTA procedures differ between EU MS, diverging data requirements for the industry and outcomes for the same products across countries exist.

Furthermore, HTA cooperation at EU level is currently funded solely through the Joint Actions and does not constitute a long-term funding and cooperation instrument. As a result, there is still a considerable duplication of work in assessing health technologies

within EU MS, and the fragmented landscape regarding HTA-procedures and methodologies complicates the situation for patients, payers and suppliers of technology(22).

At the same time, no sustainable business model for implementation after the completion of the third Joint Action in 2020 has been developed so far. According to EU Financial Regulations, recurring activities cannot be funded. Therefore, other financial options need to be identified. In this context, the question of sustainable cooperation beyond 2020 is addressed in line with the 'Better Regulation' agenda of the EC, aiming at the design and evaluation of EU policies in a transparent manner considering both evidence and stakeholder views (3, 4).

3 Study overview

In line with the Request for Specific Services, the overall aim of the study is to support the Impact Assessment process of the EC with data and evidence and, in so doing, provide key inputs for analysing the impact of different Policy Options for EU cooperation on HTA beyond 2020. Possible Policy Options for cooperation on HTA at EU level have been identified within the Inception Impact Assessment published by the EC. These are further developed by the EC in the course of the study, validated by experts and complemented by Business models/implementation mechanisms.

The aims of the study in particular are to:

- Collect data and generate evidence and provide an in-depth analysis of **what would happen in the absence of further action at EU level, including its impacts (baseline scenario)**;
- Collect data and generate evidence and provide analysis on the potential impacts of **identified Policy Options for cooperation of the EC**; and
- Collect relevant literature on HTA, with a specific focus on the European Union.

The study comprises several activities, including:

- A systematic **literature review** as well as a desk research of HTA and its use in EU MS;
- A detailed **case study** covering 40 health technologies;
- A **data collection process (survey complemented by focus groups)** for both Public Administration and industry costs and impacts of the identified Policy Options;
- **Interviews** with industry representatives; and
- An analysis of these impacts by Policy Option for different stakeholder groups.

3.1.1 An overview of these activities is provided in Table 5.

For establishing the baseline scenario, a case study comprising a product sample of health technologies has been analysed, which includes 20 Pharmaceuticals, 15 medical devices and five other technologies (including complex health interventions). Detailed information on the HTA-process each health technology underwent across EU MS was collected in the course of the case study. Additionally, the costs of performing an HTA were identified for both the technology developer and the HTA body. Finally, the case study captured the influence of the regulatory framework on technology developers. The findings from the case study were complemented with focus groups (5.3.4), interviews (7.1.13) and the literature review (5.1).

To assess the impacts of the Policy Options on the stakeholders the study team surveyed a number of economic and social health criteria (5.3.1) via an online survey, complemented by focus groups, and findings from the literature review.

The study also provided a description of the implementation mechanisms and business models (i.e. secretariat) and a calculation of the costs (see 7.2).

Table 5: Overview of activities within the study

	Baseline scenario	Impacts of identified Policy Options of the EC	Implementation mechanisms
Key questions	How do the current systems of HTA in Europe affect the key stakeholders (HTA bodies, industry, patients, etc.)?	How would the proposed options affect the key stakeholders (HTA bodies, industry, patients, etc.)? Complemented by the description of the implementation mechanisms (i.e. secretariat)	How would the proposed cooperation be coordinated?
Key indicators	Indicators on the HTA processes and outcomes, costs for industry and HTA bodies, influence of the regulatory framework on technology developers	Economic impacts (e.g. cost and administrative burden or impacts on the innovation), social impacts (e.g. access to and sustainability of health systems)	Organisational and financial aspects of the implementation mechanism
Data sources	40 case studies Survey and focus group (cost part) Interviews Literature	Survey and focus group (cost + impacts part) Own calculations for cost prognosis Interviews Literature	Survey and focus group (cost part) Information from EUnetHTA JA / other EU institutions Literature

3.2 Involvement of experts

3.2.1 Expert group

An expert group was set up to validate assumptions made during the course of the study and to create a comprehensive overview regarding the definition of the baseline scenario, the Policy Options and the corresponding business models/implementation mechanisms. This section provides an overview about the members of the expert group and their contribution, and describes the different steps of expert involvement within this study.

Based on the proposed list of experts included in the offer and further discussions between EC/CHAFEA, GÖ FP and LSE, a list of experts was defined. For this, specific attention was given to a well-balanced geographical mix. Furthermore, the study team aimed to incorporate different views on the outlook for EU cooperation on HTA. Therefore, both EUnetHTA members and experts from the scientific community in Health Policy and Health Economics with experience in HTA were selected for the expert group.

In early October 2016, 13 experts were contacted by E-Mail, highlighting the main objectives of the study, their envisaged role and the importance of the project. A letter of endorsement by EC/CHAFEA was shared with the experts as well. Twelve of the contacted experts accepted the invitation and were subsequently asked to sign a confidentiality agreement developed by CHAFEA, which was done by all experts. An overview of the members of the expert group is depicted in Table 6.

Table 6: Overview of the expert group

	Name	Position	Country
1	Jacek Walczak	Vice President Laser Analytica	PL
2	Wim Goettsch	Executive Board Chair EUnetHTA JA, Zorginstitut Nederland	NL
3	Zoltán Vokó	Prof. MSc MD PhD Head of Department Eötvös Loránd University, Budapest.	HU
4	Expert	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Germany	DE
5	Mairin Ryan	Director of HTA, Health Information and Quality Authority (HIQA), Ireland	IE
6	Marina Cerbo	Director of Innovation Research and Development, Agenas – The National Agency for Regional Health Services; Italy	IT
7	Nick Crabb	Programme Director, Scientific Affairs; National Institute for Health and Clinical Excellence	UK
8	Rosa Giuliani	ESMO (European Society for Medical Oncology)	EU
9	Francois Meyer/ Chantal Bélorgey	HAS	FR
10	Karen Facey	Past Chair HTAi Interest Sub-Group for Patient/Citizen involvement in HTA	UK
11	Reinhard Busse	Professor and Department Head for Health Care Management at Technische Universität Berlin	DE
12	Claudia Wild	Director of Ludwig Boltzmann Institute for Health Technology Assessment	AT

The involvement of experts took place in two steps. **Firstly**, a written expert consultation was initiated to receive feedback on the quality, feasibility and relevance of the POs on HTA cooperation. For this, a comprehensive document (see Annex 1) was set up, including information on the baseline scenario and the POs. Moreover, a list of impacts and indicators was presented for feedback to ensure that all relevant impacts and indicators for all stakeholder groups were covered within the study. The document for the expert consultation was sent by email on 17 November 2016 to all participating experts who were invited to comment on the issues raised. Of the 12 experts, eight responded, three experts did not respond and one expert chose not to respond because the expert perceived the approach of providing written feedback as inappropriate. Feedback and provided input was used for further discussions regarding the final version of the POs and the indicators to use for the assessment of the POs.

Secondly, experts were invited to a face-to-face meeting in Brussels on 14 March 2017. There, we discussed the preliminary findings of the study and received input on these. Representatives of the consortium, EC Services including CHAFEA and DG SANTE, and two additional guests, Julia Chamova and Raf Mertens, also participated in the meeting (see Table 6). The recommendations of the expert group both for analysis and for additional data collection processes to address potential limitations of the survey were taken into account. One major follow-up to the expert group meeting was the organisation of the focus groups (see Chapter 5.3.4) to discuss and validate the results of the survey and case studies.

3.2.2 **Peer-review process**

The study was scrutinised by scientific peer reviewers who were initially selected in cooperation with DG SANTE officers. They gave comments on the draft final study after DG SANTE's initial feedback. A personal meeting was foreseen but was not considered necessary at the end of the undertaking. The peer review time was two weeks.

Peer reviewers were:

- Senior Expert Valérie Paris, OECD
- Prof. Dr. Irina Cleemput, Belgian Health Care Knowledge Center (KCE)
- Prof. Dr. Jaime Espin, Andalusian Public Health School (EASP)

4 Policy Options

The EC has proposed core options for further cooperation at EU level in the Inception Impact assessment (1) and the Public Consultation, whose results were published in May 2017 (6).

The contractor has combined these core Policy Options with different potential business models. These were discussed, refined and further developed in close collaboration with EC/CHAFEA in the course of the study. To capture all the key points for the impact assessment, the expert group was consulted to provide feedback on and ensure the feasibility of the Policy Options/business models (see description of the expert consultation in 3.2.1).

After inclusion of expert feedback, a final version of the POs, including a baseline scenario combined with different business models, was defined. It served as the basis for the online survey on impacts (for details on the online survey see section 5.3.1)

Within this section, the key characteristics of these final POs are summarized and a short description for each of the options is given.

4.1 Status quo

The baseline Scenario is linked to the status quo of European HTA cooperation in 2016, taking possible developments until 2020 (end of EUnetHTA Joint Action 3) into account. This status quo is characterized by:

- A heterogeneous situation regarding the relevance of HTA in national decision-making processes.
- Strictly voluntary cooperation between the EC and the EU MS through (1) Joint Actions (Scientific and technical- developing methodologies and tool and performing joint assessments) and (2) the HTA Network (providing strategic guidance).
- No guarantee that any joint output is taken up in national HTA activities.

Planned Work until 2020 – expected outcomes

The general objective of the EUnetHTA Joint Action 3 (2016 – 2020) is to support voluntary cooperation at the scientific and technical levels between Health Technology Assessment bodies to validate the model for joint work to be continued after EU funding under the Health Programme. The cooperation between national and regional HTA Bodies is to meet the provisions set out by Article 15 of Directive 2011/24/EU on patient's rights in cross-border healthcare (18) and to create synergy with the strategic HTA Network set up under this Directive.

Joint Action 3 is aiming to establish an inventory of available methodological documents and tools, consequently identifying gaps and adjusting or maintaining existing guidelines and tools. Moreover, all tools should be integrated in an **Online Handbook for HTA-Doers, Early Dialogue** communication should be provided, and a tool for post-launch **evidence generation** as well as a **prioritisation process** for the topics of Joint Assessments should be developed.

In EUnetHTA JA 3, there was a higher amount of joint production work than in the last Joint Actions; namely 51 **Joint Assessments** ([21]) – 33 on Pharmaceuticals and 18 on other technologies – and 29 **so called 'Collaborative Assessments'** ([22]) – four on Pharmaceuticals and 25 on other technologies – are planned.

Until 2020, the Joint Action is financed by the 3rd Health Programme and MS' contributions in kind. A new Joint Action is not foreseen, as it is a mechanism that should pilot new cooperation mechanisms, but not fund them over the long term. Therefore, it is anticipated that after expiration, and without further EU action, MS would depend solely on their national/regional HTA procedures and budgets. Although MS will be free to cooperate regarding HTA, on what scale joint work might continue is not certain.

4.2 Key characteristics of Policy Options

The different **Policy Options** for cooperation on HTA after 2020 are defined along several **key characteristics,** focusing on HTA output, participation and uptake from MS' perspectives, organisational aspects, funding aspects and timelines. These are explained in the following:

1. The scope of the cooperation is defined by several outputs ([23]) created by a joint collaboration, comprising of:
   - Common tools and procedures, including common submission templates, an IT system with planned and ongoing assessments, common methodologies (e.g. EUnetHTA Core Model), a joint prioritization process, and cooperation on data requirements, including Horizon Scanning;
   - Performing joint Early Dialogues;
   - Performing joint Relative Effectiveness Assessments (REA can take place at time of market launch, or later – reassessment);
   - Performing joint Full Health Technology Assessments (Full HTA can take place at time of market launch, or later – reassessment); and
2. The engagement in participation and uptake ([24]) of jointly produced outputs can be either **voluntary** or **mandatory**:
   - Voluntary participation/Voluntary uptake (V/V): MS can decide if they wish to participate in the production of outputs and take up the respective output; cooperation is entirely voluntary.
   - Voluntary participation/Mandatory uptake (V/M): The participation in the creation of joint work is voluntary, meaning that MS can decide to opt in ([25]) to the joint

([21]) A Joint Assessment is defined as a prioritized topic, submission-based (using the submission templates as were developed in EUnetHTA JA2), an authoring team of two to three agencies and at least five dedicated reviewers, English as working-language, use of HTA Core Model and Guidelines, EUnetHTA procedures on stakeholder involvement (scoping meeting with manufacturer etc.), internal and external quality assurance. A Joint Assessment can be a REA or a Full HTA.

([22]) A collaborative assessment is defined by a lower level of centralized work organization, but equal criteria in quality assurance: the collaborative assessments shall include at least three to five partners, however in justified cases, two partners would be acceptable. Such constitutes a less centralised topic selection/priority selection process. English as working language, use of HTA Core Model and Guidelines, not necessarily submission based, internal QA by review by at least two other EUnetHTA partners (support by WP 4) and QA by external peer review, stakeholder involvement at one point in time (further criteria to be agreed upon).

([23]) The scope of the activities may differ between Pharmaceuticals, medical devices and other technologies.

([24]) Uptake concerns using or considering the results and findings of the HTA cooperation, reaching from jointly developed submission templates to outcomes in full HTA. The subsequent pricing and reimbursement decision would remain purely at the national level. Providers/developers also need to adhere to this process.

([25]) Opting in by MS is by output, not by individual products. E.g. once a MS has opted in for joint REA, they take part in all joint REAs – but not necessarily as an author.

cooperation. However, once a MS has opted in, the uptake of the joint work into the national setting is mandatory.

- Mandatory participation/Mandatory uptake (M/M): Both participation in the production of outputs and the uptake of these into the national setting are mandatory.

For each of the POs, different combinations of **voluntary or mandatory** participation and uptake per Output are possible.

3. For organizing the creation of these joint HTA outputs, a number of different **organisational mechanisms** are conceivable:
   - Project-based cooperation – The secretariat is set up by the MS that participate (similar to EUnetHTA).
   - EU/MS secretariat – A permanent Secretariat is established.
   - Existing EU agency – A permanent Secretariat is integrated in an already existing EU agency. This Secretariat will coordinate the work of national experts in HTA bodies in carrying out assessments. There is no further specification on which EU agency might be considered.
   - New EU agency – A permanent Secretariat is integrated in a NEW EU agency. This Secretariat will coordinate the work of national experts in HTA bodies in carrying out the assessments.
4. For financing the joint cooperation several **funding mechanisms** are conceivable:
   - EU funding, either through a Public Health program or another financial instrument
   - Funding by MS joining the collaboration; and
   - Funding through industry fees
5. Timelines for implementation of the proposed POs after 2020 range from immediately, without delay, for option 1 (i.e. 2021) to transitional periods for implementing options 4 or 5 in a new legal framework.

Table 7 provides an overview of each Policy Option and the envisaged implementation/ funding mechanism. A short summary for each Policy Option can be found afterwards.

Table 7: Overview of Policy Options

		Baseline	Non-legislative	Legislative			
		PO 1	PO 2	PO 3	PO 4 ([26])		PO 5
		No EU action after 2020	Voluntary cooperation through Public Health Programme	Legislation covering common tools and Early Dialogues	Legislation covering Joint work on REA Plus common tools and Early Dialogues		Legislation covering Joint work on Full HTA (including REA) Plus common tools and Early Dialogues
					4.1 REA V/M	4.2 REA M/M	
Outputs	Common tools, including templates, methodology	V/V	V/M	M/M	M/M	M/M	M/M
	Early Dialogue ([27])	V/V	V/M	V/M	V/M	M/M	M/M
	Joint REA ([28])	V/V	V/M	V/V	V/M	M/M	M/M
	Joint Full HTA ([6])	V/V	V/V	V/V	V/V	V/V	V/M
Implementation		No EU input	Project based cooperation	EU/MS secretariat	Existing EU agency	Existing EU agency	New EU agency
Financing		None from EU	EU+MS	EU+MS+fees from industry for Early Dialogues, joint REA and Full HTA			
Scope			All Pharmaceuticals , medical and other technologies	Tools: all Pharmaceuticals , medical technologies, other technologies (phasing in), ED: industry submission	Tools and ED see PO 3. REA: certain categories of Pharmaceuticals (e.g. centrally authorised, high value/budget impact, agreement between MS) and medical technologies (e.g. high risk, high value products) and other technologies (agreement and prioritisation between MS) – phasing in[29]		Tools and ED see PO 3, REA see PO4. For others: ad hoc agreement and prioritisation between MS

Legend. PO: Policy Option; V/V: Voluntary participation/ voluntary uptake; V/M: Voluntary participation/mandatory uptake; M/M: Mandatory participation/mandatory uptake; ED: Early Dialogue; REA: Relative Effectiveness Assessment; MS: Member State; HTA: Health Technology Assessment

([26]) Assuming that 50% of the Member States (MS) participate, a mix of high/low income, large/small MS.
([27]) ED - Early Dialogue: Here mandatory uptake means that the MS cannot repeat an ED that was done at EU level. Technology providers initiate Early Dialogues.
([28]) Either at time of market or re-assessment.
([29]) A gradual introduction of products during a transitory period that allows to manage the workload while the structures/implementation models are being developed.

4.3 Short descriptions of Policy Options

Policy Option 1. Baseline scenario - No EU action after 2020:

The 'no policy change' baseline scenario supposes that the current EUnetHTA, Joint Action 3, ends in 2020 and it is the last Joint Action on this topic, i.e. EU funding stops.

Without EU funding specifically devoted to it and/or a regulatory framework to support it, the European cooperation will be limited to the high-level policy-strategic discussions within the HTA Network of MS. According to the available budget, EC internal priority setting and the outcome of yearly negotiations between MS and the relevant EU Institutions, the EU may support ad hoc scientific research projects, for instance through the H2020 programme. MS are free to cooperate on joint output (e.g. common tools, templates, Early Dialogues, REA or Full HTA) on a voluntary basis, relying on national resources (human and financial), which are expected to remain sporadic.

Policy Option 2. Voluntary cooperation supported by the Public Health Programme:

This option foresees a voluntary cooperation model, partially supported by EU funding but without any regulatory framework.

The potential joint outputs produced through the voluntary cooperation could cover the whole spectrum; it could cover common (IT) tools, templates, methodologies; Early Dialogue; joint REA and Full HTA. To address one of the shortcomings of the current cooperation model, in particular the low uptake of joint outputs, a contractual obligation could be included in any possible future project to make EU funding subject to the uptake. Further analysis in this possibility has indicated that, while theoretically possible (provided that the negotiating parties would agree) there is no effective possibility for the EC to enforce these contractual obligations.

As the cooperation is fully voluntary, the scope of the products subject to the cooperation would not be limited.

This option would be project-based cooperation model. The costs would be co-funded by the EU and MS. Similarly to policy option 1, also for policy option 2, the source and the amount of funding is dependent on the negotiations of the Multiannual Financial Framework (within the EC and the other relevant EU Institutions) and subject to renewal in every budgeting period.

Policy Option 3. Legislation covering common tools and Early Dialogues:

Policy options 3, 4, and 5 foresee the introduction of a legal framework for HTA cooperation

In Option 3, the legal framework would cover common (IT) tools, templates, methodologies; Horizon Scanning and Early Dialogue. The participation and uptake for common (IT) tools, templates, and methodologies is mandatory. For Early Dialogues, MS can choose to participate. However, uptake is mandatory, meaning that the MS cannot repeat an ED that was done at EU level. Outside of the legal framework, MS are free to cooperate on further outputs, i.e. on REA or Full HTA on a voluntary-voluntary basis.

The product scope would vary by output. The common (IT) tools, templates and methodologies would be applicable to all technologies on which national or regional HTA is conducted. Early Dialogues would be initiated by the industry and could cover any

Pharmaceutical, medical or other technology. Since the cooperation for joint REA and Full HTA is fully voluntary, so there would be a need to establish a contractual framework – just like under option 2 – or to work on a regional basis.

Coordination on mandatory outputs would be organised by a secretariat run by the EC. The costs of the cooperation are funded by the EU, the MS and by other sources (e.g. company fees for Early Dialogues).

Policy Option 4.1. Opt-in for joint REA plus option 3:

Option 4 extends option 3 by including the joint REA in the legal framework in addition to the common (IT) tools, templates, methodologies; and Early Dialogue. The participation and uptake of the common (IT) tools, templates, methodologies and Early Dialogues is the same as in Option 3. Opt-in is foreseen in legislation for participating in the production of joint REA and mandatory uptake by those who opted in. Outside of the legal framework, MS are free to cooperate on Full HTA on a voluntary-voluntary basis.

The product scope would vary by output. For joint products covered under Option 3, the scope remains the same. For joint REA, a defined set of Pharmaceutical, medical and other technologies would be included. It would comprise Pharmaceuticals undergoing central marketing authorisation as well as Pharmaceuticals prioritised by an MS due to their importance considering products of:

- high value
- high budget impact
- responding to unmet medical needs or with significant public health impact

For joint REA on medical and other technologies, MS would be invited to consider the following technologies:

- innovative and with potentials to transform the organisation of care ('transformative technologies')
- responsive to unmet or significant medical needs
- uncertainty regarding clinical effect
- high impact on health and social care budgets
- class III implantable devices and class IIb active devices as well as Class D In Vitro Diagnostic (IVD) devices ([30])
- where the HTA study is foreseen to have impact, in particular on decision-making (pricing/reimbursement) and treatment guidelines
- Where requests were received from interested stakeholders (e.g. hospitals)

As cooperation for Full HTA is fully voluntary, the scope of the products is not defined. The coordination would be organised in an existing EU agency. The costs of the cooperation are funded by the EU, the MS and by other sources (e.g. company fees for ED and joint REA).

Policy Option 4.2. Mandatory Joint REA plus option 3:

Policy option 4.2 is essentially the same as option 4.1 with one important exception: For joint REA, both participation and uptake are mandatory.

(30) These also have the potential to exploit potential synergies with the future scrutiny mechanism of the revised medical device and IVD regulations.

Policy Option 5: Option 4.2 and Opt-in for Full HTA:

Option 5 is the most ambitious option, extending option 4.2 by including joint Full HTA in the legal framework in addition to the common (IT) tools, templates, methodologies, Early Dialogue and joint REA. The participation in and uptake of the joint outputs covered in option 3 and 4 remains the same. Opt-in is foreseen in legislation for participating in the production of joint Full HTA and mandatory uptake by those who opted in.

For outputs covered under options 3 and 4, the scope remains the same. Full HTA would be undertaken on all technologies where a joint REA is undertaken.

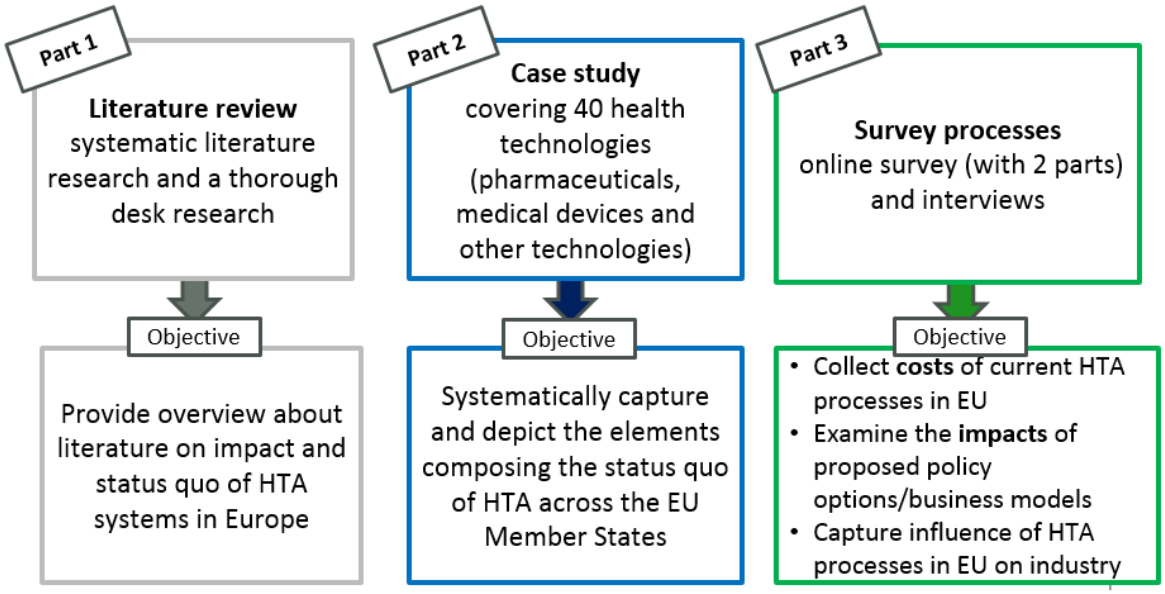
The coordination would be organised in a new EU agency. The costs of the cooperation are funded by EU, MS and other sources (e.g. company fees for Early Dialogues, joint REA and Full HTA).

5 Data Collection

In order to collect a comprehensive data set, various methods of data collection were performed. The overall data collection process consisted of three parts:

- A **literature review** comprised of a systematic literature research and a thorough desk research (see part 5.1)
- A **case study** including 40 technologies of Pharmaceuticals, medical devices and other technologies (see part 5.2)
- A **survey process** (see part 5.3) which comprised two parts, an online survey and interviews performed with health technology manufacturers. The online survey contained two separate questionnaires, one addressed to companies and associations and one addressed to MS, HTA bodies, patient organizations and health care providers (see part 5.3.1)

Figure 3: Overview about streams of activities



5.1 Literature review

The aim of the literature review was to collect the most relevant and recent literature on HTA to provide an additional evidence base for the impact assessment. Thereby, the focus was set to literature regarding EU cooperation on HTA as well as national HTA systems in European countries. Both a systematic literature search in a set of databases as well as a comprehensive desk research were performed for retrieving the relevant literature. The methodology and the results are discussed briefly in what follows.

For the **systematic literature review,** the following databases were used: Medline, Embase Cochrane Databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Methodology Register, Health Technology Assessment, NHS Economic Evaluation Database), CINAHL, ECONLIT and Scopus.

For performing the literature search, a search strategy comprising the following search terms was set up (simplified presentation, full search strategy can be in Annex 2):

(Technology Assessment, Biomedical OR Health Technology Assessment OR European public assessment study OR relative effective assessment OR outcome assessment OR process assessment clinical assessment OR joint assessment OR evidence-based medicine)

AND

(Decision-making, Organizational/ OR Health Policy/ OR International Cooperation/ OR international comparison OR international cooperation OR health policy OR European cooperation OR European collaboration)

Differences between the databases (for example, regarding different mesh terms) were considered when setting up the search strategy for each database. Search terms were searched for in titles and abstracts in English. Free-text truncation – e.g. truncation like comparison*, etc. And subject headings (e.g. Medical Subject headings (MeSH) – were used when appropriate. The identified references were collected in an Endnote® file and duplicates were removed. Afterwards, the publications were selected in two consecutive steps, following pre-defined inclusion and exclusion criteria. In general, studies were considered relevant if they were issued in the period between 2012 and 2016, written in English, French or German and published by regulators, HTA bodies and industry or stakeholder organisations.

Authors considered a study relevant, if the following criteria (inclusion criteria I1 – I5) were met:

Inclusion criteria

I1 Publication describes a **national HTA system in a European country** with regard to its structure, developments, reforms or methods applied.

I2 Publication is **comparing or reviewing two or more EU HTA systems** regarding methodological issues (e.g. clinical aspects, economic aspects), outcomes or structural components of the HTA system.

I3 Publication describes **EU cooperation/bilateral cooperation in the field of HTA** (e.g. REA, Early Dialogue) regarding joint assessment or joint procurement.

I4 Publication describes **cooperation in the field of HTA** (e.g. REA, Early Dialogue) **in non-EU countries** regarding joint assessment or joint procurement, but can be relevant to the European context.

I5 Publication is a document from **stakeholder groups** (e.g. Industry/patients) addressing HTA regarding current European cooperation or methodological issues.

A study was excluded, if the following criteria (exclusion criteria E1 – E6) were met:

Exclusion criteria

E1 HTA as a concept/political instrument is not the primary investigated subject of the publication.

E2 Study was published in a language other than English, French or German or before 2012.

E3 No clear description of the context/no abstract available.

E4 Description of non-European HTA system with no connecting factor to the topic of this study.

E5 Publication is addressing a specific technology in one country (no country comparison).

E6 Publication is a conference abstract, interview or comment.

The de-duplicated systematic literature search within the mentioned databases yielded **993 results** in total. Of these**, 96 publications were included after the second selection**.

The relevant literature has been used in the subsequent sections to put in context, verify and complement the findings of the case studies and the survey.

To identify relevant grey literature, a thorough **desk research** was performed to complement the systematic literature search. This search included Google Scholar (searching for terms such as 'HTA', 'cooperation' and 'EU') and the websites of national HTA institutes as well as international organizations, EU projects and networks within the HTA sector:

- European Union (EC particularly of DG SANTE, DG ENTR, DG, COMP, DG Research and Horizon 2020 and FP7, European Parliament, Council of the EU, CHAFEA project database, Joint research centre JRC)
- AdHopHTA
- INTEGRATE HTA
- MedtechHTA
- Advance HTA
- European Medicines Agency (EMA)
- European Network for Health Technology Assessment (EUnetHTA)
- Central and Eastern European Society of Technology Assessment in Health Care (CEESTAHC)
- Organisation for Economic Co-operation and Development (OECD)
- World Health Organization (WHO)
- Health Evidence Network (HEN)
- Health Technology Assessment international (HTAi)
- International Network of Agencies for Health Technology Assessment (INAHTA)
- The European Public Health Association (EUPHA)
- Innovative Medicines Initiative (IMI)
- International Society for Pharmacoeconomic and Outcomes Research (ISPOR)
- National HTA Institutes
- International Journal of Technology Assessment in Health Care
- Google Scholar
- International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- MedTech Europe

The websites of these institutions/organisations were searched for publications on the issue of HTA systems and EU/international HTA cooperation. This included grey literature such as HTA reports, annual reports of HTA bodies, presentations and posters. Relevant publications were provided in an Excel file. Inclusion and exclusion criteria for the systematic literature review were used as an orientation for applicability of publications.

The identified literature was read, relevant information was extracted and clustering has been used in the subsequent sections to put in context, verify and complement the findings of the case studies and the online survey.

5.2 Case study – data collection on 40 technologies

In this section, we outline the data collection process for the forty case study technology-indication pairs, which followed a process comprising four tasks:

1. The identification of a sample of suitable case studies of technology-indication pairs;
2. Primary analysis of secondary data through desk research of the identified case studies;
3. Primary data collection through the administration of an EU-wide survey of medical technology manufacturers and HTA bodies; and
4. Primary data collection through semi-structured interviews of medical technology executives.

The information retrieved was compiled into the table of indicators and follows the structure outlined below:

- Indicators in Annex 12 were filled by the desk research (publicly available data from official documents);
- Table in Annex 13 refers to the costs of performing HTA. The costs were collected through the survey delivered by GO-FP;
- Table in Annex 14 includes ten concrete examples on how HTA practices shaped industry behaviour, informed by stakeholder interviews.

Details on the process to acquire the information required and build the evidence base are provided in the sections that follow.

5.2.1 Sample selection for case studies

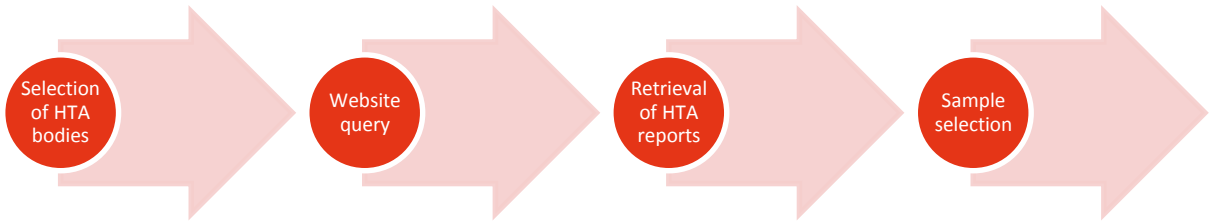
In order to understand the variability in methods and processes currently employed by different HTA bodies and the influence that different methods and processes have had on final HTA outcomes, we selected 40 technologies for in-depth analysis. The unit of measurement and analysis was the technology-indication pair, bearing in mind that the same technology could be indicated for different diagnoses. Data collection commenced in October 2016 and was completed in February 2017.

The sample was selected based on the following criteria:

- Technologies should have been marketed by at least 10 EU MS for the indication under consideration;
- Technologies would need to have been assessed between January 2012-August 2016 for the selected indication in order to include the most recent technology assessments, but, for data availability reasons, this was subsequently revised to the period from January 2006-August 2016;
- At least 5 HTA bodies across the EU should have assessed the technology; and
- The assessment information and relevant reports for each technology-indication pair should be publicly available and preference was given to technologies with a higher number of publicly available HTA reports; the minimum requirement for this purpose was 5 HTA agency reports for the same technology-indication pair in order to ensure a degree of comparability across HTA processes and outcomes.

For the selection of the sample of the health technologies, a four-step process was adopted outlined as below.

Figure 4: Selection process



First, forty one HTA bodies across all EU MS were identified and recorded. In some countries (Austria, Germany, Italy, Spain and UK), more than one HTA body was included in order to showcase the key role played by regional HTA bodies in those countries. At EU level, EUnetHTA was also included in order to account for joint assessments conducted by more than one country together. Luxembourg and Greece do not have an explicit central Health Technology Assessment process, therefore they were excluded from the final sample. In 2011, Denmark discontinued the conduct of HTA at central level, thus it was not considered for this task. Overall, most HTA bodies have an advisory function and their actual roles and manpower are quite heterogonous.

Having identified the HTA bodies, we recorded some of their key operational attributes and the methodological approaches and processes they employ. In doing so, we were able to comment on: (i) their operational model (for example, if they operate at national or regional level or if their role is regulatory or advisory); (ii) the inclusion of examples of different HTA approaches (for example, if they conduct only REAs or Full HTAs); (iii) the presence of an established agency; and, (iv) the availability of publicly available information on assessments performed. For each HTA agency, its contribution to the final pricing/reimbursement decision and the level at which it operates, were captured.

Table 6 (Annex 5) showcases (i) the competent HTA bodies by country, (ii) whether the scope of their recommendation is national or regional, (iii) the type of technologies assessed/appraised by the HTA body, iv) the role of HTA and whether it is regulatory or advisory to the final pricing/ reimbursement decision and v) whether HTA recommendations are publicly available.

Second, websites of the selected HTA bodies were queried in order to identify relevant data and HTA reports and to ascertain the feasibility of data availability across technologies and countries. Data were collected from publicly available reports only, which were posted online on the websites of the selected HTA bodies. The review commenced with the inclusion of all HTAs conducted between 1 January 2006 and 31 August 2016. Country-specific extraction tables were created in Excel, into which the data was inserted. The data was subsequently compared, aiming to identify common health technologies appraised across HTA bodies.

Third, a database was created with all common HTA technology-indication pairs, ranking them from those with the highest level of publicly available information and by the extent to which they fulfilled the predefined four main criteria outlined in the first step. After ranking the technologies by data availability, the sample of technologies was selected based on the inclusion criteria outlined in Table 8 regarding sample representativeness. For a technology to be selected for in-depth study, it would need to fulfil at least one of the inclusion criteria. Additionally, the number of combinations of different inclusion criteria outlined in Table 8 (e.g. product from a medium-sized company and Early Dialogue, or product from a large company and Early Dialogue) was factored into

the final selection of technology-indication pairs. When a technology was indicated for more than one indication, the indication with the highest number of available data and most recently marketed was selected.

The term medical device[31] covers a vast range of technologies surrounded by regulatory complexities, which needed to be reflected in the sample. In a first step, the categories given by the Global Medical Device Nomenclature (GMDN) were considered for selection to ensure a broad scope of different medical devices; the sample adopted the classification outlined by the EC in Directive 93/42/EEC Annex IX as well as the definition for active implantable medical devices and in vitro diagnostics according to Directive 90/385/EEC and Directive 98/79/EC, respectively. Overall, the medical device sample would include at least one device from each category in order to maximize its representativeness.

Table 8: Inclusion criteria

Type of technology	Criteria
All technologies	• Products from different sized companies (e.g. large, medium and SME as well as products from different therapeutic areas) • Mix of procedures –e.g. Early Dialogue (yes or no), EUnetHTA or national • Different budget impacts will be included
Pharmaceuticals	1. Product, which underwent central marketing authorization 2. Product, which underwent national marketing authorization 3. Product treating major and chronic disease (MCD) 4. Product treating orphan diseases 5. Product treating a paediatric population
Medical devices	A. Active implantable devices B. Anaesthetic and respiratory devices C. Dental devices D. Electro mechanical medical devices E. Hospital hardware F. In vitro diagnostic devices G. Non-active implantable devices H. Ophthalmic and optical devices I. Reusable devices J. Single-use devices K. Assistive products for persons with disability L. Diagnostic and therapeutic radiation devices M. Complementary therapy devices N. Biologically-derived devices O. Healthcare facility products and adaptations P. Laboratory equipment Q. Medical software

Taking into consideration that HTAs are performed on health technologies other than Pharmaceuticals and medical devices, in order to account for recent advances in health technologies other than Pharmaceuticals and medical devices, the sample included five health technologies that were neither Pharmaceuticals nor medical devices. In defining these, we searched for HTAs across screening programmes, vaccination campaigns, evaluation of surgical and non-surgical interventional procedures, stem cell therapies, innovative cancer vaccines, gene therapies and other forms of personalized medicines and screening programmes. The identified technologies were classed as 'Other Technologies' and included screening programmes and vaccines.

([31]) In this report the word 'devices' is used generically and includes medical devices and associated medical technologies.

5.2.2 Desk research and primary analysis of secondary data

The indicators (see Annex 12) were researched in the available HTA reports along with any other relevant information about the HTA process a selected technology has undergone. The relevant websites of HTA bodies and National Regulatory Agencies and Health Agencies (e.g. AIFA in Italy or the 'Base de Donnees Publiques des Medicaments' in France) were also screened to capture any information missing from the actual reports. Finally, some indicators were adjusted for the study technologies to reflect important regulatory or other endpoints that would be different across technologies. For instance, in the indicators for medical devices, the CE mark was recorded instead of marketing authorisation (MA) date; and indicators, such as the cost of the programme or the target group of the programme, were added for the 'Other Technologies' sample.

All the data were compiled in an excel spreadsheet to create an interface between qualitative and quantitative data. The information included in the excel captured the molecule name, the branded Pharmaceutical name, the HTA recommendation issued in each study country and a number of coded parameters, which were identified by reviewing the evidence considered by HTA bodies. When a product underwent more than one assessment, this was recorded and data were retrieved from the latest assessement published. After finalizing the collection of the qualitative data, the database was cleaned and, subsequently, variables were coded and categorized in order to obtain quantitative data.

Following consultation with the experts group, a number of HTA bodies were contacted to validate the collected information or obtain additional data. IQWIG, HAS and ZiN were contacted in order to validate the extracted data. Validation was mainly focused on the categorisation of the outcome decision (and whether a technology would be: 'Listed', 'Listed with Restrictions' or 'Rejected'). Data was again cross-checked following the submission of the interim study in order to minimize the likelihood of any errors of interpretation.

Each indicator was coded with one or more codes. The coded information was used to undertake qualitative analysis in order to understand processes in different settings, and for quantitative descriptive analysis, in order to understand trends across countries. This approach enabled the transfer of the qualitative value of the criteria identified to a quantitative system and to weigh their relevance both on specific countries and on the entire sample.

Overall, the qualitative and quantitative data complemented each other, allowing identification of duplication of effort and measurement of the extent of differences across case studies. This part of the analysis and the indicators that inform it is partly based on a published methodological framework, analysing the quality of evidence, its interpretation and the factors beyond costs and effects that help shape or inform decisions (23, 24).

Coding was conducted systematically and homogeneously across all technology-indication pairs, such that they were also comparable across countries. The different phases of the decision-making process were coded with a specific set of 'code/name'. This was done in order to classify the evidence within which a number of criteria that had some influence over the decision-making process were identified. In so doing, we ensured that these phases were comparable across the study countries. The different stages identified comprised the following:

- First, the final decision/HTA recommendations were captured. Final HTA decisions were divided into three groups: (a) to 'List' the technology as requested in the HTA submission for the relevant indication (e.g. positive coverage recommendation), (b) to 'Restrict' the technology to a subgroup of the indication population or recommend use under certain conditions only (e.g. restricted coverage recommendation), and (c)

to 'Reject' the technology (e.g. negative coverage recommendation) for the indication applied for. In the case of a 'restricted' outcome, the restrictions listed for the use of the technology were also captured.

- This classification was applied to all the countries except Germany (IQWIG and G-BA) and France (HAS), where the decisions comprise an assessment of the extent of clinical benefit. In these two countries, recommendations are established according to the drug's medical benefit, with two scales in both. In France, the medical service rendered (SMR) comprises four levels and determines the extent of reimbursement, whereas the improvement in therapeutic benefit (ASMR), comprises 5 levels and informs price-setting. Free pricing, subject to a ceiling based on a European average, applies for ASMR I-III ratings under the condition that the price is similar to other European countries and treatment with ASMR IV-V ratings must price their Pharmaceutical product close to the price of the treatment alternatives, or at a discount. In Germany, the added benefit classification comprises six levels and has implications for pricing (Levels 1-4: price negotiation, Levels 5-6: inclusion in reference baskets and subjecting the product to reference pricing), whereas the level of proof, composed by three categories, gives a value to the clinical effects.
- Second, the clinical (number and type of trials, final reasons supporting the clinical benefit claims) and economic (type of cost-effectiveness analysis, comparator used and final reasons supporting the cost-effectiveness) evidence produced by the manufacturer or by the HTA body was recorded. This analysis would allow the identification of overlaps in the evidence considered across the agencies and whether assessments are correlated with the same or different preferences towards evidence (e.g. requirements for indirect comparisons) or other elements.
- Third, elicited and non-elicited value judgments and stakeholder input influencing the decision were also included. Key variables among them were the severity of disease, economic and emotional burden on patients and carers, innovation of the treatment and other diseases and therapeutic characteristics relevant in the final decision. This should provide an understanding of the extent to which ethical considerations and a broader societal perspective would exert an influence on the final HTA recommendation and how they are accounted for across countries.

5.2.3 Data availability for case studies

Overall, we identified 41 HTA bodies in 25 European countries (see Annexes 16, 17 and 18). In some countries (Austria, Bulgaria, Germany, Italy, Spain and UK) more than one HTA agency were included in order to showcase the key role played by regional HTA bodies in those countries. In the UK, NICE and SMC were selected, whereas in Italy, UVEF was selected as an example of a regional HTA body, while at national level, AIFA, the Italian Medicines Agency, was the default selection, since it plays a pivotal role in the pricing and reimbursement process. At European level, EUnetHTA was also considered in order to account for the joint assessment conducted by more than one country together. Luxembourg, Greece and Denmark were excluded from the sample for the reasons explained in section 5.2.1. We found that 11 countries (Bulgaria, Croatia, Cyprus, Czech Republic, Hungary, Ireland, Latvia, Lithuania, Malta, Slovakia, Slovenia) do not make their HTA reports publicly available, while Ireland only publishes a short summary of its HTA reports for a given technology-indication pair. The relevant HTA bodies in these eleven countries were contacted in order to obtain the HTA reports on the selected technologies. We received responses from Croatia (AZZ) and Ireland (NCPE) only. Even though Croatia shared all the requested reports, Ireland (NCPE) advised that due to confidentiality between the NCPE, the final decision-maker and the applicant (i.e. the company in question), the information of the Full HTA study would remain confidential and could not be shared with third parties. Therefore, data collection from Ireland was retrieved only in terms of the short summary documents that were available online. After consultation with the experts group, we further included in our sample of the HTA

bodies two new national agencies, Hauptverband from Austria and INAMI from Belgium, and contacted to obtain data, which is not publicly available and is needed for our data collection. Finally, OGYEI in Hungary were contacted again to obtain information on the HTA evaluations they perform. Overall, 34 agencies were included in the analysis.

HTA reports that were available in the language of their country of origin were translated into English for the purpose of our analysis. When reports were not publicly available, the EC, together with LSE, requested these from the relevant HTA countries via direct email contact.

Due to lack of available evidence (HTA reports), the sample had to be modified in two cases: 'HPV testing' in the Medical Devices sample and 'cryotherapy' in the 'Other Technologies' sample. In the case of HPV testing, the replacement was made because the specific test was often included in the evaluation of cervical cancer screening programmes and not evaluated as a medical technology per se and also already captured in the 'Other Technologies' sample. This device was substituted with 'gene expression profiling and expanded immunohistochemistry tests' with the same risk class of HPV testing and appraised by five HTA bodies. In the case of cryotherapy, the reports found in the initial screening were out of scope or fell in other categories (not 'Other Technologies') leading to a lack of data. This technology was replaced by 'seasonal influenza vaccination'. Finally, a few other adjustments were made to increase the accuracy of the sample and the assessing bodies; for instance, in the 'Other technologies sample', AOTMiT was excluded because HTA is performed at regional level and not at national level – more than one report being published across regions to evaluate a programme, resulting usually in different recommendations.

The final sample of 40 technologies is displayed in tables. The sample of the 20 Pharmaceutical technologies and their indications is shown on Table 22, while the sample of medical devices is presented on Table 23. Table 24 shows the sample of 'Other technologies'.

5.2.4 Cost data extraction methods

In order to capture cost-related data, LSE designed a section of the survey delivered by GOEG (see also 5.3.1). Questions endeavoured to capture the cost of performing HTA in different European countries. The cost section was tailor-made for HTA bodies and manufacturers, respectively, and aimed to obtain information on the different cost burdens by geography and by technology. The cost section was divided into four main sub-sections. The first sub-section addressed the general cost of performing HTA (HTA bodies) or submitting an application (manufacturers). The second sub-section aimed to capture the human resource costs of performing HTA. The third sub-section was designed to capture stakeholder costs and the implementation and dissemination costs of HTA bodies, while the fourth sub-section aimed to capture the costs of evidence generation and reassessment for manufacturers. This approach was adopted due to the lack of publicly available data on costs and the 'sensibility' for the industry regarding some data collected.

It is important to highlight that to capture the real magnitude of the costs related to HTA, this set of indicators was considered at the HTA agency and industry levels and not at the technology level. This was designed to capture the costs of performing HTA in different European countries, besides costs considered in regulatory settings.

Along with these, some costing data from Chamova 2017 (2) were used to validate and complete any missing information on HTA-related costs. Specifically, overall costs captured by this study were included and compared with the overall cost information obtained by our survey.

5.2.5 Interview methods

In order to supplement results obtained by the desk research and to better capture how HTA processes in different European countries influence the decisions and the business strategy of Pharmaceutical and medical technology manufacturers, a number of interviews across different Pharmaceutical and medical device companies were conducted.

For this task, a semi-structured interview guide was developed and used at each interview. The interview guide was structured in six main sections (see Figure 5 below), to capture different elements that might affect the market entry, and decision-making or data-generation processes of manufacturers (see Annex 15). For instance, the HTA country setting and practice (e.g. the possibility of appeal or resubmission), the delays related to the HTA submission (e.g. stop of the clock), the possibility of being engaged in an Early Dialogue or rapid assessment and any other relevant comments or examples of how the HTA process may have had an influence on the manufacturer decisions and market strategy, were discussed in the interviews. Manufacturers were also queried on their experience with EUnetHTA and their thoughts on the various Policy Options put forward by the EC.

Figure 5: Discussion topics of the interviews

In selecting manufacturers to conduct these interviews, due consideration was given to the case study sample size; we ensured that the majority of interviewee companies had at least one product in our case study sample. Both interviewees from Pharmaceutical and MedTech companies were included in the interviews, while consideration was also given to the size of companies (in terms of turnover) and the implications that this might have on their ability to perform and complete/submit HTAs across settings as required. As a result, we were able to include both large and smaller Pharmaceutical and MedTech

companies. In addition to the above, the study team received requests from other manufacturers and trade associations that did not have a case study product in our list of case studies and we were therefore in a position to enlarge our interview sample.

Interviews took place between mid-January and mid-March 2017. A total of 15 manufacturer-specific interviews were conducted either face-to-face or by telephone. In a number of cases, multiple interviews were conducted with individual manufacturers in order to capture different perspectives and ensure the widest possible coverage of topics. Participants were assured that all comments and insights provided would remain anonymous. When permission was granted, interviews were recorded to facilitate the subsequent analysis. If the participant did not provide permission to record, detailed notes of the responses were taken.

The interviews were conducted seeking opinion on six areas: (1) Experience with EUnetHTA; (2) Impact of national procedures on manufacturers; (3) Usefulness of Early Dialogue and rapid assessment; (4) Additional evidence generation and resubmission processes; (5) Impact on innovation and predictability; and (6) Thoughts on EC planned POs. Each interview response was screened for relevant insights in any of the six categories. After extracting relevant information from all interviews, common insights and feedback was aggregated across companies for Pharmaceuticals and for medical devices according to each thematic area. Four types of results are presented for each thematic area: Problem/Solutions, Positive Feedback, Negative Feedback, and Additional Insights. The results of interviews with Pharmaceutical manufacturers, including associations, are presented in 7.1.13.2. The results of interviews with MedTech Industry, including associations, are presented in 7.1.13.3.

5.3 Survey process – data collection on indicators for costs and investment and impacts of POs

5.3.1 Online survey

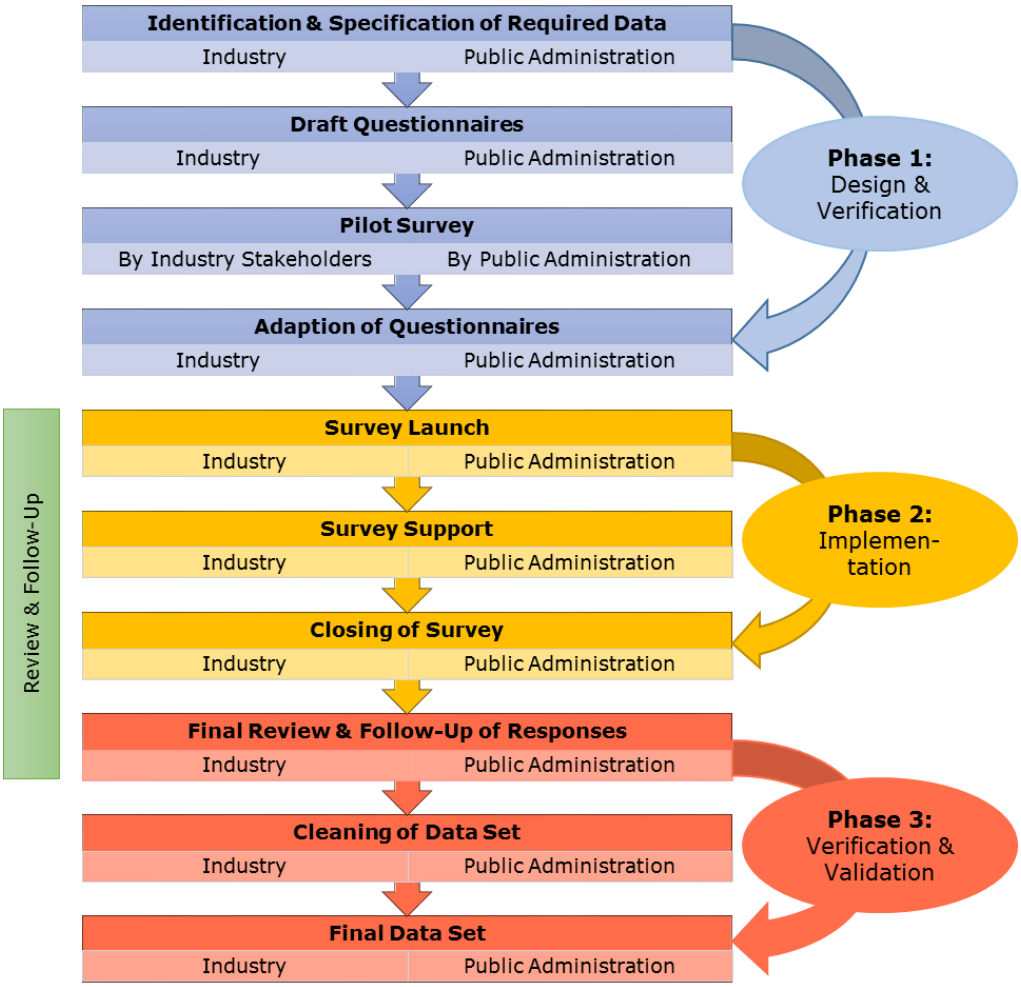
An online survey was performed with the aim to collect data on:

- **Costs of HTA processes**, e.g. Horizon Scanning, Early Dialogues, Relative Effectiveness Assessments or conduct of full Health Technology Assessments, provided by the respective stakeholders and
- **Effects** that different types of Policy Options might have on various indicators.

To keep the burden on the target group – especially in the light of other surveys including the public consultation conducted simultaneously – as low as possible, the project team decided together with EC/CHAFEA to have one survey covering both aspects. There were two questionnaires, adapted for Industry and Public Administration (other organisations).

The development and conduct of the online survey was set up in three phases and subdivided into several tasks (see Figure 6).

Figure 6: Overview of online survey process for industry and Public Administration questionnaires



Phase 1 **'Design & Verification'** started with identifying and specifying the required data from industry and Public Administration.

The heterogeneity of authorities and stakeholders addressed and their expected different perspectives led to the decision to set up two different questionnaires, one for industry stakeholders and one for Public Administration, which both followed the same format (see below).

Both questionnaires (see Annex 3 and 4) consisted of four parts:

- **Part 1** included general questions on the respective organization
- **Part 2** included questions related to the costs of HTA processes
- **Part 3** provided an overview of the different POs available to continue cooperation on HTA at EU level beyond 2020
- **Part 4** aimed to assess the respondents', i.e. organizations', perspective to estimate a potential impact on the respective indicators

The questions in Part 1 and Part 2 differed between the two questionnaires and were adapted to the respective stakeholder group (industry vs. Public Administration) taking the divergent characteristics of the HTA sector and cost components for each stakeholder

into account. Part 3 and Part 4 were identical to ensure comparability of different stakeholders' perspectives.

To capture cost-related data, LSE designed Part 2 of the survey and questions endeavoured to capture the cost of performing HTA in different European countries (for more details see 5.2.4).

The questions regarding the impacts of the different Policy Options (Part 4) were developed by GÖ FP and guided by the requirements provided within the EC's Better Regulation Guidelines (4, 5) which state several key impacts to consider. Table 9 depicts the included economic and social/health impacts. Details on the specific indicator for each impact can be found in the questionnaires (see Annex 3 and 4).

Table 9: Overview on key impacts in the survey (each impact parameter was represented by one or more indicators)

Economic impacts (EC)	**Social/health impacts (SH)**
Costs	Employment (labour market)
Administrative burden	Governance, participation and good administration
Competitiveness of EU health technology sector	Access to social protection and health systems
Innovation and research	Sustainability of health systems
International Trade	Public health
Functioning of the internal market and competition	
Consumers and households	
Macroeconomic environment	

After drafting the questionnaires for industry and Public Administration, two online questionnaires were established using the online survey tool 'Questback'®.

As a next step, the questionnaires underwent a piloting process. Different members of the consortium and other colleagues not involved in the study tested the feasibility of the questionnaires. Moreover, industry stakeholders from both, the Pharmaceutical and MedTech, sectors piloted the industry questionnaire, whereas the Public Administration questionnaire was piloted by a representative of an HTA institute. The piloting parties submitted their feedback to the questionnaires which was subsequently incorporated. In general, the feedback was positive although the questionnaires were considered quite complex. Given the short time frame, no alternative procedure was available. The layout of the questionnaires was adapted at some parts to enhance consistency.

Phase 2, **'Implementation'** started with launching the survey in mid-December 2016. To fully capture the costs of HTA processes and the impacts of the different Policy Options, the survey was distributed to a variety of stakeholder groups. These included MS authorities (government, HTA bodies, pricing and reimbursement bodies), industry (e.g. Pharma, medical technologies and other technologies), patient groups, healthcare providers (doctors, hospitals) and payers (health insurers, public health schemes).

For distributing the online questionnaire, a top-down process was used, addressing organizations at EU level and asking for their support to distribute the survey to the respective organizations or national responsible authorities. This approach was chosen to maximize the number of possible respondents. Contacts with industry associations at EU level and EUnetHTA Joint Action (JA) members were established prior to the survey launch to inform them about the upcoming survey. Moreover, a short informational

document (a 'two-pager') was sent prior to the survey launch, customised per stakeholder group.

Table 10 depicts the stakeholder groups and organisations the survey was distributed to, channelled through DG SANTE. For approaching these organisations, DG SANTE sent an email invitation including a short description of the survey, stating the objective and aim of the study, a link to the online questionnaire, short information on the structural issues of the survey tool (e.g. the possibility to go back and forward in the questionnaire) and the survey deadline of 22 January 2017. Moreover, the invitation email contained two attachments, an outline of the questionnaire and a short overview of the study.

Table 10: Overview of approached stakeholder groups

Stakeholder group	Organisation to which invitation for survey was sent for further distribution	Specific stakeholder group
Industry	EFPIA EUCOPE Medicines for Europe	Pharmaceutical sector -> distributed questionnaire to Pharmaceutical companies throughout Europe
	Medtech COCIR	Medical technologies sector -> distributed questionnaire to MedTech companies throughout Europe
	EuropaBio	Biotech sector-> distributed questionnaire to biotech companies throughout Europe
Public Administration	Ministry of Health/Health Attachés -> all MS HTA bodies -> all MS	HTA Network
	ESIP AIM	Payers
	EUnetHTA	distributed by EUnetHTA to all members
	EURORDIS EPF EU Patient	Patients
	HCD Economics University of Chester	Academic /Consultancy Sector

Simultaneous to the survey launch, survey support by GÖ FP commenced. The survey team provided support by email and by telephone to answer questions regarding technical issues as well as questions regarding the content of the online questionnaire. This service was used by several industry and Public Administration and several issues were raised – for example, regarding the framework, methodology and design of the questionnaire. In specific cases, telephone conferences with respective stakeholders were organized and answers were provided by the survey team of the consortium and representatives of DG SANTE.

Due to requests by both industry and Public Administration respondents, an extension of the period was granted and the survey was finally closed on 16 February 2017. Beforehand, two reminders were sent via E-Mail.

After closing the survey, the **'Verification & Validation'** phase started with a final review of survey responses. Throughout the duration of the survey, responses were checked for completeness and early follow-up was performed to maximize the number of responses. All respondents who did not complete the whole questionnaire were addressed by e-mail (if available) and asked to complete all parts. Moreover, persons that provided their e-mail but no further input were addressed.

The follow-up showed that some survey participants announced to disregard their previous response and that a new response would be submitted in the near future. Other survey participants asked if it was possible to receive the answers already indicated in order to continue. Several respondents from the Pharmaceutical and medical technologies industry and Public Administrations invested time to send comprehensive feedbacks by email and explain their organizations' perspective on the study and the survey.

After completing the follow-up, the data set was cleaned to retrieve a final data set for analysis. The adjustment of the data set included following tasks:

- Deletion of responses if explicitly demanded by survey participants
- Deletion of incomplete responses by participants who provided complete responses at a later time (considering responses received through the follow-up)
- Merging of incomplete responses with continued response at a later time

After obtaining the final dataset as described in part 5.3 and a first analysis of its features, several adaptions regarding the categorisation of stakeholder groups were made in order to facilitate further analysis.

Regarding the data of Public Administrations and other organisations, survey respondents were initially given eight options for indicating the type of organization. For correct analysis, the authors checked the responses for consistency within the respondents. Moreover, the responses were cross-checked with the self-categorisation given at the Open Public Consultation run by DG SANTE and the mapping study of HTA national organisations, programmes and processes done by Julia Chamova, which feed into the Impact Assessment process. Finally, four categories representing the survey participants were established, namely 1) Public Administration, 2) Academia, 3) Payers and 4) Patient Organization.

When answering to the online survey, industry stakeholders had the possibility to indicate to belong to the Pharmaceutical sector, the MedTech sector or to be operating in both sectors. Moreover, they could indicate the category 'other' and then specify. Since the group of companies that stated to be operating in both sectors or to belong to the category 'other' was quite low, these companies were categorised in line with their main business branch ([32]). As a result of the categorisation, a total of 13 companies were assigned to the medical technologies sector and 2 companies to the Pharmaceutical Industry. Company representatives were notified by email about the categorisation and asked for their consent.

([32]) Companies were informed about this re-categorisation and did not object.

5.3.2 Responses to the online survey

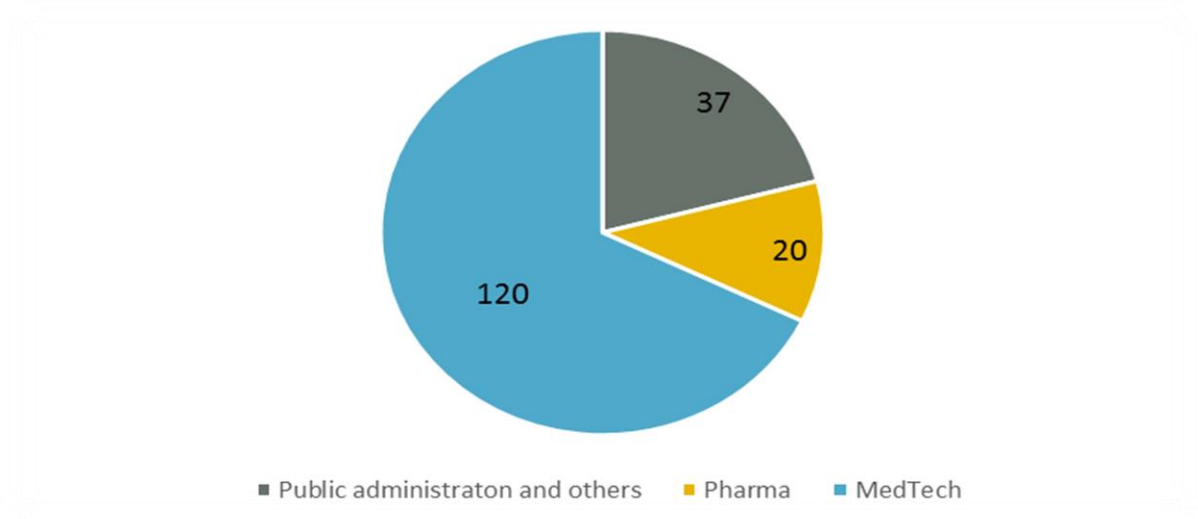
An overview about respondents to the online survey is summarized in Figure 7, including all respondents who:

- Provided solely information on the **costs** for HTA processes (Part 2 of the online survey),
- Provided solely information on the **impacts** of the different Policy Options (Part 3 and 4 of the online survey), or
- Provided information on **both parts**.

Therefore, the number of respondents differs between the datasets used for the assessment of impacts and cost of business options.

Altogether, **120 MedTech industry stakeholders, 20 Pharmaceutical Industry stakeholders and 37 stakeholders representing Public Administration and other organisations (177 in total)** participated in the online survey by responding to at least one of the parts (as stated in Figure 7).

Figure 7: Number of survey responses by stakeholder group (total n=177)

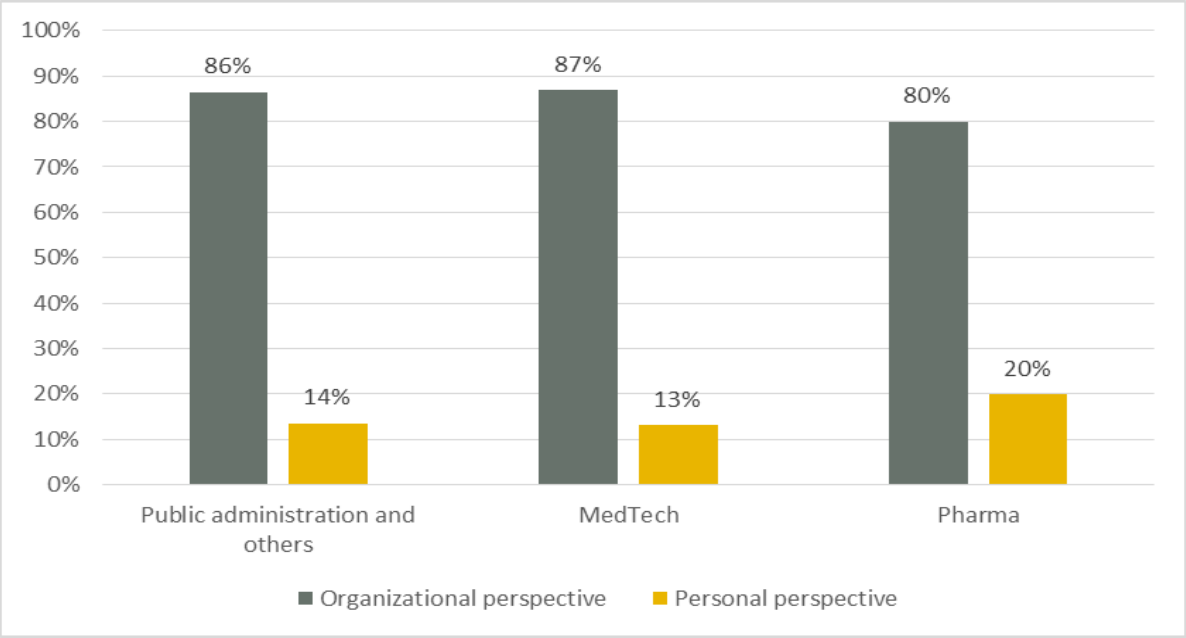


Source: GÖ FP / LSE survey 2017

Looking at the type of perspective of survey participants, 86% of the 37 respondents of Public Administrations and other organizations responded from an organisational perspective, while 14% responded from a personal perspective.

With respect to industry stakeholders, 87% of 120 survey participants from the MedTech industry indicated responses from an organisational perspective and 13% from a personal perspective. With regard to the Pharmaceutical Industry, 80% of 20 survey participants responded from an organizational perspective and 20% from a personal perspective (see Figure 8). In the analysis of responses, no distinction was made between individual and organisational responses.

Figure 8: Perspective of responses by stakeholder group



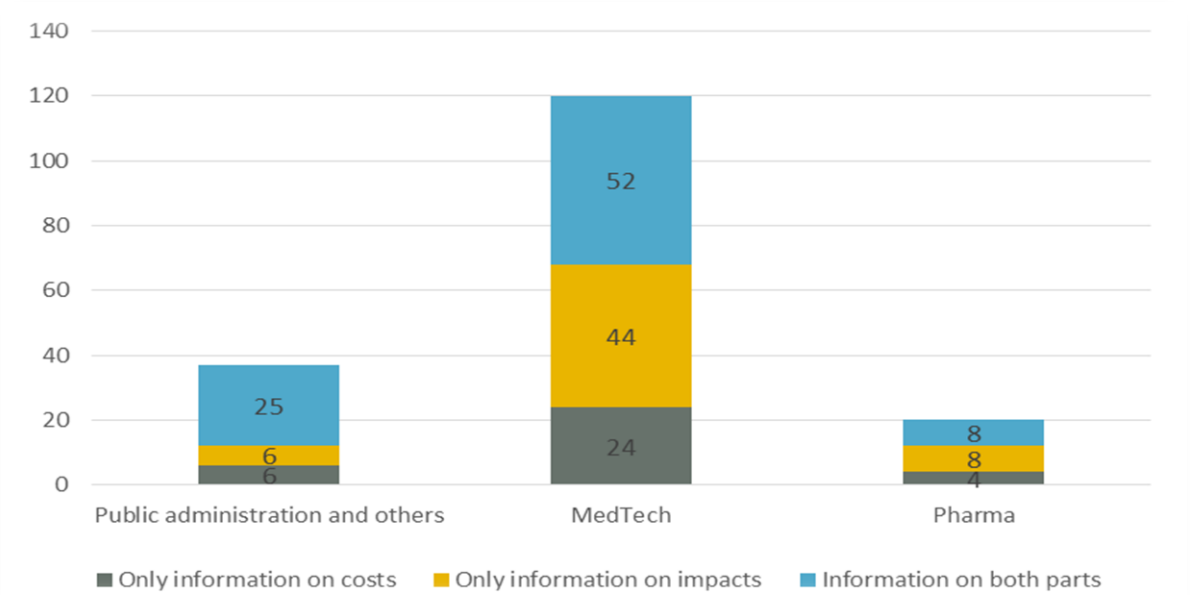
Source: GÖ FP / LSE survey 2017

Despite the extensive follow-up on incomplete responses by the authors, some respondents only indicated answers for certain parts of the survey. Either respondents, irrespective of the stakeholder group, indicated information on costs, on the impacts, or both. Some respondents provided reasons for this selective answering behaviour. For example, some stakeholders were not allowed to study costs (although they would have been treated as confidential) and other stakeholders reported that they were not in the position to have an opinion on the questions raised when assessing economic and social/health impacts.

Relating to the Pharmaceutical Industry, **out of 20 respondents, four** completed the questions on **costs, eight on the impacts and eight responded to both parts.** Regarding **Public Administrations and other organizations, from the total of 37, six respondents** answered in each case to the **part on costs/impacts only,** whereas **25 provided information on both parts.**

In conclusion, the industry respondents were less likely to respond to the cost part than the Public Administrations (which is likely to be due to the confidential nature of industry costs, which is not an issue for many publicly funded organisations). Figure 9 provides an overview of how many respondents stated information on the respective parts of the questionnaires, separated for the medical technologies industry, the Pharmaceutical Industry and Public Administration and other organisations' respondents. **Out of 120 respondents of the MedTech Industry, 24 respondents reported information on costs only, 44 on impacts only and 52 reported information on both the costs and the impacts.**

Figure 9: Number of responses by level of information per part per stakeholder group



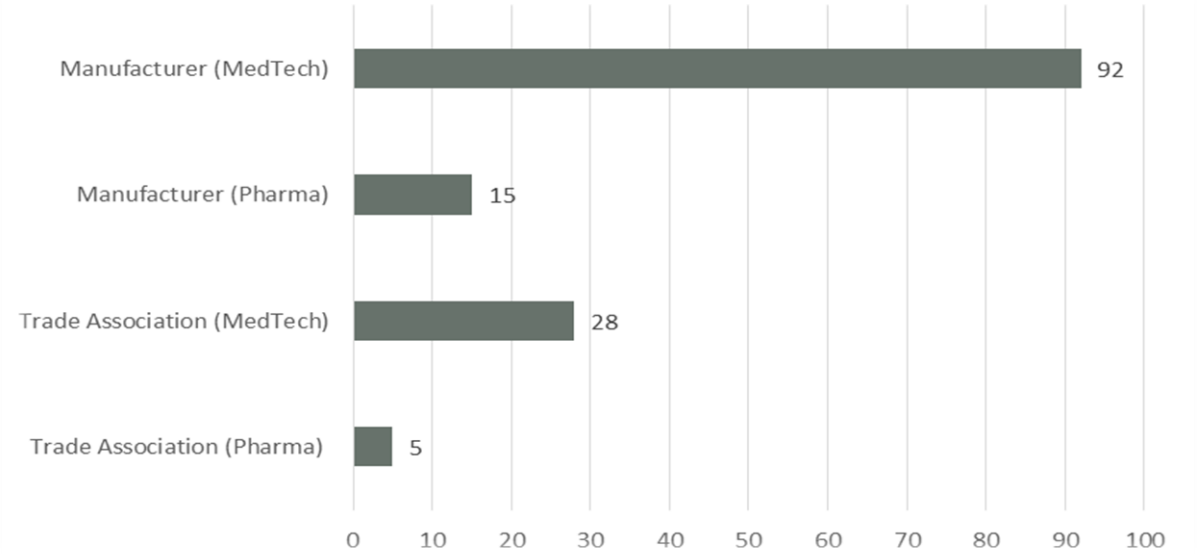
Source: GÖ FP / LSE survey 2017

Focusing on industry stakeholders, different industry sectors and types of organisations were approached. First, a distinction of companies between Pharmaceutical, medical technologies and other technologies was made in order to assess potentially differential perspectives. Secondly, industry stakeholders were asked to indicate the type of organisation, i.e. whether they represent a manufacturer or a trade association. With these two pieces of information gathered through the online survey, respondents were further categorized, aiming to display the split of respondents by Manufacturers for each product scope and Trade Associations for each product group ([33]).

Figure 10 shows the distribution of respondents according to these groups. In total, 107 of the respondents stated to be manufacturers and 33 trade associations. Out of the 107 manufacturers, 92 operate in the medical technologies sector and 15 in the Pharmaceutical sector. With respect to trade associations, 28 represented the medical technologies industry and five the Pharmaceutical Industry.

([33]) In total, eight respondents stated they were from another sector, but were grouped to the Medical Device sector based on their indicated field of work.

Figure 10: Number of responses by type of organization and industry sector



Source: GÖ FP / LSE survey 2017

While the number of respondents from the Pharmaceutical sector is considerably lower than that of the respondents from the MedTech sector (20 vs 120), looking at the respondents, it can be concluded that the major players of the sectors are well represented in the survey as 11 of the 20 biggest Pharmaceutical companies responded. Table 11 and Table 12 provide an overview about the contribution of the Pharmaceutical Industry to the survey and/or the case study and display the degree of contribution by the world's 20 biggest Pharmaceutical companies (highlighted in green) ([34]).

([34]) According to www.statista.com, 2015.

Table 11: Overview of participation in survey by Pharmaceutical companies

Company / Trade Association	National/ International	Answered part of questionnaire on:	
		Costs	Impacts
AbbVie	International	Yes	No
Biogen International GmbH	International	Yes	Yes
Boehringer Ingelheim	International	Yes	No
Celgene	International	Yes	Yes
Da Volterra	International	Yes	No
Eli Lilly & Co	International	Yes	Yes
Esteve	International	No	Yes
F. Hoffmann-La Roche AG, Pharma Division	International	Yes	Yes
Janssen: Pharmaceutical Companies of Johnson & Johnson	International	No	Yes
Medac GmbH	International	Yes	No
Merck	International	Yes	Yes
Novartis Pharmaceuticals	International	Yes	Yes
Novo Nordisk	International	Yes	Yes
Pfizer	International	Yes	Yes
Teva Pharmaceuticals	International	No	Yes
Trade Associations		**Part not asked to trade association**	
Dutch Association Innovative Medicines	National	-	Yes
EFPIA	International	-	Yes
Irish Pharmaceutical Healthcare Association	National	-	Yes
Legemiddelindustrien (LMI)	National	-	Yes
Pharmig	National	-	Yes

Green indicates members of the TOP-20 Pharmaceutical companies by sales in 2015 (www.statista.com)

As presented in Table 11**, the majority of big Pharmaceutical companies participated in the survey, the case study or both.** Four of the major Pharmaceutical companies, Sanofi, Allergan, Amgen and Shire, did not participate in any part of the data collection and did not express their interest in participating.

Referring to Table 12, **nine of the major Pharmaceutical companies were covered by the case study**. Moreover, additional companies expressed their interest in an interview in the framework of the case study. For details, please see part 7.1.

Table 12: Case study participants of Pharmaceutical Industry

Company	National/ European/ International
Astellas Pharma Europe B.V.	European
AstraZeneca AB	International
Bayer Pharma AG	International
Boehringer Ingelheim International GmbH	International
Bristol-Myers Squibb	International
Celgene Europe Limited	European
Eli Lilly Nederland B.V.	European
Gentium S.r.l.	International
Genzyme Therapeutics Ltd	International
Gilead Sciences International Ltd	International
Janssen-Cilag International N.V.	International
Novartis Europharm Ltd	European
Otsuka Pharmaceutical Europe Ltd	European
PTC Therapeutics International Limited	International
ThromboGenics NV	International
Vertex Pharmaceuticals (Europe) Ltd	European

Green indicates members of the TOP-20 Pharmaceutical companies by sales in 2015 (www.statista.com)

The following table shows the top 10 MedTech companies and their participation in the survey. With six out of the 10 biggest MedTech companies, more than half of these were represented in the survey, some of them with multiple replies from different countries. Since MedTech companies often fall into the category of small- or medium-sized companies, the representation of large companies can be seen as sufficient.

Table 13: Overview of participation in survey by top 10 MedTech companies[35]

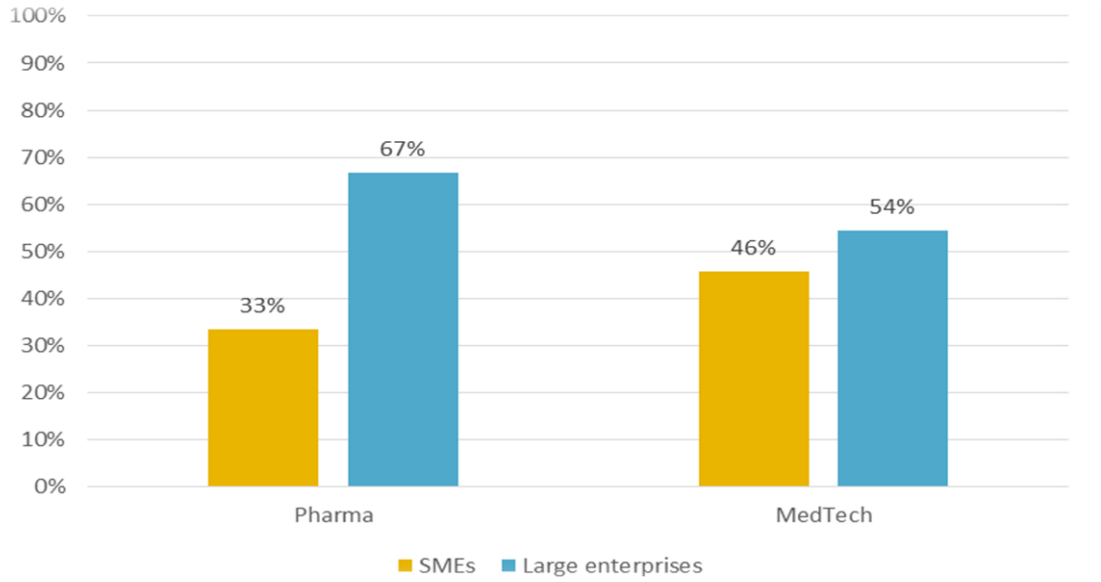
Company / Trade Association	National/ International	Answered part of questionnaire on:	
		Costs	Impacts
1 Medtronic	International	Yes	yes
2 Johnson & Johnson (medical device segment)	International	Yes	yes
3 Philips Healthcare (Royal Philips Electronics)	International	No	yes
4 GE Healthcare(General Electric)	International	No	Yes
5 Fresenius (medical care segment)	International	Yes	Yes
6 Siemens Healthineers (Siemens)	International	No	No
7 Cardinal Health (medical segment)	International	No	No
8 Becton, Dickinson (medical segment)	International	Yes	Yes
9 Baxter (medical products segment)	International	Yes	Yes
10 Stryker	International	Yes	Yes

Green indicates members of the TOP-10 MedTech companies by sales in 2015 (www.statista.com)

Looking at the participation of SME (small- or medium-sized) Pharmaceutical and medical technologies manufacturers (see Figure 11), **33% of 15 Pharmaceutical companies were small- or medium-sized and 67% large companies**. Regarding the **medical technologies industry, 46% of 92 companies were small- or medium-sized, whereas 54% were large** companies.

([35]) Medical Design & Outsourcing annual 2016.

Figure 11: Responses by company size for Pharmaceutical and MedTech manufacturer



Source: GÖ FP / LSE survey 2017

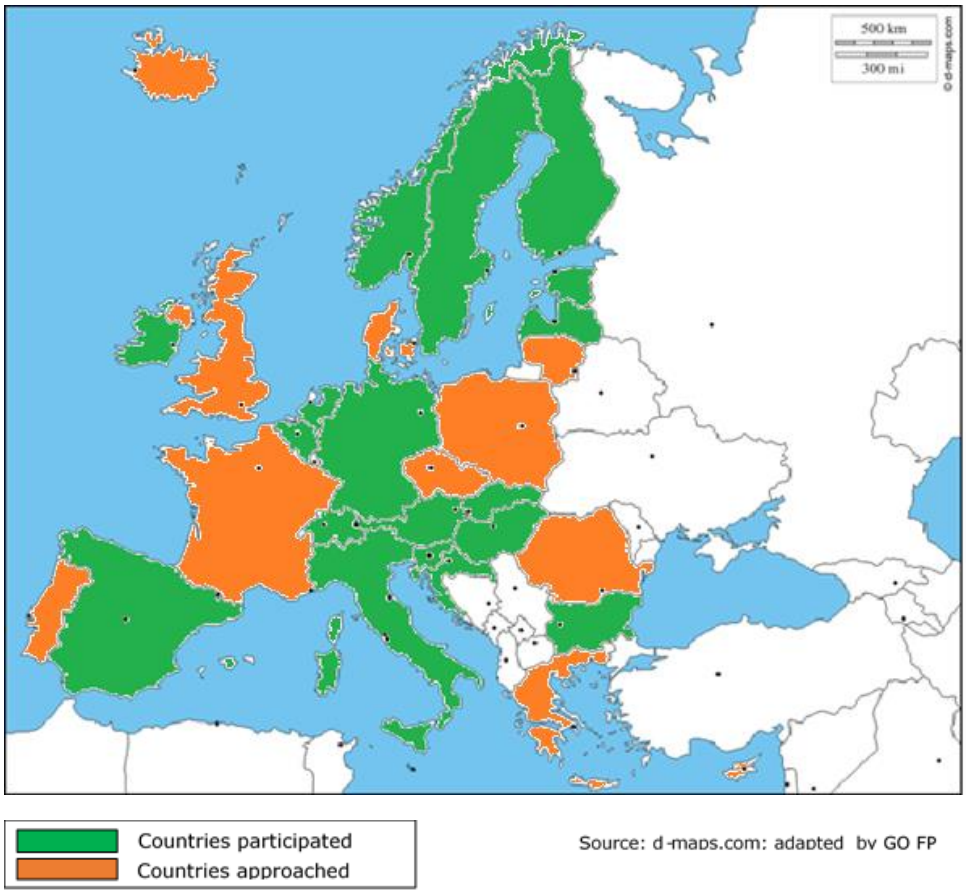
With respect to Public Administrations and other organizations, Figure 12 illustrates the level of participation across the addressed countries.

Respective organizations of countries marked in green were approached and participated in the survey, while countries marked in orange were approached but did not respond to the survey. We received responses from **19 different countries, meaning that 62% of all addressed countries submitted at least one response**.

Overall, **a good geographic distribution is visible, covering both large and small countries as well as different types of HTA systems**.

When comparing the participating institutions of Public Administration with the taxonomy of HTA systems described in section 6.1, **each type of HTA system is represented by at least one body.**

Figure 12: Participation of Public Administrations and other organizations



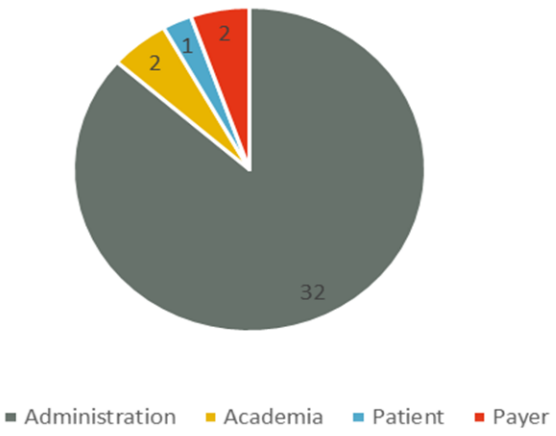
The highest number of survey responses for Public Administration was obtained by **Spain**, **followed by Italy**, which might be due to the high number of regional HTA bodies in these countries.

When it comes to arm's-length bodies, two responding countries are clustered to this HTA system with advisory role, three responding countries to a regulatory role and eight responding countries are clustered to an HTA system with an arm's lengths body with coordinating role.

HTA systems with an incorporated or integrated HTA function are represented with one country that has an independent HTA function within an insurance body and five countries that have an incorporated or integrated HTA function, thereby using HTA to determine pricing or coverage decisions.

Two of the responses were given by European Associations, namely the European Society of Cardiology and the European Patients' Forum. The participation rate by patient groups was low, but one explained, for instance, that they focussed on replying to the Public Consultation that was ongoing in parallel instead. Moreover, the first part of the questionnaire (cost of HTA processes) was not relevant for such organisations.

Figure 13: Number of responses by type of organization for Public Administration and other stakeholders



Source: GÖ FP / LSE survey 2017

Similar to the distinction by organizational type and sector for industry stakeholders, stakeholders of Public Administration and other organizations had to indicate the type of organization as well.

32 representatives of Public Administrations participated, two responses were received from academia, two from payer organizations and one representative of a patient organization responded to the online survey (see Figure 13).

Due to the low number of responses from academia, patients and payers, it was decided that these responses are treated individually and in the overall analysis will focus on the administrations (HTA bodies).

5.3.3 Limitations and challenges

Despite all efforts regarding a sound methodical approach the contractors and the EC/CHAFEA project, officers were faced with several challenges during the project. The contractors took a number of measures to mitigate risks as much as possible (see 5.4), but some of the challenges arising were caused by the overall context of the study.

Examples are several parallel activities and ongoing surveys ([36]) that caused a high burden of work to some members of the target group and made huge efforts necessary to obtain a significant number of responses and input.

Even with all efforts to communicate the objectives, tasks and expected deliverables of the study (including a number of additional meetings and personal talks with both members of industry and Public Administration), some participants have found the online survey very complex and difficult to respond to.

([36]) Several other researchers conducted studies in the field of HTA in 2016 that also included surveys for data collection and involved similar stakeholders. Secondly, the public consultation issued by the EC shortly before this survey resulted in respondents mixing up these two separate undertakings that served two different purposed (evidence generation vs. collection of opinions).

This is illustrated by the following issues raised by respondents and within the expert group meeting:

- The survey on impacts captured expectations and opinions of stakeholders, rather than facts about the future and should be interpreted as such. However, due to the nature of impacts investigated it was not possible to gather 'hard facts' for some of the indicators, especially because effects between indicators are interwoven
- Regarding the planned methodology, some respondents called for sensitivity analysis (which was performed and planned from the beginning) and questioned the accuracy of the metering scheme from -100 to +100 in Part 4 of the questionnaire. It was pointed out that the results show general trends, but should not drive quantitative conclusions.
- Respondents claimed to be overwhelmed with the complexity of the questionnaire, citing complex Policy Options and the large number of indicators (note: indicators are based on the EU 'Better Regulations Guideline' (5) which requires the assessment of a number of impacts).
- At the same time, it was stated that the options described mainly the legislative framework, but not how the system would function (e.g. whether the new system would work centralized and efficiently or whether it would become an ineffective bureaucracy, or how it would affect the quality of the reports).
- The non-applicability of the survey to some stakeholders was addressed, e.g. small- and medium-sized MedTech companies who do not perform HTAs.
- It was questioned whether separate questionnaires for Pharmaceuticals, medical technologies or other technologies should be given.
- Technical issues were raised, e.g. on the required format of response or accessing the online questionnaire.

Another major challenge was that, at the time of the survey's development, the planned Policy Options were not fixed and were thus slightly modified in collaboration between EC Services and the contractors. Furthermore, a number of respondents claimed that they would have rather commented on the different business models separately and not in combination with one of the Policy Options. This led to different interpretations by the respondents and a need for cautious interpretation of results by the project team. However, evaluating both Policy Options and Business models in one step was necessary to minimize complexity and was in line with the assignment.

Finally, we want to point out that the topic is of high (political) relevance to industry, MS, EC services and other stakeholders such as patients with very differing ideas and perceptions of the role of HTA in national systems and Europe. Despite all efforts in communication it is clear that some of the positions cannot be converged easily. This explains some of the concerns expressed.

5.3.4 **Focus groups**

As a follow-up to the online survey focus group meetings were set up with stakeholders from Public Administration and industry to discuss the results of the online survey and to gather additional insights and feedback to the findings.

Three meetings were set up in Brussels: one for Public Administration, one for the Pharmaceutical Industry and one for the medical technologies industry.

All survey respondents from the Pharmaceutical Industry and all survey respondents from the Medical technologies industry, which also answered to the follow-up question on HTA experience, were invited by email. For the focus group meeting with Public Administration, one meeting of the EUnetHTA Executive board was utilized and results were discussed with these experts.

In all three focus group meetings results for the following impact topics were discussed:

- Costs
- Administrative burden
- Innovation and Research
- Public Health
- Sustainability of health systems

A similar structure was followed for each meeting. First, the study team presented each impact, showing only the results of the respective stakeholder group within a power point presentation. After each presented impact, experts were asked for open feedback first. Afterwards, specific questions were asked by the study team in case of specific issues that needed clarification.

Minutes were taken compiling the discussed items and conclusions drawn within the discussions. These were shared with the members of the focus groups afterwards and are included in Annex 6, 7 and 8.

Overall, the findings of the study were confirmed by the focus groups with some specific remarks. The details are included in the relevant sections of the description of impacts.

5.3.5 Limitations

A number of limitations arise from the methodological approach outlined in the previous sections.

First, the research analyses HTA recommendations rather than final coverage decisions. If the HTA body has an advisory role, the final decision-maker may or may not adopt the recommendation in the final coverage decision. In practice however, evidence suggests that HTA recommendations are translated into final decisions and are implemented.

A second limitation is the different level of detail in the evidence across the different HTA bodies. For example, TLV often do a public-only short summary of the decision, leaving out a significant amount of detail. The publicly available HTA reports, which have been analysed in this study, may not contain all the information and discussions that were associated with the final decision. However, the main reasons for the final recommendations were clearly identified in all the reports. As a result, and despite different levels of detail being provided, the evidence base compiled offers a good overview of the different decision-making processes.

A third limitation is the assumption around transparency in the decision-making processes from HTA bodies, as the study focuses mainly on secondary evidence and the publicly available HTA report(s) and information provided to justify the decision. Information about the context within which the decision was taken may not have been captured.

Fourth, there are a number of limitations relating to the data collection process specific to HTA processes. Several gaps were identified in compiling the indicator table; these were mainly around two areas: first, the timeline for HTA and final decision and second, delays incurred during the HTA process, e.g. 'stop of the clock' situations. On a number of occasions, the date of the dossier submission to the HTA body and the date of pricing and reimbursement decision were not publicly available or were not possible to retrieve from HTA body websites. Additionally, it was not possible to capture information on the delays faced by the companies in the submission of HTAs, such as the number and the length of 'stop-the-clock' situations. In an attempt to capture some of this information, tailor-made questions were added to the survey as well as the interviews. However, these questions aim to capture these data from the technology developer and HTA body points of view, rather than at the technology-indication level.

Fifth, there were a number of functional differences across HTA bodies and different levels of transparency, which exerted an influence on the analysis. For example, HTA agency roles are not homogeneous. HTA processes also differ across countries and this may give rise to the problem of comparability across HTA appraisals. For example, in countries with a well-established HTA system (e.g. France, Sweden, UK and Germany), it was possible to clearly draw common points between HTA appraisals, whereas the same common points were not present in countries where HTA processes are supplementary to national reimbursement decisions (e.g. Austria) or were integrated into a broader model of reimbursement, where HTA is one of the criteria (e.g. Italy). This difference in competences and processes is also reflected in the different level of detail across the different HTA bodies. For example, TLV often compiles a public-only short summary of the decision, leaving out a significant amount of detail. The publicly available HTA reports, which have been analysed in this study, may not contain all the information and discussions that were associated with the final decision. Different levels of transparency in the decision-making processes of the HTA bodies may help explain gaps in the data. Indeed, some HTA bodies do not publicly share their timeline in assessing a medical technology; finally, some information is kept confidential following requests from the technology developer. Despite the above, the main reasons for the final recommendations were identified in all case study reports. We can, therefore, conclude that despite different levels of detail being provided, the results offer a good standard of the key elements the led to and/or influenced the decisions at HTA level.

5.4 Further actions undertaken for data collection

Several actions were undertaken in the course of the study to maximize the amount and the reliability of data, facts and figures gathered by different data collection processes.

With regard to the **case study**, several requests to HTA bodies across Europe were made in the course of the study, asking for HTA assessments that were not publicly accessible. This aimed at maximising the number of HTA assessment per technology-indication pair.

Several members of HTA bodies remarked that questions regarding the current **costs of HTA processes** (Section 2 in the online survey) were too detailed for them to respond to, since only data on a more aggregated level could be provided. Therefore, an additional questionnaire was set up to survey the different cost components of performing HTA on a more aggregated level. This questionnaire was sent to EUnetHTA members, aiming to increase the available amount of data for assessing the baseline costs of this stakeholder group (see Annex 23). In total, eight responses were received to this follow-up questionnaire in addition to the responses received in the survey**.**

In order to increase the soundness of **survey responses**, follow-up questions were launched for companies of the MedTech industry in order to allow for more in-depth analysis. Respondents to the online survey received three follow-up questions with the intention to assess their level of experience with HTA processes. They were asked if their company:

- Was involved in an Early Dialogue process with at least one product in the EU/EEA
- Had an HTA submission for at least one product in an EU/EEA country
- Why Policy Option 3 was rated to be significantly more expensive than Policy Option 2, asking for a brief explanation

24 company representatives responded to this follow-up. Five companies were involved in an Early Dialogue and a HTA submission with at least one product in the EU/EEA region, eight survey participants indicated being neither involved in an Early Dialogue nor in a HTA submission with at least one product in the EU/EEA region, and 11 companies stated that they were not involved in an Early Dialogue but had at least one product subject to HTA in the EU/EEA region.

Follow-up questions to focus group meetings (5.3.4) were addressed to industry representatives of both industry sectors.

For Pharmaceutical companies, this included the following questions: 'Can you give us further information on additional data that is requested by HTA bodies in the context of a REA/Full HTA process? In particular an estimate how often it is required; typically by which MS; through which way was this collected; and any further information on the costs'.

MedTech companies were approached with the questions: 'How do you define transformative medical technologies? Could you please give examples for these? Do you have an estimation about their number per year?'

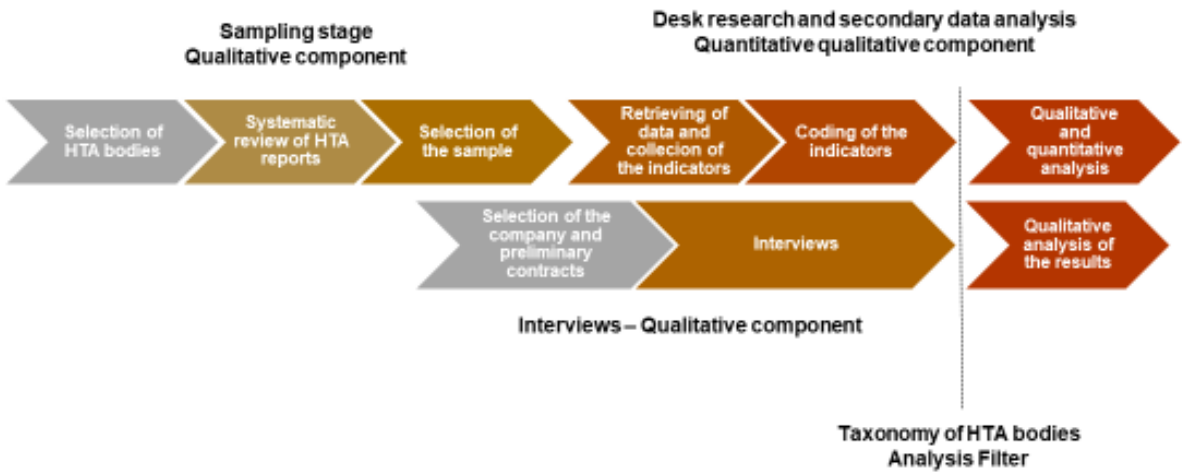
Due to the low response rate of stakeholders in **patient organisations**, an additional follow-up was started to collect further information. The follow-up included interviews with three representatives of patient organisations, consumer organisations and public health cooperatives at EU level.

6 Analytical approach

6.1 Baseline scenario

The aim of the case studies is to systematically capture and depict the elements composing the status quo of HTA across EU MS. In order to capture the baseline scenario of HTA bodies in the Europe Union, a multistage mixed qualitative-quantitative analytical approach was adopted. The different stages are shown in Figure 14 and comprise a sampling phase, a desk research and analysis of secondary data stage, a round of interviews and a final quantitative and qualitative analysis of the data retrieved.

Figure 14: Analytical approach baseline scenario



This approach was adopted in order to understand the variability in methods and processes currently employed by different HTA bodies across the EU and to capture duplication of efforts in HTA by combining quantitative and qualitative elements.

For the sampling phase, a systematic review of HTA reports was conducted. This aimed to maximise the information from the sample as well as fulfil all selection criteria. Additionally, it enabled the selection of an objective sample, representing – as much as possible – the heterogeneity of HTA processes and eliminating the need for data validation by the respective agencies. The HTA body perspective, rather than the industry perspective, was considered in our selection.

The next phase in the HTA data collection and analysis was based on a standardised analytical framework developed and applied to compare and evaluate HTA evidence using a mixed methods approach ([51, 52]).

This framework was adapted to fulfil the scope of this study. It enables the translation of qualitative information into quantitative data by coding a set of variables contained in HTA reports. Breaking down the HTA decision processes into three key stages, the framework enables an in-depth understanding and systematic comparison of HTA evidence across countries, including criteria accounted for within, e.g. clinical trials, cost-effectiveness model and beyond, e.g. stakeholder influence or social value judgements, standard methods of HTA. The criteria selected to perform the analysis matched the key components required by the indicators identified comprising: (1) the clinical and economic evidence; (2) the timeline of the process; (3) the inclusion of external considerations and stakeholder opinion; and (4) the final decision/recommendation.

The first component enabled an understanding of the type and the quantity of evidence considered across countries, while the second dealt with the timeline of the process from Marketing Authorization (MA) to HTA decision/recommendation. The third component analysed the value judgments made throughout the assessment process and stakeholder input considered by HTA bodies, while the final component provided information on the final recommendation and different effects on market access (economic and clinical limitations).

In order to capture the level of agreement by different HTA bodies across Europe, Cohen's Kappa scores were calculated across the sample, providing a measure of the degree to which two or more bodies concur in the type of assessment of the studied technologies and the final decision (25). By examining the inter-rate reliability coefficient calculated using the Kappa statistic, it was possible to assess the level of agreement across different HTA bodies. Independently of the Kappa score, the proportion of agreement between some agencies were also calculated within each of the Kappa's categories separately in order to overcome the 'Kappa paradox' (26).This paradox causes the Kappa statistic to be estimated in a distorted manner, especially when the sample of assessed technology-indication pairs is different across countries and assumes values that often lead to underestimation of the actual concordance present in the data. In order to overcome this, a sample of technology-indication pairs was selected that is common across the highest number of agencies to showcase the level of agreement/concordance and disagreement.

The interpretation of Kappa values is performed based on the following guidelines: $K<0.2$ = poor agreement; $0.21<K \leqslant 0.4$ = Fair agreement; $0.41<K \leqslant 0.60$ = Moderate agreement; $0.61<K \leqslant 0.80$ = Good agreement; $K> 0.80$ = Very good agreement (Table 14).

Table 14: Kappa score agreements level

Poor agreement	<0.20
Fair agreement	0.21-0.4
Moderate agreement	0.41-0.6
Good agreement	0.61-0.8
Very good agreement	0.8-1

In the final data analysis and in order to capture the heterogeneity and the different role of HTA bodies across Europe, a published taxonomy of HTA body categories was employed in order to filter results. Analysis has been conducted for the entire sample as well as for the subcategories depicted in the taxonomy.

Currently, the role and the function of HTA bodies can vary based on their scope within the healthcare system. The taxonomy differentiates the HTA bodies based on their level of integration within governmental bodies and the functions they perform (27). The two broader categories comprise '**HTA bodies at Arm's length'** and **'HTA function which is integrated'**; the former are independent bodies and autonomous from governmental agencies, while in the latter the HTA function is integrated within a governmental body.

Each HTA body is further characterised according to its function as an Advisory, Coordination or Regulatory entity. An advisory body (e.g. NICE in England and HAS in France) provides recommendations to governmental bodies on coverage decisions to be implemented at national or regional level, whereas a regulatory body is directly accountable/responsible for the final pricing and reimbursement decision (e.g. AIFA, TLV). Lastly, coordination bodies mainly collect, produce and disseminate assessments research results.

This taxonomy was used in order to draw a clear line distinction between assessment and appraisals, distinction made in a regulatory and organizational context, leading to different system implications. 'Assessment' is defined as the collection and synthesis of evidence focusing on the traceability/replicability of results. It triggers HTA and usually provides information to providers in supporting investments coverage decisions on Health technologies. 'Appraisal' is the act of contextualizing evidence and formulating coverage recommendations and resource implications, i.e. defining impact and applicability (8, 9). Negative or positive recommendation contained in an assessment does not necessarily imply a final negative or positive coverage decision.

Embedding the multi-stage methodology in the taxonomy serves two purposes: first, to contribute to the understanding of the key factors considered in the HTA decision-making process, allowing the identification of possible duplication of assessment across EU MS and second, to capture the heterogeneity of the current HTA baseline scenario in a systematic way.

6.2 Policy Options and business models

6.2.1 Multi-criteria analysis

In order to carefully assess the different impacts of the proposed Policy Options on the various stakeholder groups, a multi-criteria analysis (MCA) was adopted.

The aim of an MCA is to support the analysis of multi-criteria environments (in the case of this study multiple impacts) and also to facilitate decision-making processes. In this study the MCA was preliminary used for compiling and analysing the stakeholder survey results (see section 7.3) as well as additional information gathered through various measures. MCA is considered suitable particularly for questions, which:

- Need to consider multiple impacts
- Need to visualise different points of view (need for cross-examination in terms of different stakeholders)
- Do not necessarily require or allow for a monetary evaluation of decision outcomes
- Have to be tackled with a strong participatory component (stakeholder involvement) (28)

Nearly all these criteria are fully met by the questions this study addresses, some of them will be further described in the following steps (based on a categorisation in the publication 'Multi-criteria Analysis: a Manual') (29), which were incorporated and performed embedding the results gathered through the stakeholder survey (see section 5.3.1).

6.2.1.1 Establishment of the decision context

The first step of an MCA addresses the establishment of the decision context, meaning the aims of the analysis should be clearly identified and that all structures surrounding this should be examined. This includes the identification of relevant stakeholder groups.

Based on that, key players for HTA cooperation in Europe in the future were identified and clustered for the survey and subsequent analysis in three main stakeholder groups:

- Public Administrations
- The Pharmaceutical Industry
- The MedTech Industry

For other stakeholders that were initially addressed in the survey, such as patient organizations or academia, survey results could finally not be taken into account due to a very low response rate leading to risk for distortion in the analysis results. Whenever there are effects identified on patients or health professionals, these are pointed out in the relevant sections in 7.3. Within the three main stakeholder groups, further distinctions were made possible through the design of the online survey by asking about, for example, experience in HTA production or the size of the company.

Sub-group analyses were performed throughout the study including:

- Subgroups based on company size: SMEs and large companies for both industry sectors (Pharmaceutical and MedTech Industry) were grouped and compared to each other.
- Separate analysis was done for MedTech Industry, comparing companies with declared HTA experience to companies without HTA experience.
- Separate analysis for MedTech Industry comparing those who actually stated costs for HTA activities with those who did not.

6.2.1.2 Identification of the options under consideration

The survey questionnaire, on which the MCA was based, aimed at examining the identified Policy Options (POs) compared to the status quo. POs were proposed by DG SANTE in the inception impact assessment and were further developed throughout the course of the study in close collaboration with DG SANTE and with the involvement of the expert group.

The POs compared in the MCA were (see chapter 3.2 for details):

- Policy Option 1: Baseline scenario - No EU action after 2020
- Policy Option 2: Voluntary cooperation supported by the Public Health Programme
- Policy Option 3: Legislation covering Common Tools and Early Dialogues
- Policy Option 4.1: Opt-in for Joint REA plus option 3
- Policy Option 4.2: Mandatory Joint REA plus option 3
- Policy Option 5: Option 4.2 and Opt-in for Full HTA

6.2.1.3 Identification of criteria that reflect the value associated with the consequences of each option

An important step of the MCA process relates to the definition of the specific criteria which are utilized for assessing the effects of the different options.

For developing these criteria, the list of impacts that have to be considered was defined by the EC's Better Regulation Guidelines (5) which served as a starting point. After reviewing these potential impacts some were disregarded straight away due the fact that no connection between the European cooperation on HTA process and the impact existed, which is the case for example for environmental impacts. This was done based on the experience of the study team and in close collaboration with the project team from DG SANTE.

After the relevant impact areas were defined, indicators were developed for each of the impacts (ranging from 2-8 indicators per impact) in order to ensure a detailed assessment and to capture all relevant aspects for each impact area. In order to ensure that all relevant impacts and indicators for all stakeholder groups were covered, these were presented to an expert group in the course of a structured questionnaire process (see 5.3 for details), which fed back on the scope and the content. Experts were asked to:

- Rate the indicator with regard to its relevance for assessing the POs' impacts

- Comment on the indicator
- Add sources of information or references to literature, if known
- Add relevant but missing indicators

Final impacts for the stakeholder survey, clustered by economic criteria (EC) and social health (SH) impacts were therefore carefully selected and included the following impacts:

	Economic impacts (EC):
EC1	Costs
EC2	Administrative burden
EC3	Competitiveness of EU health technology sector
EC4	Innovation and research
EC5	International Trade
EC6	Functioning of the internal market and competition
EC7	Consumers and households
EC8	Macroeconomic environment
	Social/health impacts (SH)
SH1	Employment (labour market)
SH2	Governance, participation and good administration
SH3	Access to social protection and health systems
SH4	Sustainability of health systems
SH5	Public health

The aim of the online survey with regard to usability for the multi-criteria analysis was to gather an **estimate of the relative importance of impacts per stakeholder group** and an understanding of **the direction (positive or negative) of influence of the different impacts**.

Regarding the relative importance of impact, it should be noted that MCA sometimes is further developed into MCDA (multi-criteria decision analysis), which is a recognized method for decision support in policy assessment and allows for systematic comparison and also ranking and weighing of different options across several criteria. Therefore, initially the stakeholder survey contained a part on the assignment of weights for each impact. Stakeholders were asked to assign weights for each of the impacts to reflect their relative importance to the Policy Option.

Initially it was planned to combine this information with the answers gathered by impact and Policy Option to obtain the most preferred Policy Option per stakeholder group including the relevance of impacts. Yet, this step has not been performed due to the low number of respondents providing both information, as this would have led to uncertainty of results and was considered misleading regarding the presentation and interpretation of results by the experts, the study team and the EC.

Regarding the direction of influence of the different impacts, because the results from the stakeholder survey had to feed into the multi-criteria analysis, questions were designed respectively in a quantitative way, leaving room for the stakeholders to add further comments on each response. Respondents were asked to assess each policy option according to their economic and social impacts. Thereby, they were indicating for each impact whether the respective indicators may decrease (-) or increase (+) for each policy option on a range from -100 to +100. This procedure allowed for the assessment of each Policy Option in a comparable manner. The decision to use this multi-criterial approach therefore was also based on the fact that a broad range of impacts needed to be addressed and a majority of the considered impacts could not be expressed in monetary terms (see criteria in 6.2.1.1).

6.2.1.4 Description of the expected performance of each option against the criteria and examination of the results

Results of the multi-criteria analysis are presented per impact type and per stakeholder group. For each impact type, relevant indicators as well as an aggregated value is presented. For some aggregated values, single indicators had to be inverted to assure for a correct interpretation of data. This was because for some indicators an increase (meaning a value between 0 and +100) is positive (e.g. increase in innovation), while for some indicators an increase is considered negative (e.g. increase in costs).

To increase the validity and reliability of the results of the MCA derived from the online survey with different groups of stakeholders, all results were interpreted and supported by further information, such as literature or feedback gathered through interviews with Pharmaceutical and MedTech industry as well as focus groups. For a thorough description and explanation of these results, see chapter 7.2.

For creating an overview table on impacts the quantitative survey results (mean values) were translated into the following categories:

Table 15: Allocation of quantitative results to effect categories:

Ranges of mean value per impact		Attributed effect category	Abbreviation
100	71	Strong positive effect	+ + +
71	43	Moderate positive effect	+ +
43	14	Slight positive effect	+
14	-14	neutral (+ or – representing the direction of the answers, as indication even if the expected effect is low)	0
-14	-43	slight negative effect	-
-43	-71	Moderate negative effect	- -
-71	-100	Strong negative effect	- - -

The categorization was subsequently adjusted into a positive or negative direction in case more information was available for the specific impact, which amplified or alleviated the survey responses. For this, a two-step process was applied. In the first step, members of the study team did this adjustment separately after reviewing the available information per impact. In the second step, estimates were compared, discussed and finalised after agreement.

6.2.1.5 Data plausibility check

Several data plausibility checks were performed. These are explained and their results are described in section 7.3.7.

6.2.2 Cost prognosis

The cost prognosis consisted of:

1. The estimation of voluntary or mandatory **joint outputs** and related **savings in national outputs** of the proposed POs.
2. Specific implementation mechanisms including common tools

Output production included four outputs:

- **Common tools** (including templates and methodology)
- **Early Dialogue** (ED)
- **Joint REA**
- **Joint Full HTA** (as displayed in Table 7 in section 4.2)

Each Policy Option outlined a specific set of voluntary and/or mandatory output production and was matched with an envisaged implementation mechanism.

The proposed **implementation mechanisms** were:

- Project-based cooperation
- An MS secretariat
- An EU secretariat located at EC level
- The integration of such a Secretariat into an existing EU agency
- Creation of a new EU agency

An implementation mechanism without EU funding was not considered in this study since intergovernmental cooperation without EU input is strictly the responsibility of the MS.

The business models presented are the **basis for further developments and represent illustrative scenarios**. Outputs and implementation mechanisms were assessed separately to allow for adaptations and the possibility to develop additional POs at a later stage without the need for additional assessment.

Cost prognosis of **HTA outputs** was based on **several sources:** Information obtained by Chamova 2017 (2) and provided from EUnetHTA members; data gathered through the survey conducted for this study plus additional follow-up on costs; focus group input by Public Administrations, the Pharmaceutical Industry and MedTech Industry which were used for validating and improving comprehension of the survey data; and expert validation throughout the whole study process. Additional sources used for the prognosis are quoted directly, if applicable. Information obtained through the baseline scenario (section 7.1.12) was included, if applicable. Many assumptions had to be made where data/information were not available. They are outlined in subsections 6.2.2.1 to 6.2.2.5. A sensitivity analysis was performed to account for related uncertainties.

Costs will be estimated for the Year 2020 onwards, i.e. plus the implementation period. Costs will be premeditated as total costs per year. All costs are expressed in 2016 Euro.

6.2.2.1 Assumptions on cost elements for the output related prognosis

One task of the project team was to give input to the EU Impact Assessment regarding the likely evolution of cost for coordinated HTA in Europe. The overall cost impacts regarding the production of outputs for each stakeholder group (MS, EU and industry) were calculated by the number of expected additional products per Policy Option (including national adaptation) minus the expected reduction in output volumes (e.g. fewer national full reports, fewer manufacturer submission reports at national level). For this, a number of assumptions had to be made regarding e.g., the overall scope of technologies per option or the level of voluntary uptake:

- HTA processes may inform (national) reimbursement decisions as well as evidence generation for a new technology. They also give input to national policy strategies / general issues on health care provision, the creation of quality standards, guidelines etc. ***Assumption:*** *(Future) EUnetHTA outputs (REA, Full HTA) will focus on providing information for national reimbursement (or other policy) decisions after-market launch or e.g. change of indication.*
- Current HTA systems are heterogeneous across Europe, ranging from systems where HTA processes explicitly (including legal provisions) inform reimbursement decisions (including legal provisions) to systems with HTA processes not directly informing reimbursement decisions and (few) systems without an established HTA process. Therefore, the expected consequences of the five POs at national level will vary between countries – with regard to regulative changes as well as potential cost savings. It can be argued that countries doing many HTA-reports per year will be able to gain more savings by replacing national activity through joint activity than countries doing only a few reports each year (leaving aside, of course, other impacts such as enhanced transparency). The amount of national savings thereby is related to the number of joint outputs and the overlap between joint and (current) national output. ***Assumption:*** *For the sake of calculation of estimated costs, the MS were grouped according to the 'annual HTA output volume' as follows:*
    - **Group 1**: MS with a high number of reimbursement-related HTA outputs per year (above an assumed cut-off-value of 60 reports per year for Pharma and 50 reports per year for MedTech)
    - **Group 2**: MS with a rather low number of reimbursement related HTA reports per year (below an assumed cut-off-value of 60 reports per year for Pharma and 50 reports per year for MedTech)
    - **Group 3**: MS with no or purely 'informative' HTA systems (and low number of HTA reports per year)

    Each category was further grouped by:
    - Countries/systems([37]) where (reimbursement-related) reports are mainly produced by HTA bodies (with no or some evidence/data submission provided by industry)
    - Countries/systems ([38]) where (reimbursement-related) reports are mainly produced by industries and reviewed by HTA bodies (or reimbursement authority)

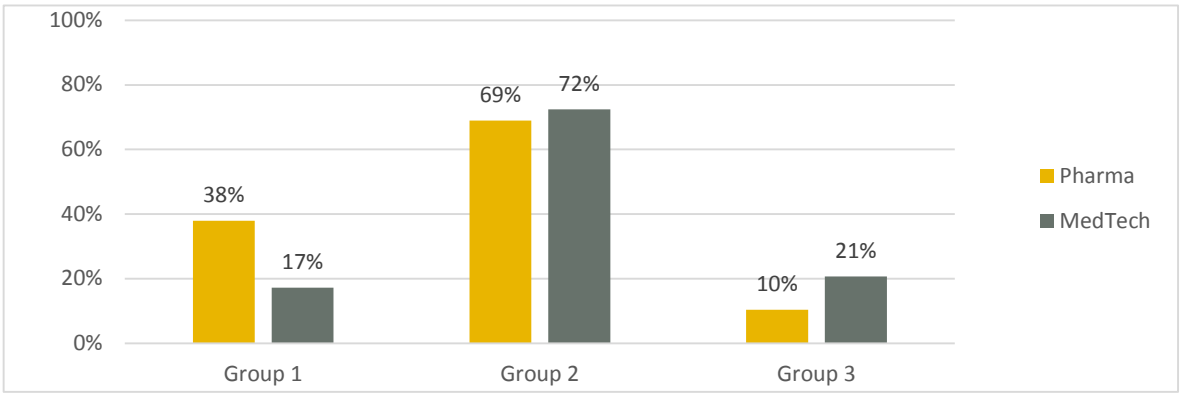
Whereas it was also recognised that countries may, e.g. have systems follow different Types across sectors (such as following Type A for Pharmaceuticals and Type B for MedTech), sometimes, this might also be mixed within the product sectors, e.g. one of the HTA bodies undertakes HTA and analysis and produces HTA reports mainly on their own, while another country would mainly review industry submissions.

The study team categorised the countries based on data and information derived from Chamova 2017 (2), which included 29 countries. The consistency check of the obtained results contained a match with information of EUnetHTA JA3 WP7, as far as it was available to date. Figure 15 shows the percentage of countries within each of the groups.

Figure 15: Percentage of 29 countries within three groups according to annual HTA output volume

([37]) Some countries have two systems (HTA-body-based = A. as well as industry-based = B.) within **one** branch (MedTech or Pharma).
([38]) See above.

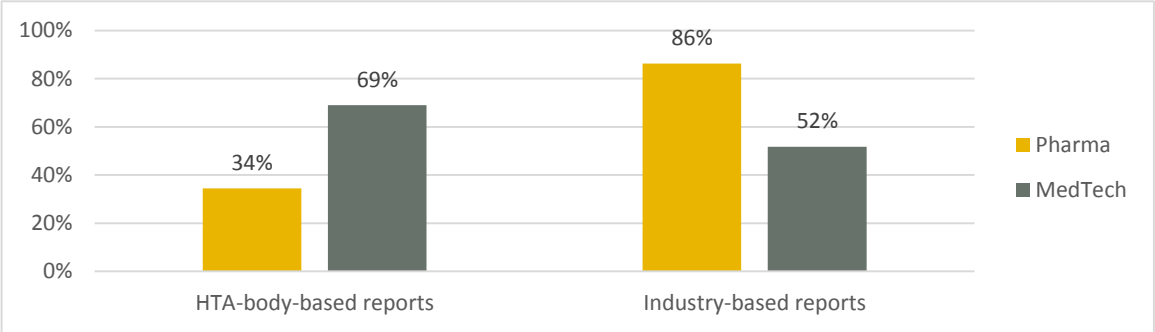
Group 1: 60 or more reports per year for Pharma and 50 or more reports per year for MedTech



Group 2: less than 60 reports per year for Pharma and 50 reports per year for MedTech
Group 3: Countries with no study production or purely 'informative' HTA system)
Source: Authors, based on Chamova 2017

Figure 16 depicts the percentage of countries with HTA body-based reports and that of countries with industry-based reports. Figures do not add to 100% as, even within the same sector (Pharmaceuticals or MedTech), some countries have a system that can be attributed to two groups (as described above).

Figure 16: Percentage of 29 countries with HTA body-based reports vs. countries with industry-based reports



Source: Authors, based on Chamova 2017

Countries with mandatory uptake of REA or Full HTA have to implement changes within their existing systems, e.g. with regard to regulations for national reimbursement submissions, either changing existing regulations and/or setting new ones.

Assumptions:

- **Pharmaceuticals**: Requirements for manufacturer submissions for reimbursement at national level (at least within the outpatient sector) will be harmonised to a certain degree, e.g. with regards to fully using the joint assessments and adding some national aspects, such as cost effectiveness analysis. Otherwise, there is no reduction in the duplication of reimbursement submissions for industry.
- **Medical technologies (MedTech)**: If evidence from the manufacturer is required by national HTA or reimbursement bodies for interventions connected to medical technologies, the requirements for manufacturer submissions will be harmonised to a certain degree as described above.

6.2.2.2 Assumptions on the predicted joint output per Policy Option

Table 16 depicts the expected likely number of joint outputs, the proportion of countries that are expected to opt in and the underlying sources of assumptions, if available, for assessments on Pharmaceutical products. For options with voluntary participation and mandatory uptake, a proportion of countries that 'opt in' (section 4.2) was defined. According to the definition of POs for this study (section 4.3), countries that opt in for REAs and HTAs are obliged to consider ALL joint assessments within their national decision-making process. Countries that opt in for Early Dialogues must not repeat Early Dialogues at national level (at least if completely transferable). Countries who participate in one or more joint Early Dialogue are required to opt in.

Table 17 displays assumptions on the expected amount of joint output, the proportion of countries who are expected to opt in and underlying sources for assumptions, if available, for assessments on medical devices. For options with voluntary participation and mandatory uptake, a proportion of countries who 'opt in' (see also section 4.2) must be defined. Countries with opt in for REAs and HTAs are obliged to consider ALL joint assessments within their national decision-making.

Table 16: Cost prognosis assumptions for the Pharmaceutical sector

	Pharma 2020+			
	Number of joint output per year	*Source (if available)*	Proportion of countries opting in (***)	*Source (if available)*
Early Dialogue (*)				
PO2, V/M	8-10	Planned amount for Pharma based on EUnetHTA JA3 2019-2020 (Grant Agreement p. 178 resp. '65 / 220') resp. SEED (currently 11 reports, thereof eight on Pharmaceuticals)	Min. 30%	Proportion based on current SEED consortium (14 institutions out of 10 countries did SEED-reports, thereof nine have been involved in Pharmaceutical reports)
PO3, V/M	30	As above, but higher because of more incentives for industry for initiating EDs	Min. 30%	Proportion based on current SEED consortium, see above
PO 4.1, V/M	30	As above, but higher because of more incentives for industry for initiating EDs	Min. 30%	Proportion based on current SEED consortium, see above
PO 4.2, M/M	30	As above, but higher because of more incentives for industry for initiating EDs	100%	Defined by Policy Option
PO5, M/M	30	As above, but higher because of more incentives for industry for initiating EDs	100%	Defined by Policy Option
REA				
PO2, V/M	10	EUnetHTA JA 3 forecast for Joint HTAs + 20%	17%	Assumption based on EUnetHTA JA 2 experience: Institutions of five countries have been the (main) authors of a Pharmaceutical REA ([39]). Five countries had uptakes 'used in direct decision-making' ([40]) (on four Pharmaceutical reports).
PO3, V/V	0	As there is no central funding no joint output is assumed. However there may be intergovernmental activities and related uptake.		
PO 4.1, V/M	40	Includes all centrally authorized new active substances, estimates based on EMA annual study	17%	see above
PO 4.2, M/M	40	Includes all centrally authorized new active substances, estimates based on EMA annual study	100%	Defined by Policy Option
PO5, M/M	40	Includes all centrally authorized new active substances, estimates based on EMA annual study	100%	Defined by Policy Option
Full HTA				
PO2, V/V	0	Assumption based on the low current output of Full HTA and on prevailing methodological uncertainties in EUnetHTA Joint Actions as to what should be included within a European economic analysis (ECO domain) (**)	NR	
PO3, V/V	0	See above	NR	
PO 4.1, V/V	0	See above	NR	
PO 4.2, V/V	0	See above	NR	
PO5, V/M	7	Based on the ratio 1:6 for 'core HTA' versus REA in EUnetHTA JA2	17%	Assumption based on the number of countries with authoring institutions of core HTA of Pharmaceuticals in EUnetHTA JA2

SEED = Shaping European Early Dialogues for health technologies Group (http://www.earlydialogues.eu/has/?page_id=10), NR=Not relevant
*) These assumptions have not been incorporated within final calculations as it was not possible to include Early Dialogues in a detailed cost prognosis due to a lack of data on the current costs and quantities of Early Dialogues (see 0).
) Moreover, it needs to be considered that especially economic analysis mainly plays a role for the reimbursement decision, which however will remain at national level.*) As there are no sources or straightforward reasoning to assume differing rates between groups of countries (see 6.2.2.1), the same opt-in rate is applied to all countries.

([39]) http://www.EUnetHTA .eu/joint-assessments
([40]) *http://www.EUnetHTA .eu/national-uptake*

Table 17: Cost prognosis assumptions for the MedTech sector

	MedTech 2020+			
	Number of joint output per year	*Source (if available)*	Proportion of countries opting in (***)	*Source (if available)*
Early Dialogue (*)				
PO2, V/M	3-5	Planned amount for MedTech based on EUnetHTA JA3 2019-2020 (Grant Agreement p. 178 resp. '65 / 220') resp. SEED (currently 11 reports, thereof 3 on medical devices)	Min. 30%	Proportion based on current SEED consortium (14 institutions out of 10 countries did SEED-reports, thereof nine have been involved in MedTech reports)
PO3, V/M	10	As above, but higher because of more incentives for industry for initiating EDs	Min. 30%	Proportion based on current SEED consortium, see above
PO 4.1, V/M	10	As above, but higher because of more incentives for industry for initiating EDs	Min. 30%	Proportion based on current SEED consortium, see above
PO 4.2, M/M	10	As above, but higher because of more incentives for industry for initiating EDs	100%	Defined by Policy Option
PO5, M/M	10	As above, but higher because of more incentives for industry for initiating EDs	100%	Defined by Policy Option
REA				
PO2, V/M	5	EUnetHTA JA 3 forecast for Joint HTAs + 20%	21%	Assumption based on EUnetHTA JA2 experience: Institutions of six countries have been (main) authors of a MedTech REA ([41]). Five countries had uptakes 'used in direct decision-making' ([42]) (on six MedTech reports).
PO3, V/V	0	As there is no central funding no joint output is assumed. However there may be intergovernmental activities and related uptake.		
PO 4.1, V/M	25	Assumption based on information provided by DG SANTE	21%	see above
PO 4.2, M/M	25	Assumption based on information provided by DG SANTE	100%	Policy Option
PO5, M/M	25	Assumption based on information provided by DG SANTE	100%	Policy Option
Full HTA				
PO2, V/V	0	Assumption based on the low current output of Full HTA and on prevailing methodological uncertainties in EUnetHTA Joint Actions as to what should be included within a European economic analysis (ECO domain) (*)	NR	
PO3, V/V	0	See above	NR	
PO 4.1, V/V	0	See above	NR	
PO 4.2, V/V	0	See above	NR	
PO5, V/M	4	Based on the ratio 1:6 for 'core HTA' versus REA in EUnetHTA JA2	21%	Assumption based on the number of countries with authoring institutions of core HTA of MedTech in EUnetHTA JA2

SEED = Shaping European Early Dialogues for health technologies Group (http://www.earlydialogues.eu/has/?page_id=10), NR=Not relevant
*) These assumptions have not been incorporated within final calculations as it was not possible to include Early Dialogues in a detailed cost prognosis due to a lack of data on the current costs and quantities of Early Dialogues (see 0).
**) Moreover, it needs to be considered that especially economic analysis mainly plays a role for the reimbursement decision which however will remain on the national level.
***) As there are no sources or straightforward reasoning to assume differing rates between groups of countries (see 6.2.2.1), the same opt in rate is applied to all countries.

([41]) http://www.EUnetHTA .eu/joint-assessments
([42]) http://www.EUnetHTA .eu/national-uptake

6.2.2.3 Assumptions on the reduction of national output per Policy Option

With the production of (voluntary or mandatory) **joint outputs**, a decrease **in outputs at national level** can be expected, leading to potential savings. These savings depend on the overlap between joint and national output. That is, not all of joint output may be relevant at national level. Countries that opt in have to consider all relevant joint output within national decision-making.

Countries without 'opt in' may still use parts of relevant joint outputs in national decision-making. In this part, assumptions on the amount of reduction of national outputs per Policy Option are presented. These parameters have been set separately for the three groups as defined in 6.2.2.2. Table 18 depicts assumptions made for Pharmaceutical products and Table 19 for medical technologies.

Table 18: Assumptions on national output reduction in the Pharmaceutical sector

	Pharma					
	Group 1 (60 or more reports per year)	***Source (if available)***	**Group 2** (less than 60 reports per year)	***Source (if available)***	**Group 3** (no or purely 'informative' HTA system)	***Source if available or Assumption***
Early Dialogue						
Not enough data are available at national level to make realistic assumptions on the amount of national output reduction. However, it is fair to assume that higher savings could be realised in the case of mandatory options (PO 4.2 and 5). We assume that industry has incentives to initiate joint EDs on those products for which they currently need to conduct a number of national EDs. Just under half of the countries conducts (if only irregularly) EDs at status quo, in probably 4-5 main markets (Chamova 2017). Therefore, it can be assumed that with option 4.2 and 5 one joint ED replaces at least 4-5 national EDs (given that joint ED will be completely transferable to local settings).						
REA						
PO2, V/M with opt in	100% of **joint** output replaces national output	Assumption: in countries with national outputs exceeding 60 reports per year all 10 joint REAs will be relevant and therefore can replace national output.	25% of **national** output is replaced	Assumption: on average only 25% of the 10 joint REAs are assumed to be relevant for countries' decisions that have less than 60 reports per year.	0%	Assumption because of zero to low current output
PO2, V/M without opt in	1 national output per year is replaced by joint output	Assumption: Even those countries that did not opt in will (be able to) take up one joint REA on a voluntary basis.	0%	Assumption: in countries with less than 60 reports per year and who did not opt in there won't be an uptake out of the 10 joint REAs for direct decision-making	0%	Assumption because of zero to low current output
PO3	NR because non joint output is assumed, see Table 16					
PO 4.1, V/M with opt in	100% of **joint** output replaces national output	Assumption: in countries with national outputs exceeding 60 reports per year all 40 joint REAs will be relevant and therefore can replace national output.	50% of **national** output is replaced	Assumption: on average 50% of joint output is assumed to be relevant for country' decisions (see also assumption for group 1).	0%	Assumption because of zero to low current output
PO 4.1, V/M without opt in	50% of **joint** output replaces national output	Assumption: Even those countries that did not opt in will (be able to) take up one half of assessments on a voluntary basis.	25% of **national** output is replaced	Assumption: on average 25% of joint output is assumed to be relevant *and* attractive for country' decisions.	0%	Assumption because of zero to low current output
PO 4.2, M/M **PO5**, M/M	100% of **joint** output replaces national output	Assumption: in countries with national outputs exceeding 60 reports per year all 40 joint REAs will be relevant and therefore can replace national output.	50% of **national** output is replaced	Assumption: on average 50% of joint output is assumed to be relevant for countries' decisions (see also assumption for group 1).	0%	Assumption because of zero to low current output
Full HTA						
PO2, V/V	NR because no joint output is assumed, see Table 16					
PO3, V/V	NR because no joint output is assumed, see Table 16					
PO 4.1, V/V	NR because no joint output is assumed, see Table 16					
PO 4.2, V/V	NR because no joint output is assumed, see Table 16					
PO5, V/M with opt in	50% of **joint** output replaces national output	Assumption - based on Chamova 2017 (2) (roughly half of the MS do – if only rarely – a Full HTA study at national level)	25% of **joint** output replaces national output	Assumption by the authors (to be tested in sensitivity analysis)	0%	Assumption because of zero to low current output
PO5, V/M without opt in	20% of **joint** output replaces national output	Assumption by the authors (to be tested in sensitivity analysis)	20% of **joint** output replaces national output	Assumption by the authors (to be tested in sensitivity analysis)	0%	Assumption because of zero to low current output

Table 19: Assumptions on national output reduction in the MedTech sector

	MedTech					
	Group 1 (60 or more reports per year)	***Source (if available)***	**Group 2** (less than 60 reports per year)	***Source (if available)***	**Group 3** (no or purely 'informative' HTA system)	***Source if available or Assumption***
Early Dialogue						
Not enough data are available at national level to make realistic assumptions on the amount of national output reduction. However, it is fair to assume that higher savings could be realised in case of mandatory options (PO 4.2 and 5). Industry has strong incentives to initiate joint EDs on those products for which they currently need to conduct a high number of national EDs. The potential will, however, be lower than for Pharmaceutical products since company size varies to a higher degree with a larger amount of only locally operating companies and with generally less activity related to EDs (see section 7.1.12.3). Moreover, not every joint ED will be completely transferable to local settings (SEED study, p. 26).						
REA						
PO2, V/M with op in	50% of **joint** output replaces national output	Assumption: in countries with national outputs exceeding 50 reports per year one half of all 25 joint REAs will be relevant and therefore can replace national output. This is based on the large heterogeneity of medical devices as well as on the perceived heterogeneity of the product scope of MS HTA systems for medical devices (Chamova 2017) (2) as well as on the larger amount of only locally operating companies.	10% of **national** output is replaced	Assumption: on average 50% of joint output is assumed to be relevant for countries' decisions (see also assumption for group 1).	0%	Assumption because of none to low current output
PO2, V/M without op in	1 national output per year is replaced by joint output	Assumption: Even those countries that did not opt in will (be able to) take up one joint REA on a voluntary basis.	0%	Assumption: in countries with <60 reports per year and who did not opt in there won't be an uptake out of the 10 joint REAs for direct decision-making	0%	Assumption because of zero to low current output
PO3	NR because non joint output is assumed, see Table 16					
PO 4.1, V/M with op in	50% of **joint** output replaces national output	Assumption: in countries with national outputs exceeding 50 reports per year, one half of all 25 joint REAs will be relevant and therefore can replace national output. This is based on the large heterogeneity of medical devices as well as on the perceived heterogeneity of the product scope of MS HTA systems for medical devices (Chamova 2017) (2) as well as on the larger amount of only locally operating companies.	50% of **national** output is replaced	Assumption: on average 50% of joint output is assumed to be relevant for countries' decisions (see also assumption for group 1).	0%	Assumption because of zero to low current output
PO 4.1, V/M without op in	25% of **joint** output replaces national output	Assumption: Even those countries that did not opt in will (be able to) take up one half of assessments on a voluntary basis.	25% of **national** output is replaced	Assumption: on average 25% of joint output is assumed to be relevant *and* attractive for countries' decisions.	0%	Assumption because of zero to low current output
PO 4.2, M/M **PO5**, M/M	50% of **joint** output replaces national output	Assumption that in countries with national outputs exceeding 50 reports per year one half of all 25 joint REAs will be relevant and therefore can replace national output. This is based on the large heterogeneity of medical devices as well as on the perceived heterogeneity of the product scope of MS HTA systems for medical devices (Chamova 20172) as well as on the larger amount of only locally operating companies.	50% of **national** output is replaced	Assumption: on average 50% of joint output is assumed to be relevant for countries' decisions (see also assumption for group 1).	0%	Assumption because of zero to low current output
Full HTA						
PO2, V/V	NR because no joint output is assumed, see Table 16					
PO3, V/V	NR because no joint output is assumed, see Table 16					
PO 4.1, V/V	NR because no joint output is assumed, see Table 16					
PO 4.2, V/V	NR because no joint output is assumed, see Table 16					
PO5, V/M with opt in	50% of joint output replaces national output	Assumption - based on Chamova 2017 (2) (roughly half of the MS do - if only rarely - a Full HTA)	25% of joint output replaces national output	Assumption by the authors (to be tested in sensitivity analysis)	0%	Assumption because of zero to low current output
PO5, V/M without opt in	10% of joint output replaces national output	Assumption by the authors (to be tested in sensitivity analysis)	10% of joint output replaces national output	Assumption by the authors (to be tested in sensitivity analysis)	0%	Assumption because of zero to low current output

6.2.2.4 Assumptions on cost elements for the implementation mechanisms

For assessing the costs of the implementation mechanism under consideration several assumptions with regard to the specific cost elements are necessary. The assessment of implementation mechanisms included potential one-time investment costs and operating costs. Expertise of former and current JA leaders of EUnetHTA , EUnetHTA JA budget calculations, a study on analysing the structure of EU agencies (30), the EU staff regulations (31) and former impact assessments for the establishment of EU agencies, namely eu-LISA (European Agency for the Operational Management of large-scale IT Systems in the Area of Freedom, Security and Justice), EFSA (European Food Safety Authority) and EASA (European Aviation Safety Agency), formed the basis for the respective calculations and underlying assumptions.

For each of the implementation mechanisms it is planned that output production is fully coordinated comprising the following outputs (see Table 1 for details):

- Common tools, including templates, methodologies
- Early Dialogue
- joint REA
- joint Full HTA

Calculations for implementation mechanisms are based on the assumption of an annual output production of the respective policy option (see 6.2.2.1 for details).

Personnel costs for implementation mechanisms of a project-based cooperation or an MS secretariat as well as different price levels of MS were accounted for by indexing the calculations based on the EU salary scheme to national price levels.

6.2.2.5 Assumptions on Governance structure

Presented information on the potential Governance structures was developed in close collaboration with EC. The governance structure of future EU cooperation in the field of HTA includes 5 different business models ([43]):

- Project-based cooperation (PO2)
- A permanent secretariat hosted by a MS (PO 3)
- A permanent secretariat hosted by the EC (PO 4.1)
- A permanent secretariat hosted by an existing EU agency (PO 4.2)
- A permanent secretariat hosted by a new EU agency (PO 5)

The main difference in the organisational structure between the five models can be observed between the project-based cooperation (PO2) on the one hand and the establishment of a permanent secretariat (PO 3-5) on the other hand. Regardless of the type of cooperation, there are common elements to the governance structure, which are defined by the joint outputs. For every calculation, the number of potential outputs was linked to the assumptions for the POs and business models.

([43]) Other combinations of policy options with business models are possible as well (e.g. a new agency already for PO 4.1) but the presented variants are considered as the most plausible ones, with experts and DG SANTE.

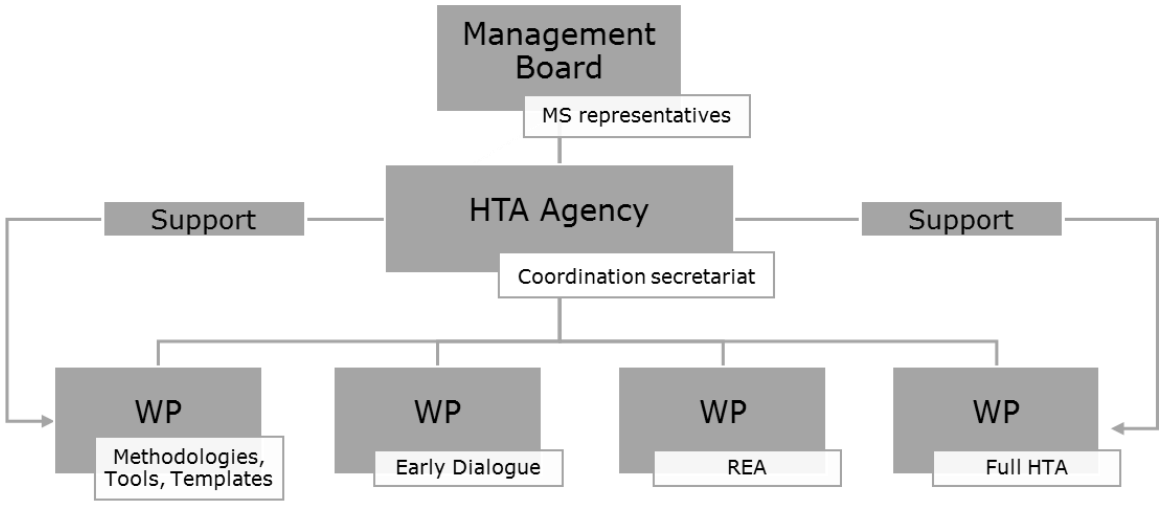
Project-based cooperation

In MS-driven, project-based cooperation, (PO 2), one HTA agency is responsible for the overall coordination. The work is conducted in Work Packages (similar to EUnetHTA JAs) by different HTA bodies for the duration of the project.

The **management board** is responsible for overall governance and consists of representatives from participating MS, which should meet quarterly to discuss topic prioritisation, progress with outputs, and any other relevant issue to provide guidance on and steer the cooperation.

Support functions, e.g. administrative support for coordination meetings, scientific support to perform basic consistency checks on joint outputs, IT support and communication functions will be provided by the central coordination secretariat of the respective HTA agency; and production of the outputs will be managed by the individual work packages. The following figure depicts an illustrative presentation of the governance structure of PO 2, project-based cooperation.

Figure 17: Potential governance structure PO2

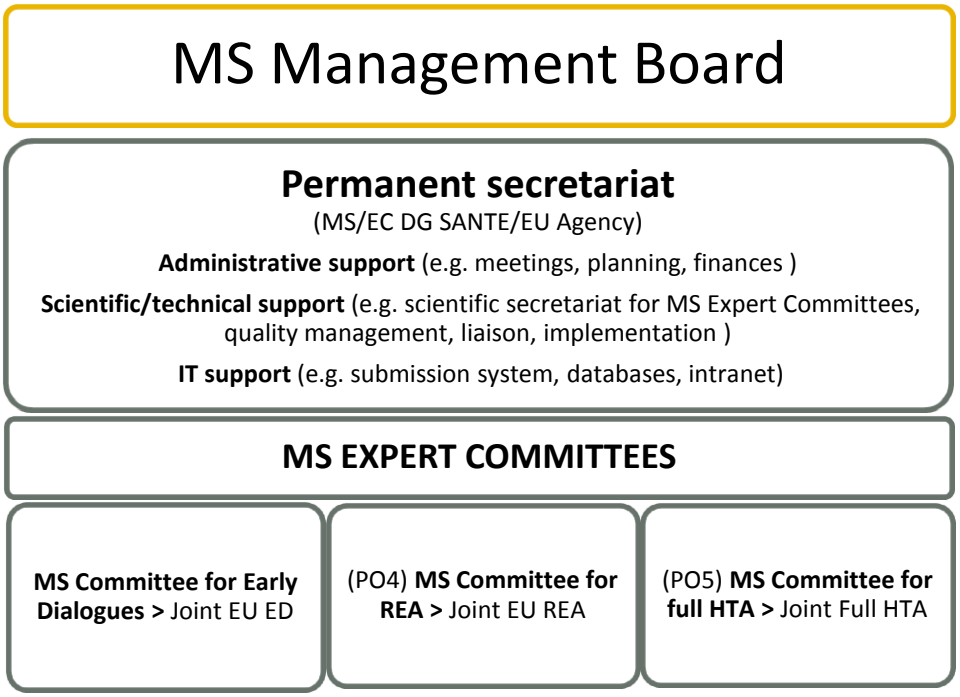


In addition to the anticipated governance structure, it should be noted that project-based cooperation is implemented for a limited period of time. Hence, project-based cooperation requires specific processes (before and after) and has associated costs that may not provide optimal conditions for long-term sustainability and efficiency.

Permanent secretariat

The overall structure of permanent cooperation (PO 3-5) is depicted in Figure 18:

Figure 18: Potential governance structure permanent secretariat



The **management board** is responsible for overall governance and consists of representatives from participating MS, which should meet quarterly to discuss topic prioritisation, progress with outputs and any other relevant issue to provide guidance and steer the cooperation.

The permanent **secretariat** provides **central support,** including administrative, scientific/technical and IT support. The secretariat may be hosted by the EC, a MS or located in an existing or new EU agency.

The tasks of this permanent secretariat would include:

Administrative support

- Organisation of meetings, travel arrangements and other administrative issues relevant to the overall coordination and to the operation of the Management Board and Expert committees;
- Finance, especially important with regards to handling reimbursement of national experts and any industry fees, and legal aspects (e.g., on taxing);
- Communication (including studying and documentation); and
- Providing support to Management Board.

Scientific/technical support (scientific secretariat to output-producing HTA bodies and MS expert Committees)

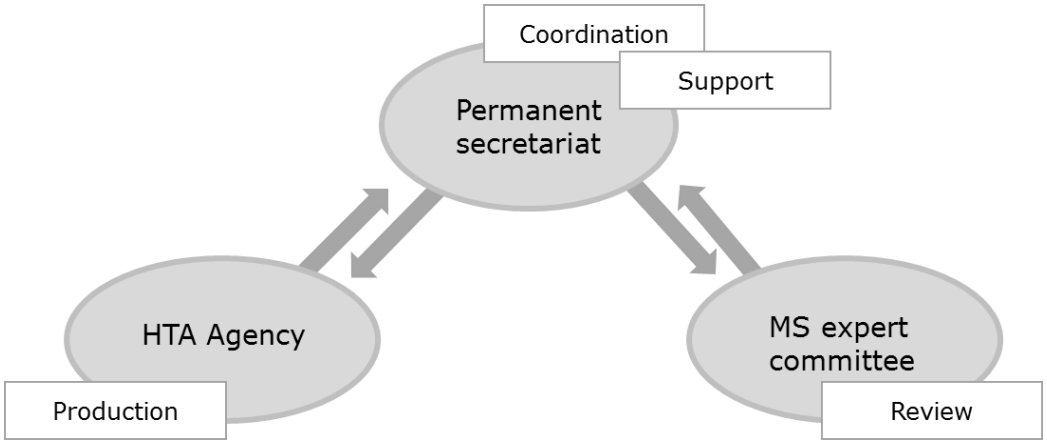
- Support the production of output (Standard Operating procedures for identifying and organising the work of experts from national authorities in MS Expert Committees; provide scientific/technical support to authors and co-authors of the joint outputs);
- Quality management (both from a scientific and editorial perspective);
- Liaison with stakeholders (patients, industry, health professionals, academia, payers etc.); and
- Provide support for national implementation (e.g. training).

IT support, particularly for the intranet, communication tools, POP-Database ([44]) and support to MS regarding these matters; and

Legal support on contract law, development of templates and legal advice on contractual agreements.

Production of the different joint outputs is contracted to HTA bodies and outputs produced are reviewed by the members of respective committees. The basic workflow for this process is shown in Figure 19.

Figure 19: Organisational workflows for permanent secretariat



As displayed in Figure 19, output production and review of outputs are two separate processes. Output is going to be produced by one author and one co-author of a national HTA body. Experts from participating MS, who are part of the MS expert committee, will review outputs to ensure the quality of the outputs and consideration of national agendas. Author and co-author will be present for meetings but exempted from committee responsibilities if they are members of the committee. Both experts from HTA bodies and MS committees receive reimbursement of their expenses per diem for their work.

Initially, three committees on Early Dialogues, REAs and Full HTAs (depending on the respective policy option) would be established. Additional ad hoc or permanent commit-

([44]) The EUnetHTA Planned and Ongoing Projects (POP) database allows HTA agencies to share information with each other on planned, ongoing or recently published projects conducted at the individual agency.

tees or working groups on other tasks, e.g. development of methodologies, might be established.

The structure of the committees would be as follows:

- **Committee for Early Dialogues**:
  The committee includes 18 members from MS with extensive experience in HTA, 5 members from countries with less-extensive experience in HTA (on a rotational basis) and 3 external experts from various fields, e.g. health professionals, patient representatives, etc.). Meetings will take place four times per annum.
- **Committee for REAs**:
  The committee consists of 29 representatives of EU 28 and Norway (including one MS Chair) and four co-opted members to provide additional scientific advice. The committee meets eight times per annum to discuss and review outputs.
- **Committee for full HTAs**:
  The committee consists of 29 representatives of EU 28 and Norway (including one MS Chair) and four co-opted members to provide additional scientific advice. The committee meets four times per annum to discuss and review outputs.

Reflecting on the structure of committees, quorums and voting procedures need to be determined in a transparent matter (by developing Rules of Procedure). Members will be required to declare potential conflicts of interest.

Online voting and e-meetings with a suitable tool might be an option to reduce the workload and time needed for travelling, thus also reducing costs.

Presented governance structures require similar tasks (see Table 20). Nonetheless, support functions can be more readily centralised in a permanent cooperation model as compared to project-based cooperation. This is expected to increase the efficiency of processes and ensure greater consistency in outcomes. It would also enable national agencies and their experts to keep a primary focus on the scientific work and not on the administrative and coordination functions, which supports production of high quality joint outputs (e.g. organisation of meetings, interaction with experts from other countries and/or stakeholders etc.).

When estimating the resource needs of the permanent cooperation models (MS secretariat for PO3; EU secretariat hosted by the EC based for PO4.1; Existing EU agency for PO4.2; and a new EU agency for PO5), similar structures were identified. In other words, the cooperation model is determined by the outputs and the tasks necessary for delivering these outputs. The hosting institution (i.e. a MS Agency, the EC, an existing or new EU Agency) will have an impact on the calculations ([45]) as coordination and support effort increases, depending on the scope of outputs, but no major impact on the functions to be performed is expected as there are specific requirements related to high-cost investment.

The different legal and formal requirements for integrating the cooperation model, including a central Secretariat and its governing bodies, into an existing national or EU agency or founding a new EU agency, are subject to national or EU decision-making processes and therefore are not within the scope of this study.

Besides the overall governance structure, staff compositions for implementation mechanisms for each policy option (PO 2 to PO 5) were identified according to envisaged tasks.

([45]) The different price levels of Member States were accounted for by indexing the calculations based on the EU salary scheme to national price levels.

Table 20 shows the **estimated staff composition for the respective scope of joint output production** (see Table 20 &

Table 21 for specifications) taking the expected participation of MS into account. The scope of the implementation mechanisms was set as follows (rounded figures in Full Time Equivalents (FTE)):

Table 20: Characteristics and staff needed of potential implementation mechanisms for 65 joint REA

Implementation Mechanism	Characteristics

Project-based cooperation	• Central cooperation management (Leading partner)
	• Human resources (**total 12 + 3 (IT) FTE**):
	  ○ Lead manager (1 FTE)
	  ○ Lead scientific officer (1 FTE)
	  ○ Project manager (3 FTE)
	  ○ Financial officer (1 FTE)
	  ○ Communication/IT officer (1 FTE)
	  ○ Project management assistant (3 FTE)
	  ○ Administrative assistant (1-2 FTE)
	• Decentralised output management included in output production calculation for Work Packages
	• MS expert committee
	• Time horizon: 5 years
	• Tasks: Support functions
	• Maintenance of IT tools, methodology and templates (3 FTE)

Permanent Secretariat (PO3)	• Central coordination management
	• Human resources: (**total 14 FTE**)
	  • Head (1 FTE)
	  • **Administrative support (total 4 FTE)**
	  ○ Head of administration (1 FTE)
	  ○ Project Manager (1 FTE)
	  ○ Administrative staff (2 FTE)
	  • **Scientific/technical support (total 6 FTE)**
	  ○ Head (1 FTE)
	  ○ Scientific officers (2 FTE)
	  ○ Methodology, guidelines, templates (2)
	  ○ Administrative staff (1 FTE)
	  • **IT (total 3 FTE)**
	  ○ Internal support l (1 FTE)
	  ○ Maintenance of tools and databases (2 FTE)
	• Output production contracted to HTA bodies
	• MS expert committee on ED
	• Time horizon: Permanent
	• Tasks: Central support (including administrative, scientific/technical, IT support, legal support), maintenance of tools, methodology and templates

Permanent secretariat (PO4.1)	• Central coordination management
	• Human resources: (**total 31 FTE**)
	  • Head (1 FTE)
	  • **Administrative support (total 11 FTE)**
	  ○ Head of administration (1 FTE)
	  ○ Project Manager (4 FTE)
	  ○ Administrative (6 FTE)
	  • **Scientific/technical support (total 15 FTE)**
	  ○ Head (1 FTE)
	  ○ Scientific officers (7,5 FTE)
	  ○ Methodology, guidelines, templates (2,5 FTE)
	  ○ Administrative (4 FTE)
	  • **IT support (total 4 FTE)**
	  ○ Internal support (1,5 FTE)
	  ○ Maintenance of tools and databases (2,5 FTE)
	• Output production contracted to HTA bodies
	• MS expert committee on ED and REA
	• Time horizon: Permanent
	• Tasks: Central support (including administrative, scientific/technical, IT support, legal support), maintenance of tools, methodology and templates

Permanent Secretariat (PO4.2)	• Central coordination management • Human resources: (**total 34,5 FTE**) • Head (1 FTE)

	• **Administrative support (total 11 FTE)**
	  o Head of administration (1 FTE)
	  o Project Manager (4 FTE)
	  o Administrative (6 FTE)
	• **Scientific/technical support (total 18,5 FTE)**
	  o Head (1 FTE)
	  o Scientific officers (9,5 FTE)
	  o Methodology, guidelines, templates (2,5 FTE)
	  o Administrative (5,5 FTE)
	• **IT support internal (4 FTE)**
	  o Internal support (1,5 FTE)
	  o Maintenance of tools and databases (2,5 FTE)
	• Output production contracted to HTA bodies
	• MS expert committee on ED and REA
	• Time horizon: Permanent
	• Tasks: Central support (including administrative, scientific/technical, IT support, legal support)), maintenance of tools, methodology and templates

New EU agency (PO5)	• Human resources: (**total 45,5 FTE**)
	• Head (1 FTE)
	• **Administrative support (total 16 FTE)**
	  o Head of administration (1 FTE)
	  o Project Manager (6 FTE)
	  o Administrative (9 FTE)
	• **Scientific/technical support (total 23,5 FTE)**
	  o Head (1 FTE)
	  o Scientific officers (11 FTE)
	  o Methodology, guidelines, templates (3 FTE)
	  o Administrative (8,5 FTE)
	• **IT (total 6 FTE)**
	  o Internal support (2 FTE
	  o Maintenance of tools and databases (3 FTE)
	• Output production contracted to HTA bodies
	• MS expert committee on ED, REA and Full HTA
	• Time horizon: Permanent
	• Central support (including administrative, scientific/technical, IT support, legal support), maintenance of tools, methodology and templates

As depicted in the table, the staff composition of PO 3 is low due to the low number of expected outputs. According to the assumptions made in 6.2.2.2, output production is limited to 40 Early Dialogues p.a.

Relating to the staff composition of PO 4.1 and PO 4.2, differences in staff resources result from the V/M or M/M participation rate of MS for the Policy Options (for assumptions see 6.2.2.2).

Estimates on staff resources included output of 40 Early Dialogues and/or 65 REAs (40 on Pharmaceuticals, 25 on medical technologies) and/or 11 Full HTAs (7 on Pharmaceuticals, 4 on medical technologies) depending on the respective policy option. Cost estimates on maintenance of tools, methodologies and templates was separately assessed to correspond with the description of Policy Options displayed in Table 7, but will be integrated in the coordination unit for all options with a permanent secretariat. For potential development of tools, methodologies and templates, final cost estimates include a lump sum (Table 56).

Prognosed output production is relevant for the period until structures and processes are well-established. After that adaption to EMA processes, i.e. an increase from 65 REAs to 115 REAs (38 on Pharmaceuticals, 25 on medical technologies), covering all centrally authorized new substances and indications is recommended. Accordingly, staff composition would increase for POs 4.1, 4.2 and 5 due to expanded output production (Table 21).

Table 21: Characteristics and staff needed of potential implementation mechanisms for 115 joint REA

Implementation Mechanism	Characteristics

Permanent secretariat (PO4.1)	• Central coordination management
	• Human resources: (**total 38 FTE**)
	  • Head (1 FTE)
	  • **Administrative support (total 11 FTE)**
	  ○ Head of administration (1 FTE)
	  ○ Project Manager (4 FTE)
	  ○ Administrative (6 FTE)
	  • **Scientific/technical support (total 22 FTE)**
	  ○ Head (1 FTE)
	  ○ Scientific officers (12,5 FTE)
	  ○ Methodology, guidelines, templates (2,5 FTE)
	  ○ Administrative (6 FTE)
	  • **IT support (total 4 FTE)**
	  ○ Internal support (1,5 FTE)
	  ○ Maintenance of tools and databases (2,5 FTE)
	• Output production contracted to HTA bodies
	• MS expert committee on ED and REA
	• Time horizon: Permanent
	• Central support (including administrative, scientific/technical, IT support, legal support), maintenance of tools, methodology and templates

Permanent Secretariat (PO4.2)	• Central coordination management
	• Human resources: (**total 44 FTE**)
	  • Head (1 FTE)
	  • **Administrative support (total 11 FTE)**
	  ○ Head of administration (1 FTE)
	  ○ Project Manager (4 FTE)
	  ○ Administrative (6 FTE)
	  • **Scientific/technical support (total 28 FTE)**
	  ○ Head (1 FTE)
	  ○ Scientific officers (16FTE)
	  ○ Methodology, guidelines, templates (2,5 FTE)
	  ○ Administrative (8,5 FTE)
	  • **IT support (total 4 FTE)**
	  ○ Internal support (1,5 FTE)
	  ○ Maintenance of tools and databases (2,5 FTE)
	• Output production contracted to HTA bodies
	• MS expert committee on ED and REA
	• Time horizon: Permanent
	• Central support (including administrative, scientific/technical, IT support, legal support), maintenance of tools, methodology and templates

New EU agency (PO5)	• Human resources: (**total 54,5 FTE**)
	  • Head (1 FTE)
	  • **Administrative support (total 16 FTE)**
	  ○ Head of administration (1 FTE)
	  ○ Project Manager (6 FTE)
	  ○ Administrative (9 FTE)
	  • **Scientific/technical support (total 32,5 FTE)**
	  ○ Head (1 FTE)
	  ○ Scientific officers (17,5 FTE)
	  ○ Methodology, guidelines, templates (3 FTE)
	  ○ Administrative (11 FTE)
	  • **IT support (total 5 FTE)**
	  ○ Internal support (2 FTE)
	  ○ Maintenance of tools and databases (3 FTE)
	• Output production contracted to HTA bodies
	• MS expert committee on ED, REA and Full HTA
	• Time horizon: Permanent
	• Central support (including administrative, scientific/technical, IT support, legal support), maintenance of tools, methodology and templates

6.2.2.6 Limitations

Current HTA outputs are heterogeneous across Europe regarding methods, included domains, timelines and available resources. HTA reports may also differ in scope, e.g. single technology (STA) vs. multi technology assessment (MTA), initial assessment vs. reassessment, and therefore costs for a REA or a Full HTA may vary considerably. Although a broad range is assumed for the base case costs of REAs and Full HTAs and their estimation is done separately for HTA bodies, the Pharmaceutical and the MedTech-industry (submission reports) this has to be interpreted with caution.

Data sources for current costs and quantities of outputs at MS level have gaps and uncertainties (main sources: data derived from online survey plus additional follow-up, discussions with experts, stakeholders and DG SANTE, Chamova 2017 (2), cross-checked with other sources where possible, and judged by authors' own experience). In some cases, exact figures on the current amount of national output are not available, but known to be higher than zero. Overall annual numbers and thus annual savings within the Policy Options at MS level may therefore be underestimated to some degree.

Early Dialogues are included in the prognosis of expected production costs, but due to a lack of data on the current national costs and quantities, the related expected savings in 'production costs' at national level cannot be calculated. Moreover, it may be assumed that ED leads to a reduction in additional evidence generation requested by HTA bodies. This could not be integrated for the same reason (Moreover, nearly none of the survey respondents reported a reduction in HTA costs due to Early Dialogues, see also Table 36 and Table 37).

Regarding changes in HTA-expenses at national level, it is neglected that there may be an uptake of Joint Output (and related savings or costs) for other purposes than reimbursement decisions. Also, the long term overall impact of centrally organised mandatory HTA outputs on national HTA systems e.g. in terms of transparency, standardisation or methodological quality cannot be quantified.

Expenses associated with the adaptation of national regulations for mandatory uptake of REA/HTA cannot be quantified either, but have to be taken into account (see also 6.2.2.1).

All assumptions and calculations for the output-related cost prognosis are mainly based on data from 29 countries (that are included in Chamova 2017) (2), EMA reports and EUnetHTA findings and were at least partly discussed with experts and DG SANTE.

An adjustment of national costs/prices for purchasing power parity (PPP) was planned. But with rather low response rates and many inherent uncertainties, this would add a misleading semblance of precision. Additionally, estimates of costs per REA, HTA etc. are based mainly on survey responses from all over Europe – so it may be assumed that differing PPPs are roughly already in the ranges.

The Business Models combine output production and implementation mechanisms according to the Policy Options displayed in Table 7, Policy Option 1 is linked to the implementation mechanism without EU input. According to the assumption made in the analytical approach, projects without EU input are strictly the MS' responsibility. Hence, a business model for Policy Option 1 and an implementation mechanism without EU input is not covered within this study.

7 Results

7.1 Case study – baseline scenario

The aim of this case study is to systematically capture and depict the elements composing the status quo of HTA processes across the EU MS.

We compared and analysed a sample of 40 health technologies to identify the elements composing the value assessments of health technologies across difference European countries. This objective would be achieved identifying the final HTA recommendations and/or the recommended restrictions in order to include or suggest the inclusion in the benefits catalogue of each country of a specific product and how these and the length of the process differed or aligned across settings. Indeed, the systematic analysis identified:

- The presence of assessment and the final decision taken by HTA bodies, capturing the possible duplications;
- How HTA is currently used in different contexts and, if so, what clinical and economic evidence were used in conducting the assessments;
- The timeline in performing the process across different country setting; and
- The costs related to the HTA process.

This allowed an understanding of the variability in methods and processes currently employed by different HTA bodies across the EU and enable the identification of possible duplication of efforts or cases where greater consensus is needed around HTA processes and methods. It also contributed to identifying areas where greater consistency and transparency in the criteria used for decision-making can be improved.

Given the length of this report and the peculiarities arising from specific subsections of the results, the discussion section is structured along the presentation of the results.

7.1.1 Description of the sample

Initially, 2 576 HTA reports for Pharmaceutical products, 423 HTA reports for medical devices([46]) and 94 HTA reports for "Other Technologies" were identified, all together amount-ing to 3,093 reports. Applying the search criteria, 111 common Pharmaceutical-indication pairs, 20 common medical device-indication pairs and ten common "Other Technologies" indication pairs were identified across at least five EU MS, from which we selected the purposive sample based on to the process outlined in 5.2.1.

Across different categories of health technologies the case study sample included:

- 20 Pharmaceutical-indication pairs (Table 22 and in more detail in Annex 9)
- 15 medical device-indication pairs (Table 23 and in more detail in Annex 10)
- Five other Technology-indications pairs (Table 24 and in more detail in Annex 11)

Looking at the main features of the sample, three Pharmaceutical products were marketed by an SME, whereas all remaining products were marketed by large Pharmaceutical companies. Three out of 20 Pharmaceutical products were existing molecules considered for a new indication, whereas 17 were considered for the first time by EMA.

([46]) The word 'devices' is used generically and includes medical devices and associated medical technologies.

As shown in the following tables, a wide range of disease areas were included, comprising three orphan drugs, four Pharmaceuticals treating chronic diseases and four technologies indicated for a paediatric population. The sample includes molecules approved by EMA from 2011 until 2015 (Table 22).

Table 22: Pharmaceutical – indication pair sample

GENERIC NAME	BRANDED NAME	INDICATION
Abiraterone	Zytiga®	Treatment of metastatic castration-resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel- based chemotherapy regimen.
Aclidinium Bromidum	Eklira Genuair®	Maintenance bronchodilator treatment for relieving symptoms in adults with illness chronic obstructive pulmonary disease (COPD).
Alemtuzumab	Lemtrada®	For adult patients with relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.
Apremilast	Otezla®	Treating moderate to severe plaque psoriasis
Ataluren	Translarna®	Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older
Canagliflozin	Invokana®	Treatment of Diabetes Mellitus Type 2
Dapagliflozin	Forxiga®	Forxiga is indicated in adult diabetes type II patients aged 18 years and over, for the improvement of glycemic control in the form of monotherapy if diet and exercise do not ensure proper control of blood glucose levels in patients for whom metformin use is not appropriate because of intolerance.
Defibrotide	Defitelio®	Defitelio is indicated for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.
Ivacaftor	Kalydeco®	Treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene.
Mirabegron	Betmiga®	Treatment of symptoms of overactive bladder
Nivolumab	Opdivo®	Treatment of advanced (unresectable or metastatic) melanoma
Nintedanib	Ofev®	Treatment of Idiopathic Pulmonary Fibrosis (IPF).
Ocriplasmin	Jetrea®	Treatment of vitreomacular traction (VMT).
Ofatumumab	Arzerra®	In combination with chlorambucil or benda-mustine for the treatment of chronic lymphocytic leukemia (CLL) in patients for this disease not previously treated and which are not eligible for a treatment based on fludarabine
Omalizumab	Xolair®	Treatment of adults, adolescents and children (Aged 6 to <12 years) with asthma
Pasireotide	Signifor®	Treatment of adult patients with Cushing's Disease for whom surgery is not an option or for whom surgery has failed
Ramucirumab	Cyramza®	Treatment of advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy
Rilpivirine	Edurant®	In combination with other antiretroviral medicinal products for the treatment of human immunodefi-ciency virus type 1 (HIV-1) infection in antiretroviral treatment-naive adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml.
Riociguat	Adempas®	Treatment of adult patients with WHO Functional Class (FC) II to III with inoperable CTEPH, persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity
Sofosbuvir	Sovaldi®	In combination with other Pharmaceuticals, for the treatment of Chronic hepatitis C (HCC) in adults

In the case of medical devices, different brands were included across different countries, reflecting the heterogeneity of the European market and of medical devices. In total, 15 branded medical devices were included and five types of medical devices for which the brand was not specified. As shown on Table 23, these covered a wide range of disease areas. In order to have a representative sample of different type of technologies, we included ten invasive medical devices, four non-invasive devices and one in-vitro technology.

Table 23: Medical device-indication pair sample and disease areas included

Medical device type	Disease area
Endovascular stents	Cardiovascular disease
Home haemodialysis device	Kidney diseases
Transcatheter implantable devices	Cardiovascular disease
Balloon Eustachian Tuboplasty	Diseases of the ear
Oscillometric blood pressure monitor	Cardiovascular disease
High intensity focused ultrasound (HIFU)	Prostate cancer
Gene expression profiling diagnostics	Oncology
Positron emission tomography (PET)	Oncology
Cochlear implants	Deafness
Left ventricular assist devices	Cardiovascular disease
LASER KTP	Prostate cancer
Self-monitoring coagulometers	Diabetes
Nucleic acid amplification tests (NAATs)	Infectious diseases
Duodenal-jejunal bypass sleeve	Obesity
Vitro fertilisation (IVF)	Fertility

This heterogeneity is further enhanced in the 'Other Technologies' sub-sample, where the evaluations might include different products/tests/technologies under an evaluation due to differences in public health programmes across countries and the availability of the respective technologies. Some of the reports in this sub-sample offer a comparison between technologies in the context of a screening program or vaccination rather than an evaluation of the whole program per se.

As shown on Table 24, three vaccination programmes and two cancer screening programmes were included. It is important to highlight that the 'Other Technologies' sample includes different products/tests/technologies under evaluation due to differences in public health programmes across countries and the availability of the technology included in the program.

Table 24: Other technology – indication pair sample and disease areas included

Intervention name	Description	Disease area
HPV Vaccination	Role of vaccination against human papillomavirus in reducing the risk of cervical cancer.	Oncology
Colorectal cancer screening	Screening programme aiming to identify people who appear healthy but may be at increased risk of a colorectal cancer.	Oncology
Pneumococcal vaccination	Vaccination programme to prevent pneumococcal disease (IPD)	Streptococcus pneumonia
Rotavirus vaccination	Rotavirus vaccination is programme to protect against rotavirus infections. Usually part of the childhood vaccination programme for babies aged 8 weeks and 16 weeks.	Acute gastroenteritis
Cervical cancer Screening programme	Gynaecological cancer screening programme with the use of a smear (PAP) test	Oncology

7.1.2 Assessments conducted across the sample

Based on the selection of the 40 technologies, we retrieved a total of 321 reports and performed an in-depth analysis on those based on the methodology discussed in section 6.1. As shown by Table 25, Table 26 and Table 27, 229 reports were retrieved for the 20 Pharmaceutical sample, 46 for the 15 Medical Device sample and 31 across the 'Other Technologies' sample.

The evidence showed that in the Pharmaceutical sample, the same Pharmaceutical-indication pair has been evaluated at least by 10 agencies with an average across the sample of 13.5 agencies evaluating the same Pharmaceutical-indication pair out of 19 HTA bodies considered.

By contrast, the current situation in HTA for medical devices and 'Other Technologies' is less developed and established in comparison to the Pharmaceuticals. Indeed, in the medical devices and other technologies samples, the number of HTA evaluations was lower. On average, one device or one 'Other Technology' was evaluated by six agencies with at least four countries evaluating the same medical device.

These trends are related to the peculiarity of the Medical devices market. Whereas Pharmaceutical products have a well-established pathway from Marketing Authorization to HTA evaluation and an established HTA process in a large number of European countries, medical devices and other technologies follow heterogeneous rules or processes regarding their evaluation. This is also reflected in the sample selected. Indeed, Pharmaceuticals were selected only if they had undergone an evaluation for the exact same indication across settings. In the medical device sample, there would be the same type (but with a different branded name or/and a different manufacturer). Additionally, medical devices should have undergone an evaluation for the same disease area and not the exact same indication. This is because the market for medical devices is intrinsically different from that of Pharmaceuticals, with a higher level of competition from market entry onwards. While HTA has been largely developed for Pharmaceuticals, there appears to be a need for adaptation to and development of established HTA processes for the medical devices sector as well (32).

Table 25: Pharmaceutical products assessment across settings

Pharmaceuticals Included	UK-NICE	UK-SMC	Ireland-NCPE	France-HAS	Belgium-KCE*	Italy- AGENAS	Italy- UVEF	Sweden- TLV	Germany-IQWIG***	Germany-G-BA***	Croatia-Azz	Finland-Fimea	Spain-AEMPS	Spain-AQuAs	Spain-Avalia	[illegible] University of Tardu and [illegible]	Lithuania-VASPVT	Austria-LBI-HTA	Austria-GÖG	EUnetHTA	Nether-ldans-ZIN	Romania-NAMMD	Portugal-Infarmed	Poland-AOTMiT	Italy-AIFA**	TOTAL ASSESSED
Abiraterone	✓	✓	✓	✓	X	X	✓	✓	✓	✓	X	X	X	X	X	X	X	X	X	X	✓	✓	✓	✓	✓	13
Aclidinium Bromidium	X	✓	✓	✓	X	X	X	✓	✓	✓	X	X	✓	✓	X	X	X	X	X	X	✓	✓	✓	X	✓	12
Alemtuzumab	✓	✓	✓	✓	X	X	X	✓	✓	✓	X	X	✓	X	X	X	X	X	X	X	✓	✓	X	✓	✓	12
Apremilast	✓	✓	✓	✓	X	X	X	✓	✓	X	X	X	✓	X	X	X	X	X	X	X	✓	X	X	✓	✓	10
Ataluren	✓	✓	✓	✓	X	X	X	X	✓	✓	X	X	✓	X	X	X	X	X	X	X	X	✓	X	✓	✓	10
Canagliflozin	✓	✓	✓	✓	X	X	X	✓	✓	✓	X	X	✓	✓	X	X	X	X	X	✓	✓	✓	X	✓	✓	14
Dapagliflozin	✓	✓	✓	✓	X	X	X	✓	✓	✓	X	X	X	✓	X	X	X	X	X	X	✓	✓	✓	✓	✓	13
Defibrotide	X	✓	✓	✓	X	X	X	X	X	✓	X	X	X	X	X	X	X	✓	X	X	✓	X	X	✓	✓	8
Ivacaftor	X	✓	✓	✓	X	X	X	✓	✓	✓	X	X	✓	✓	X	X	X	X	X	X	✓	X	X	✓	✓	11
Mirabegron	✓	✓	✓	✓	X	X	X	✓	✓	✓	X	X	X	✓	X	X	X	X	X	X	✓	X	X	X	✓	10
Nivolumab	✓	✓	✓	✓	X	X	X	✓	✓	✓	X	✓	✓	X	X	X	X	X	X	X	X	✓	X	✓	✓	12
Nintedanib	✓	✓	✓	✓	X	X	X	✓	✓	✓	X	X	✓	✓	X	X	X	X	X	X	✓	✓	X	✓	✓	13
Ocriplasmin	✓	✓	✓	✓	X	X	X	✓	✓	✓	X	X	X	X	X	X	X	X	X	X	✓	X	✓	✓	✓	11
Ofatumumab	✓	✓	✓	✓	X	X	✓	✓	X	X	X	X	✓	✓	X	X	X	X	X	X	✓	X	✓	✓	✓	12
Omalizumab	✓	✓	✓	✓	X	X	X	✓	X	✓	X	X	X	X	X	X	X	X	X	X	X	✓	✓	✓	✓	10
Pasireotide	X	✓	✓	✓	X	X	X	X	✓	✓	X	X	X	X	X	X	X	X	X	X	X	✓	X	✓	✓	8
Ramucirumab	✓	✓	✓	✓	X	X	X	✓	✓	✓	X	✓	✓	X	X	X	X	X	X	✓	✓	✓	X	✓	✓	14
Rilpivirine	X	✓	✓	✓	X	X	X	✓	✓	✓	X	X	X	X	X	X	X	X	X	X	✓	X	✓	✓	✓	10
Riociguat	X	✓	✓	✓	X	X	X	✓	✓	✓	X	X	✓	✓	X	X	X	X	X	X	✓	✓	X	✓	✓	12
Sofosbuvir	✓	✓	✓	✓	✓	X	X	✓	✓	✓	✓	X	✓	X	X	X	X	X	X	X	✓	✓	✓	✓	✓	15
TOTAL ASSESSED	14	20	20	20	1	0	2	17	17	18	1	2	12	8	0	0	0	1	0	2	16	13	8	18	20	

Note: Ticks indicate that the technology has been assessed, while crosses indicate that the technology has not been assessed. Countries with no HTA reports publically available have been excluded from this table (e.g. Hungary, Bulgaria, Cyprus, Slovenia, Latvia, etc.) Countries with no HTA reports publically available have been excluded from this table (e.g. Hungary, Bulgaria, Cyprus, Slovenia, Latvia, etc.) ; It may be the case that we have included national regulatory bodies to capture also agencies that perform HTA on the side of theire regulatory role.

Legend: NICE: National Institute for Health and Clinical Excellence (NICE); SMC: Scottish Medicines Consortium; TLV: Dental and Pharmaceutical Benefits Board; HAS: Haute Autorité de Santé; GÖG: Gesundheit Österreich GmbH; LBI-HTA: Ludwig Boltzmann Institute for Health Technology Assessment; KCE: Belgian Health Care Knowledge Centre; NCPHA: The National Center of Public Health and Analyses; MoH: Ministry of Health; AZZ: Agencija za kvalitetu i akreditaciju u zdravstvu i socijalnoj skrbi; FIMEA: Finnish Medicines Agency KELA: Kansaneläkelaitos; IQWIG: Institute for Quality and Efficiency in Healthcare; G-BA: Gemeinsame Bundesausschuss; NCPE: National Centre for Pharmacoeconomics; HIQA: Health Information and Quality Authority AIFA: Agenzia Italiana del Farmaco UVEF: Unità di valutazione dell'efficacia del farmaco; AGENAS: Agenzia Nazionale per i servizi sanitari regionali; ZVA: Zalu valsts agentura; VASPVT: Valstybinė akreditavimo sveikatos priežiūros veiklai tarnyba; ZiN: Zorginstituut Nederland AOTMiT: Agencja Oceny Technologii Medycznych i Taryfikacji; Infarmed: Instituto Nacional da Farmácia e do Medicamento; NAMMD: National Agency for Medicines and Medical Devices; CADIME: Centro Andaluz de Documentación e Información de Medicamentos; AquAS: Agència de Qualitat i Avaluació Sanitàries de Catalunya; ISCII: Instituto de Salud Carlos III OSTEBA: Basque Office for Health Technology Assessment; AETSA: Andalusian Agency for Health Technology Assessment; SECS: Servicio de Evaluacion del Servicio Canario de salud. (*KCE does not have a mandate for Pharmaceuticals but it performed an economic evaluation of the Hepatitis C treatments comprising also Sofusbuvir (**) For AIFA the reports were not publicly available but the decision was published in Gazzetta Ufficiale (***) The two German bodies IQWIG and G-BA work in the same HTA process; if an assessment is done twice it does not constitute a duplication. Source: The Authors.

Table 26: Medical device assessment across settings

Medical Devices Included	UK-NICE	UK- SHTG	Ireland-NCPE	France-HAS	Belgium-KCE	Italy-AGENAS	Sweden-TLV	Germany-IQWIG*	Germany-G-BA*	Croatia-Azz	Finland-Fimea	Spain-ISCII	Spain-AQuAs	Spain-Avalia	Spain-OSTEBA	Estonia-University of Tartu and Fuse	Lithuania-VASPVT	Austria-LBI	Austria- GÖG	EUnetHTA	Netherlands-ZiN	Romania-NAMMD	Portugal-Infarmed	Poland-AOTMiT	TOTAL ASSESSED
Endovascular stents	✓	x	x	✓	x	✓	x	x	x	✓	x	x	x	x	x	x	x	x	✓	x	✓	x	x	x	6
Home haemodialysis device	✓	x	x	✓	✓	✓	x	x	x	x	x	x	x	✓	x	x	x	x	x	x	x	x	x	x	5
Transcatheter implantable devices	x	✓	x	✓	x	x	x	x	x	x	x	x	x	x	✓	x	x	✓	x	✓	✓	x	x	x	6
Balloon Eustachian Tuboplasty	✓	x	x	x	x	✓	x	x	x	✓	x	x	x	x	x	x	x	x	x	✓	x	x	x	x	4
Oscillometric blood pressure monitor	✓	x	x	✓	x	✓	✓	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	4
High intensity focused ultrasound (HIFU)	✓	x	x	✓	✓	✓	x	✓	x	x	x	x	x	x	x	x	✓	✓	x	x	✓	x	x	x	8
Self-monitoring coagulometers	✓	✓	x	✓	✓	✓	x	x	x	x	x	x	x	x	x	✓	x	x	✓	x	x	x	x	x	7
Positron emission tomography (PET)	x	x	x	x	✓	✓	x	✓	x	x	✓	x	✓	x	✓	x	x	x	x	x	x	x	x	x	6
Cochlear implants	✓	x	x	✓	✓	x	✓	x	x	x	✓	x	✓	x	x	x	✓	x	x	x	✓	x	x	x	8
Left ventricular assist devices	✓	x	x	✓	✓	✓	x	x	x	x	x	x	x	x	x	✓	x	x	x	x	✓	x	x	x	6
LASER KTP	✓	x	x	✓	✓	x	x	✓	x	x	✓	x	x	✓	x	x	x	✓	x	x	✓	x	x	x	8
Gene expression profiling diagnostics	✓	x	✓	x	✓	x	x	✓	x	x	✓	x	x	x	x	x	x	x	✓	x	✓	x	x	x	7
Nucleic acid amplification tests (NAATs)	✓	x	x	✓	✓	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	3
Duodenal-jejunal bypass sleeve	✓	x	x	✓	✓	x	x	x	x	✓	x	x	x	✓	x	x	x	x	x	✓	✓	x	x	x	7
In-vitro fertilisation (IVF)	x	x	x	✓	x	x	✓	✓	x	x	x	x	x	x	x	✓	x	x	x	x	✓	x	x	x	5
TOTAL ASSESSED	**12**	**2**	**1**	**12**	**11**	**8**	**3**	**5**	**0**	**3**	**4**	**0**	**2**	**3**	**2**	**3**	**2**	**3**	**3**	**3**	**9**	**0**	**0**	**0**	

Note: Ticks indicate that the technology has been assessed, while crosses indicate that the technology has not been assessed. Some HTA bodies (e.g. HAS and KCE) have published more than one report for type of medical devices. In this table however, the reports of these HTA bodies are counted as one. Countries with no HTA reports publically available have been excluded from this table (e.g. Hungary, Bulgaria, Cyprus, Slovenia, Latvia, etc.) It may be the case that we have included national regulatory bodies to capture also agencies that perform HTA on the side of theire regulatory role.
Legend: NICE: National Institute for Health and Clinical Excellence (NICE); SMC: Scottish Medicines Consortium; TLV: Dental and Pharmaceutical Benefits Board; HAS: Haute Autorité de Santé; GÖG: Gesundheit Österreich GmbH; LBI-HTA: Ludwig Boltzmann Institute for Health Technology Assessment; KCE: Belgian Health Care Knowledge Centre; NCPHA: The National Center of Public Health and Analyses; MoH: Ministry of Health; AZZ: Agencija za kvalitetu i akreditaciju u zdravstvu i socijalnoj skrbi; FIMEA: Finnish Medicines Agency KELA: Kansaneläkelaitos; IQWIG: Institute for Quality and Efficiency in Healthcare; G-BA: Gemeinsame Bundesausschuss; OGYEI: Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet; NCPE: National Centre for Pharmacoeconomics; HIQA: Health Information and Quality Authority AIFA: Agenzia Italiana del Farmaco UVEF: Unità di valutazione dell'efficacia del farmaco; AGENAS: Agenzia Nazionale per i servizi sanitari regionali; ZVA: Zalu valsts agentura; VASPVT: Valstybinė akreditavimo sveikatos priežiūros veiklai tarnyba; ZiN: Zorginstituut Nederland AOTMiT: Agencja Oceny Technologii Medycznych i Taryfikacji; Infarmed: Instituto Nacional da Farmácia e do Medicamento; NAMMD: National Agency for Medicines and Medical Devices; CADIME: Centro Andaluz de Documentación e Información de Medicamentos; AquAS: Agència de Qualitat i Avaluació Sanitàries de Catalunya; ISCII: Instituto de Salud Carlos III OSTEBA: Basque Office for Health Technology Assessment; AETSA: Andalusian Agency for Health Technology Assessment; SECS: Servicio de Evaluacion del Servicio Canario de salud. *(*)* The two German bodies IQWIG and G-BA work in the same HTA process; if an assessment is done twice it does not constitute a duplication. Source: The Authors.

Table 27: Other technology assessment availability

Other Technologies Included	UK-NICE	UK-SMC	Ireland**	France-HAS	Belgium-KCE	Italy-AGENAS	Sweden-TLV	Germany-IQWIG*	Germany-G-BA*	Croatia -Azz	Finland-Fimea	Spain-ISCII	Spain- AQuAs	Spain-Avalia	Spain-OSTEBA	Spain-SESCS	Spain-AETSA	Estonia- University Tartu	Estonia- EHIF	Lithuania- SMCA	Lituania-National Health Service (NHS)	Austria-LBI-HTA	Austria- GÖG	Austria-Hauptverband	EUnetHTA	Nethelands-ZiN	Romania -NAMMD	Portugal -Infarmed and SNS***	TOTAL ASSESSED
HPV Vaccination	X	X	✓	✓	✓	X	X	X	X	X	X	✓	X	X	X	X	X	✓	X	X	X	✓	X	✓	X	X	X	✓	8
Colorectal Cancer Screening	X	X	✓	✓	✓	X	X	✓	✓	X*	✓	X	X	X	X	X	X	✓	X	X	X	✓	*X	✓	✓	X	X	X	10
Pneumococcal Vaccination	X	X	✓	X	✓	X	X	X	X	X	X	X*	X	✓	X	X	X	✓	X	X	X	X	*X	X	X	X	X	X	4
Rotavirus Vaccination	X	X	✓	X	✓	X	X	X	X	X	X	✓	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	3
Cervical cancer screening	X	X	X	✓	✓	X	X	✓	X	X	X	X*	✓	✓	X	X	X	X	X	X	X	✓	X	X	X	X	X	X	6
TOTAL ASSESSED	0	0	4	3	4	0	0	2	1	0	1	2	1	2	0	0	0	3	0	0	0	3	0	2	1	0	0	1	

Note: Ticks indicate that the technology has been assessed, while crosses indicate that the technology has not been assessed. Countries with no HTA reports publically available have been excluded from this table (e.g. Hungary, Bulgaria, Cyprus, Slovenia, Latvia, etc.) It may be the case that we have included national regulatory bodies to capture also agencies that perform HTA on the side of theire regulatory role.

Legend: NICE: National Institute for Health and Clinical Excellence (NICE); SMC: Scottish Medicines Consortium; TLV: Dental and Pharmaceutical Benefits Board; HAS: Haute Autorité de Santé; GÖG: Gesundheit Österreich GmbH; LBI-HTA: Ludwig Boltzmann Institute for Health Technology Assessment; KCE: Belgian Health Care Knowledge Centre; NCPHA: The National Center of Public Health and Analyses; MoH: Ministry of Health; AZZ: Agencija za kvalitetu i akreditaciju u zdravstvu i socijalnoj skrbi; FIMEA: Finnish Medicines Agency KELA: Kansaneläkelaitos; IQWIG: Institute for Quality and Efficiency in Healthcare; G-BA: Gemeinsame Bundesausschuss; OGYEI: Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet; NCPE: National Centre for Pharmacoeconomics; HIQA: Health Information and Quality Authority AIFA: Agenzia Italiana del Farmaco UVEF: Unità di valutazione dell'efficacia del farmaco; AGENAS: Agenzia Nazionale per i servizi sanitari regionali; ZVA: Zalu valsts agentura; VASPVT: Valstybinė akreditavimo sveikatos priežiūros veiklai tarnyba; ZiN: Zorginstituut Nederland AOTMiT: Agencja Oceny Technologii Medycznych i Taryfikacji; Infarmed: Instituto Nacional da Farmácia e do Medicamento; NAMMD: National Agency for Medicines and Medical Devices; CADIME: Centro Andaluz de Documentación e Información de Medicamentos; AquAS: Agència de Qualitat i Avaluació Sanitàries de Catalunya; ISCII: Instituto de Salud Carlos III OSTEBA: Basque Office for Health Technology Assessment; AETSA: Andalusian Agency for Health Technology Assessment; SECS: Servicio de Evaluacion del Servicio Canario de salud. (*) shows available reports before 2006-thus, not included in the analysis. (**) Different bodies are performing/requesting the assessment. (National Cancer Registry Ireland Health Information and Quality Authority, National Immunisation Advisory Committee) (***) In Poland, HTA assessments are also performed at county level. However, we considered only the national programmes (*) The two German bodies IQWIG and G-BA work in the same HTA process; if an assessment is done twice it does not constitute a duplication. Source: The Authors.

On the number of assessments conducted by country, the Kappa score was calculated (Annexes 16, 17 and 18) to show the level of agreement in the number of product assessments performed.

The comparison of the presence of assessment across countries reflected in the Kappa score show a better level of agreement in assessing health technologies in the Pharmaceutical sample than in the medical devices and 'Other Technologies' samples. It is important to acknowledge that looking at the level of agreement across countries when assessing a Pharmaceutical product and across all Pharmaceutical products, Annex 16 shows that the majority of Kappa scores indicate poor levels of agreement, but the results may be skewed due to the Kappa paradox. Indeed, as discussed earlier, the Kappa statistic is sensitive to the distribution of the marginal totals and can lead to an over- or underestimation of agreements levels.

To interpret the actual level of agreement, it is necessary to take into account the different topic selection criteria used by different HTA bodies when deciding what technology should be assessed. In other words, the common sample assessed across countries can be very small, because not all countries assess all technologies and the priority setting mechanisms for HTA vary across settings. For instance, SMC (Scotland) and HAS (France) assess all new Pharmaceuticals approved by EMA and marketed in the country; the same holds for bodies such as AIFA (Italy) and G-BA (Germany) and IQWIG (Germany). Other bodies are far more selective on which technologies they select assess and the criteria with which they select technologies for assessment.

For example, NICE (UK) and ZiN (The Netherlands) have a list of criteria on selecting the technologies that will undergo the review process. Such criteria may be the burden of disease, resource impact, clinical and policy importance, potential factors affecting the timelines for the guidance to be produced and likelihood of guidance having an impact on public health and quality of life. Finally, it is important to acknowledge that KCE (Belgium) does not have the mandate of assessing Pharmaceutical products and, therefore, just one product was identified, affecting the reliability of the Kappa score results.

This has led to results across the agencies assessing all the new products on the market and indeed would seem to indicate that this agreement is very poor. However, if we examine the percentage of agreements across bodies that routinely assess all technologies that are submitted to them (Table 28) a high level of agreement is obtained.

Table 28: Proportion of agreement of the recommendation of HTA reports

Proportion of agreement	HAS	G-BA	SMC	IQWIG	AIFA
HAS		**0.9**	**1**	**0.85**	**1**
G-BA	**0.9**		**0.9**	**0.8889**	**0.9**
SMC	**1**	**0.9**		**0.85**	**1**
IQWIG	**0.85**	**0.8889**	**0.85**		**0.85**
AIFA	**1**	**0.9**	**1**	**0.85**	

Therefore, if we take into account the results across those bodies, having at least a score of 0.21, **results show a mainly fair level of agreement**, with 45% of the agencies reaching a Kappa score between 0.21 and 1.

The trend is not confirmed in the medical devices sample, where the number of assessment is lower and fragmented across the sample. This is shown mostly by a poor Kappa score ($K<0.20$) in the assessment of medical devices across agencies (70% of the cases studied).

Looking at the other technologies sample, the level of agreement is generally poor with 64% of the HTA bodies achieving a poor level of agreement (K<0.2) and 36% achieving an agreement between fair (0.21<K<0.4) to very good (0.81<K<1).

7.1.3 Concluding remarks on assessments conducted across technologies

The analysis from the preceding section suggests that, across the range of Pharmaceutical products considered, there is a fair level of agreement across HTA bodies, also taking into account the type of HTA body and the level of HTA development in the study countries.

Different indicators confirm this broad level of agreement across HTA bodies. First, the average number of HTA reports assessed across the sample is high (13.5 out of 20 products). Second, the Kappa score calculated and adjusted for proportions of agreement on the availability of HTA reports shows that countries with established HTA bodies tend to assess the same number of Pharmaceutical products and the same drug-indication pairs.

This is confirmed specifically when considering regulatory HTA bodies such as HAS (France), G-BA (Germany) and AIFA (Italy) due to their topic selection process (evaluating all new Pharmaceuticals submitting an application for marketing in their respective countries) as well as high level of agreement among other HTA bodies, such as TLV (Sweden) and NICE (England) or INFARMED (Portugal).

Considering the landscape of medical technology, this clearly differs from Pharmaceutical products. The level of agreement in the availability of HTAs showed by the kappa score is mainly poor. Among others, this is testament to the fragmentation of the MedTech sector and the variability with which HTA bodies select medical technology targets for assessment.

Finally, the 'Other Technologies' sample shows a low level of agreement across countries as well. This may be related to the low number of agencies actively engaging in HTA for this category of technology (n=14), the lack of publicly available HTA reports, the country priorities relating to public health interventions, including, for example, differences in vaccination programs due to different interventions considered, or the different policies employed in implementing preventive programs. As a result, it is difficult to draw conclusions from this part of the sample.

7.1.4 HTA recommendations

A categorisation was applied initially to all countries in an attempt to allow preliminary comparisons. Final HTA outcomes (assessment) were divided into three categories: (a) Positive recommendation, (b) Mildly positive recommendation and (c) Negative recommendation. These categories were linked to different types of recommendation and to the commonly accepted categorisation of the outcome (appraisal and pricing and reimbursement decision) between: a) to list the drug as requested in the HTA submission (e.g. positive coverage recommendation), (b) to restrict the drug to a subgroup of the population or under certain conditions (e.g. restricted coverage recommendation), and (c) to reject the drug (e.g. negative coverage recommendation).

In the case of 'Other Technologies', we are considering the outcome as restricted/mildly positive when policy recommendations had been made and there is a need of further clinical studies/evidence or clearer decision-making processes.

Table 29: Preliminary categorisation of recommendation

Colour	Assessment recommendation	Category
	Rejected	Negative
	Listed with Criteria	Mildly positive (restricted)
	Listed	Positive
ND	No decision	
N/A	Not applicable	

Following expert advice, the categorisation of outcomes presented captures and clusters different categories of decisions as well in order to capture the heterogeneity of the current situation. For instance, in Germany the HTA bodies do not reject any Pharmaceuticals but give an assessment of the extent of clinical benefit.

Across the entire sample, 66% (n=242) of the technologies were positively assessed with or without restrictions. Breaking down this figure, and excluding IQWIG and HAS, where the benefit is ranked instead of producing a yes/no decision, across the positive recommendations, 62% (n=123) were acceptances with restrictions whereas the remaining 35% (n=75) were fully accepted (no restrictions).

Across the sample of **Pharmaceuticals** and **medical devices** this trend was confirmed with 81% and 64% respectively receiving a positive recommendation, of which 63% and 59% respectively received a restricted recommendation. Across the '**Other Technology**' sample, most of the recommendations were restricted (66%).

Due to the limited availability of reports in the medical devices and other technologies samples, the Kappa score for these technologies was not possible to estimate. This is because of the Kappa paradox.

Contrary, in the Pharmaceutical sample where no availability issues were faced, a sample of Pharmaceuticals was selected to test the Kappa score of the HTA outcomes. This is presented in Table 30.

Looking at the level of agreement calculated with Kappa score, the results show that 69% showed a 'poor' agreement in final decisions, 24% a 'fair' agreement and 7% a 'moderate' agreement; this highlighted the heterogeneity across HTA bodies in assessing the HTA evidence.

Table 30: Kappa score - Consistency of HTA recommendation across of Pharmaceutical products sample

Kappa scores	UK-NICE	UK-SMC	Ireland-NCPE	France-HAS	Sweden-TLV	Germany-IQWIG	Germany-G-BA	Spain-AEMPS	Spain-AQuAs	Netherlands-ZIN	Romania-NAMMD	Portugal-Infarmed	Poland-AOTMiT
UK-NICE		0.22	0.31	0.00	0.07	0.00	0.00	N/A	0.00	0.58	0.25	0.00	0.03
UK-SMC	0.22		0.15	0.00	0.14	0.00	0.00	0.33	0.22	0.18	0.32	0.15	0.00
Ireland-NCPE	0.31	0.15		0.00	0.00	0.00	0.00	0.14	0.31	0.45	0.05	0.50	0.00
France-HAS	0.00	0.00	0.00		0.00	0.00	0.00	0.00	0.24	0.00	0.00	0.00	
Sweden-TLV	0.07	0.14	0.00	0.00		0.00	0.00	0.29	0.07	0.24	0.07		0.22
Germany-IQWIG	0.00	0.00	0.00	0.00	0.00		0.00	0.23	0.33	0.00	0.00	0.00	0.07
Germany-G-BA	0.00	0.00	0.00	0.00	0.00	0.00		0.00	0.22	0.38	0.00	0.00	0.05
Spain-AEMPS	N/A	0.33	0.14	0.00	0.29	0.23	0.00		N/A	0.04	0.22	0.50	1.00
Spain-AQuAs	0.00	0.22	0.31	0.24	0.07	0.33	0.22	N/A		0.13	0.25	0.41	0.28
Netherlands-ZIN	0.58	0.18	0.45	0.00	0.24	0.00	0.38	0.04	0.13		0.37	0.11	0.05
Romania-NAMMD	0.25	0.32	0.05	0.00	0.07	0.00	0.00	0.22	0.25	0.37		0.17	0.17
Portugal-Infarmed	0.00	0.15	0.50	0.00		0.00	0.00	0.50	0.41	0.11	0.17		0.08
Poland-AOTMiT	0,0267	0.00	0.00		0.22	0.07	0.05	1.00	0.28	0.05	0.17	0.08	

Note: The table includes values where there is a common sample of products across agencies. Based on this, a number of agencies have been excluded, notably Croatia (AZZ), Finland (Fimea), Austria (LBI), EUnetHTA , Italy (UVEF), and Belgium (KCE). N/A: this quantity cannot be calculated." This occurs only when data entries in the above table include a substantial proportion of zero..

Again, the results should be considered carefully because in the cases of HAS, IQWIG and G-BA, their classification algorithms were mainly binary due to the type of HTA they perform, which skews the results towards Kappa 0. The results across these agencies would seem to indicate that this agreement is really very poor. However, if we look at the percentage of agreements in *HTA outcomes* in comparison with these agencies (Table 31), a high level of agreement, especially between IQWIG, G-BA and HAS, can be shown. The reason for the discrepancy between the unadjusted level of agreement and Kappa is affected by prevalence of the finding under consideration and, for very low values of Kappa, may not necessarily reflect low rates of overall agreement.

Table 31: Proportion of agreement on outcomes

Proportions of agreement	HAS	G-BA	SMC	IQWIG
HAS		**0.8824**	**0.6111**	**0.8824**
G-BA	**0.8824**		**0.5882**	**1**
SMC	**0.6111**	**0.5882**		**0.5455**
IQWIG	**0.85**	**1**	**0.5455**	

The calculation of the Kappa score was not possible for medical device outcomes due to their heterogeneity, showing agreement to always be below 0.

Looking at the Kappa score for the outcomes in the 'other technologies' sample, agreement in decision outcomes between HTA bodies was not significant, suffering from limitations due to the small sample. However, as is shown in Annex 19, 22 out of 26 decisions were to restrict the health intervention, clearly showing agreement in decisions across countries.

7.1.5 Clinical and economic restrictions

A number of clinical and economic restrictions were identified in the HTA reports of the study sample. These have a different level of impact on the actual situation, based on the role and the function of the HTA bodies. Following expert opinion in capturing the different restrictions, we clustered these based on their respective influence on the regulatory setting, particularly in what concerns reimbursement decisions (see Annex 20). For instance, in the case of HAS we classify the level of reimbursement of Pharmaceuticals (0%, 35%, 65%) as 'economic restrictions' while in England (NICE) and Scotland (SMC), economic restrictions were identified if managed entry agreements (patient access schemes) were present. Only direct arrangements related to HTA reports were captured in order to shed light on the differences at HTA level, not regulatory.

All restrictions have been identified and coded across all reports, and classified into two main categories: clinical restriction, related to the clinical benefit/ratio of the treatment and economic restriction, related to the cost-effectiveness and budget impact of the health technology.

Clinical restrictions

Across the entire sample, the most common type of restriction was clinical, imposed in 56% (n=69) of all cases. For the Pharmaceuticals sample, results show that the most common clinical restrictions are to subgroups of patients (67%) followed by therapeutic pathways (18%) (Figure 15). As shown in Figure 20 and

Figure 21, this trend is confirmed at HTA agency level, where Pharmaceuticals are commonly restricted to a specific subgroup.

A common clinical restriction across all types of technologies was recommending the health technology only for certain subgroups. A *subgroup restriction* refers to a restriction of the indication to a specific subgroup of patients in a disease stage, whereas a *therapeutic pathway restriction* is related to a specific pre-treatment requirement or a specific treatment to use in combination with the evaluated technology.

For Pharmaceuticals and medical devices, common restriction types were *specialist* and *setting restrictions*. The first one is related to a health technology that can be prescribed only by a specialized physician (e.g. only by a neurologist), whereas setting restrictions refer to a condition on the location where the treatment can be prescribed (e.g. only in hospital settings).

For Pharmaceuticals, *pathway and renewal restrictions* were also identified as restrictions relating to a specific therapeutic pathway to be followed by patient and physician in using the product in question or, conditional renewal upon receiving new clinical data or reassessment.

In the medical device sample the most common clinical restrictions were subgroups (67%) followed by the therapeutic pathway (32%). Specifically, the last set of restrictions referred to the use of the given technology only as an alternative or after the failure of other treatments.

In the 'Other Technologies' sample, the type of restrictions differed significantly from Pharmaceuticals and medical devices. Technology-specific is a recommendation made for one technology (vaccine or screening) over another, whereas programme design is a recommendation made regarding various features of the programme in order to improve the clinical performance of the entire programme. In this sample, the most common clinical restriction was related to a technology specific-feature (58%) followed by programme design (34%) (Figure 22).

Economic restrictions

For Pharmaceuticals and medical devices, the economic restrictions were categorized between the suggestion of price negotiation and/or the presence of a risk-sharing agreement (e.g. PAS in UK).

For 'Other Technologies', three main types of economic restrictions were captured: (1) subgroup economic restrictions, referring to the case when a programme is recommended for specific patient groups or a programme is not recommended for specific patient group, considering their cost-effectiveness; (2) technology-specific restrictions, when a recommendation is made for one technology (vaccine or screening) over another considering their cost-effectiveness; and (3) programme design restrictions, when recommendations are being made regarding various features of the programme in order to improve the clinical performance and the cost-effectiveness of the whole programme.

Economic restrictions were mainly present in the Pharmaceuticals sample, with the 64% referring to the introduction of a risk-sharing agreement (RSA) in reimbursing the product and 14% requesting further price negotiation.

In the medical devices sample, only five economic restrictions were identified with a main focus on the use of special price negotiations with the regulatory agency responsible for reimbursement decisions.

Figure 20: Clinical restrictions - Pharmaceuticals sample (n=89)

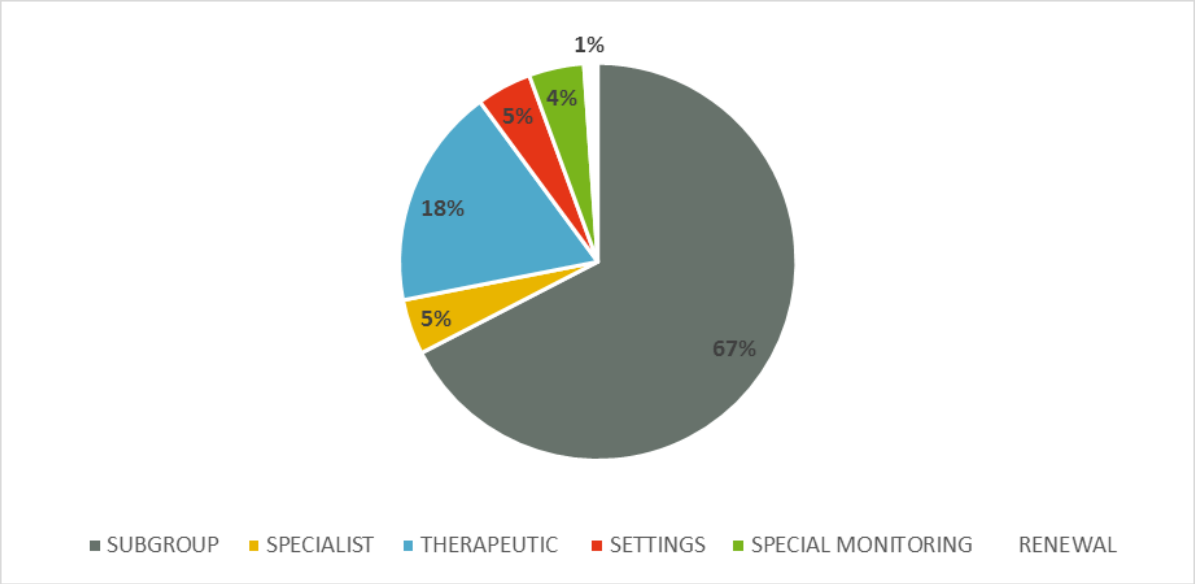


Figure 21: Clinical restrictions by Agency - Pharmaceuticals sample (n=89)

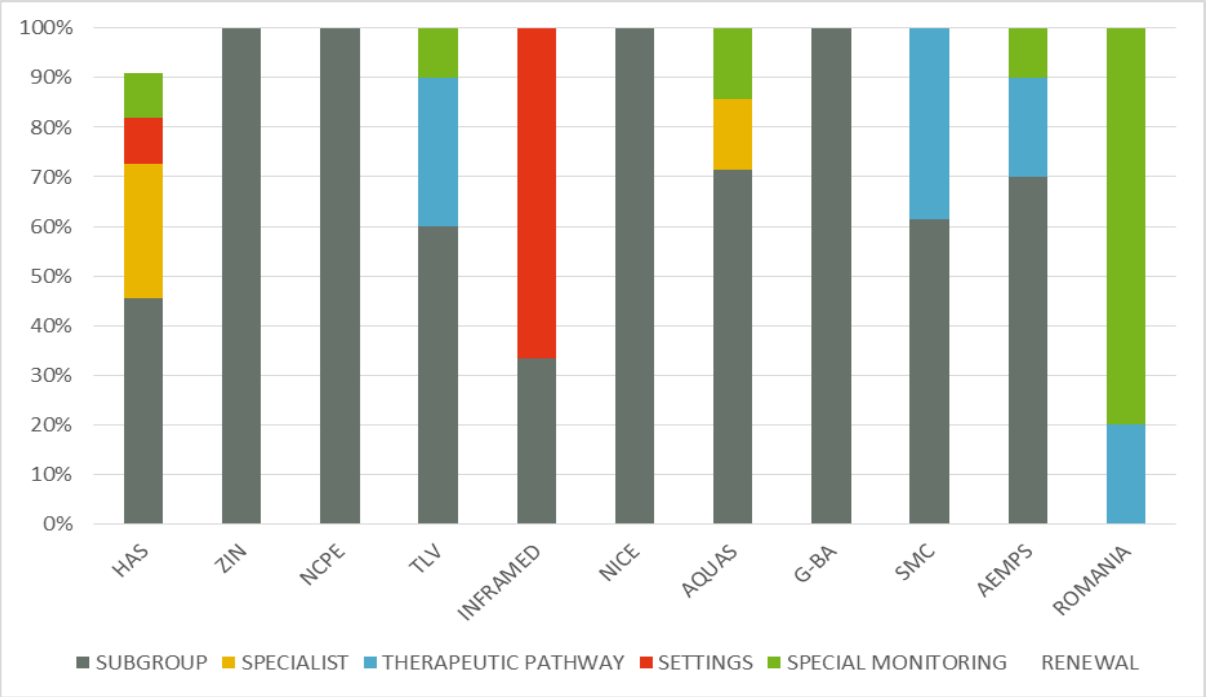
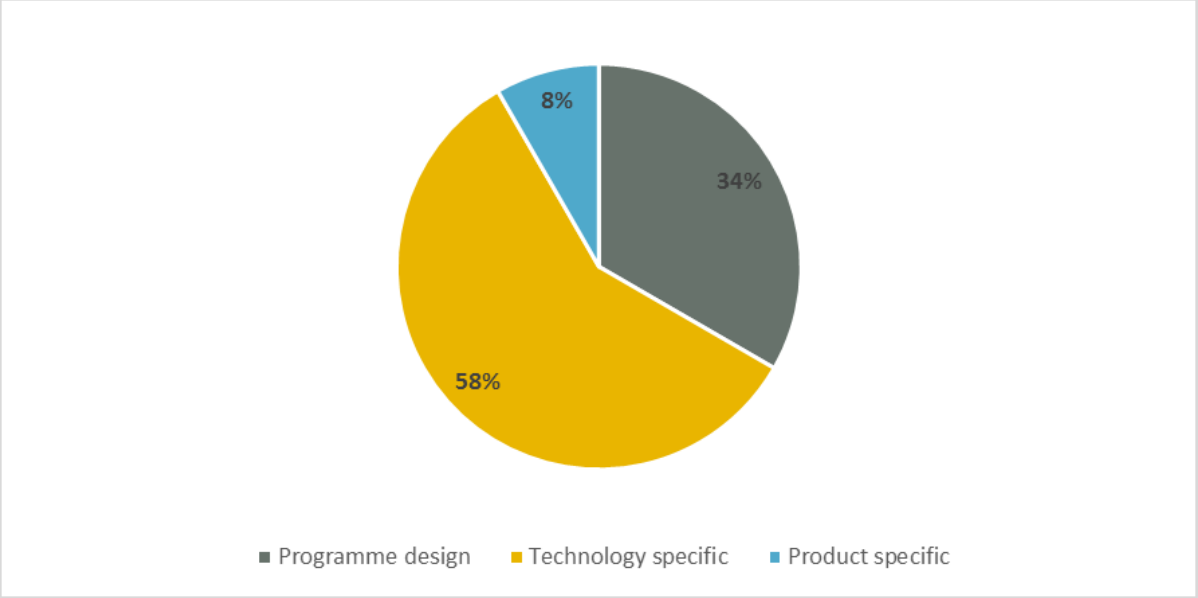


Figure 22: Clinical restrictions – 'Other Technologies' sample (n=41)



7.1.6 Concluding remarks on HTA recommendations

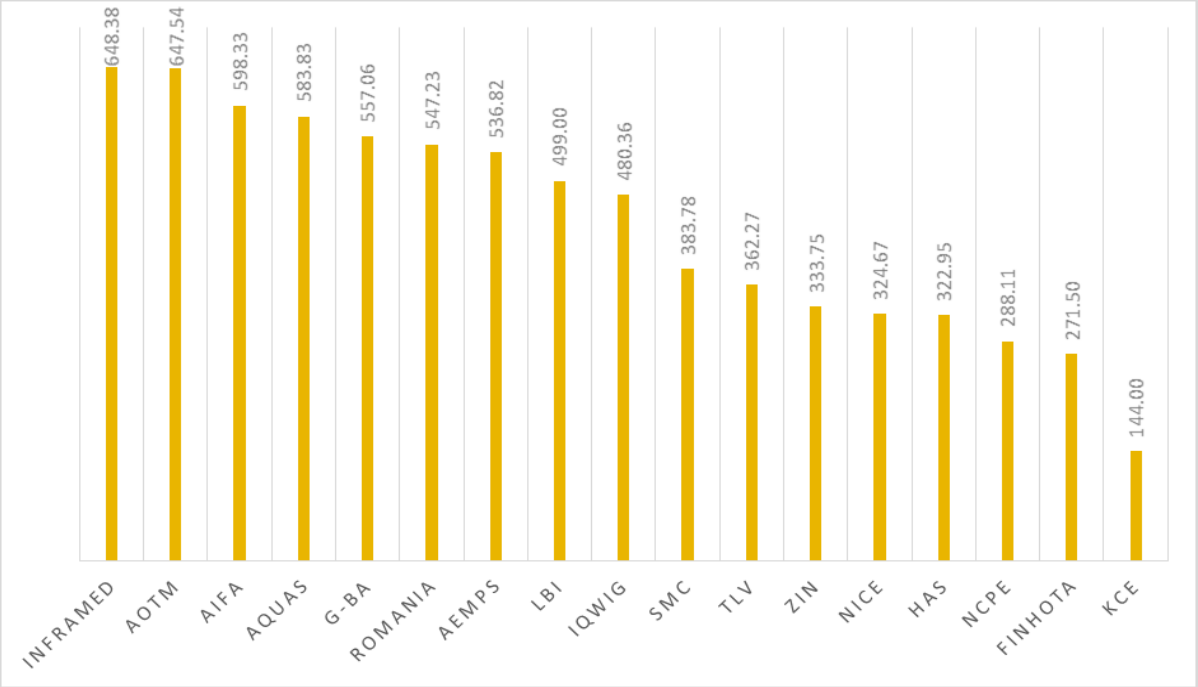
With regards to HTA recommendations across countries, our results suggest that agreement in recommendation outcomes between HTA bodies remains poor, despite a general trend favouring 'List with restrictions´ recommendations. This result is particularly prevalent in the Medical devices sample, where substantial inter-country variability in HTA recommendations is observed across countries.

When studying the final outcome of HTA processes, it is important to consider the differences between assessment, defined as the analytical process of gathering and summarizing information about a health technology, and appraisal, which refers to the process of making a decision about whether or not a health technology should be covered, taking into account assessment information but also a number of other factors and dimensions of value. Nevertheless, a clear distinction between assessment and appraisal is not present in all countries. In some cases, decision-making is closely integrated with the HTA process. Consequently, the outcomes captured have a different effect on the health system of each country and cannot be weighted equally.

7.1.7 HTA timelines relative to Marketing Authorisation (MA)

As shown by Figure 23, on average, the longest time in evaluating a Pharmaceutical was taken by INFARMED and AOTMiT (648 and 647 days, respectively) after Marketing Authorization (MA). The results for FINHOHTA, KCE and LBI should be considered carefully due to the small sample size (FINHOHTA n=2; KCE=1, LBI=1).

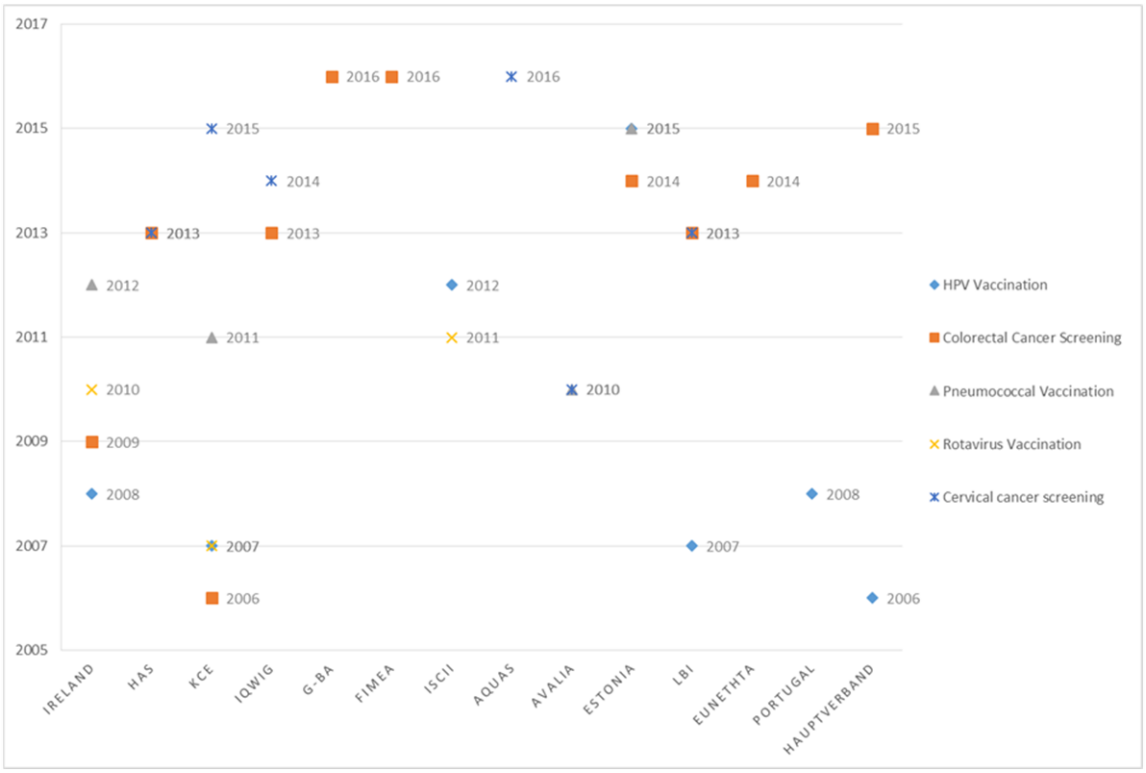
Figure 23: Lag time between MA and publication date by Agency in days



In the medical technology sample, looking at the average lag time between the CE marking date and the submission of an HTA, the timing is much longer, around 60 months. However, the data should again be interpreted with caution, due to the scarcity of publicly available data on CE mark dates. Across HTA bodies, on average the time lag between evaluations was 3 years, the longest time lag being for duodenal sleeves assessed by EUnetHTA in 2013 and by KCE in 2006.

When analysing 'Other Technologies', it is important to acknowledge the time lag between evaluations of similar programmes across different countries. Figure 24 shows the publication dates of the HTA reports of the selected 'Other Technologies' across the respective HTA bodies. For instance, KCE (Belgium) evaluated colorectal cancer screening in 2006, whereas FIMEA (Finland) and G-BA (Germany) evaluated the programme in 2016.

Figure 24: Report publication dates ('Other Technologies' sample)



7.1.8 Clinical evidence

Across the Pharmaceutical sample, on average four clinical studies were considered per HTA assessment; a total of 536 trials or studies were considered. Figure 25 shows that, across the entire Pharmaceutical sample, all HTA bodies had a preference towards phase III clinical trials, followed by phase II trials and other sources of evidence. Specifically, phase III RCTs accounted for the majority of the evidence submitted (62% n=334), followed by phase II trials (10% n=51), indirect comparisons (6% n=52), with the remaining 30% being a range of other types of evidence such as HTA reports (n=26) extensions (n=13) and observational studies (n=11).

Focusing on the proportion of type of trials by HTA bodies,

Figure 26 clearly shows that Phase III trials are preferred across the sample, with the exception of Romania and Croatia (AZZ), where the assessment is mainly based on HTA reports produced by other countries (HTA referencing).

Considering the comparator presented, the most commonly used trial comparators were placebo. On average, 61% of 338 primary trials included a placebo or did not include any comparator and the remaining 39% included a direct comparator. No comparator was considered when the trials include a comparison of different doses of the study drug.

Across the medical devices sample, Figure 27 shows a clear preference for RCT trials (28%) followed by observational studies (17%) and safety studies (19%). On average, the HTA considered four clinical studies per medical technology.

Considering the comparator presented, the most commonly used trial comparators were the current standard of care. However, the larger number of trials considered were uncontrolled therefore, they did not have a comparator.

Across the 'Other Technology' sample, on average six clinical studies were presented with a general preference for literature reviews (89%). This might be related to the general scope of these types of HTA evolutions, which are looking at all the different aspects of public health programmes and not solely to the clinical and cost-effectiveness of the technologies under evaluation.

Figure 25: Type of clinical evidence considered across the Pharmaceutical sample

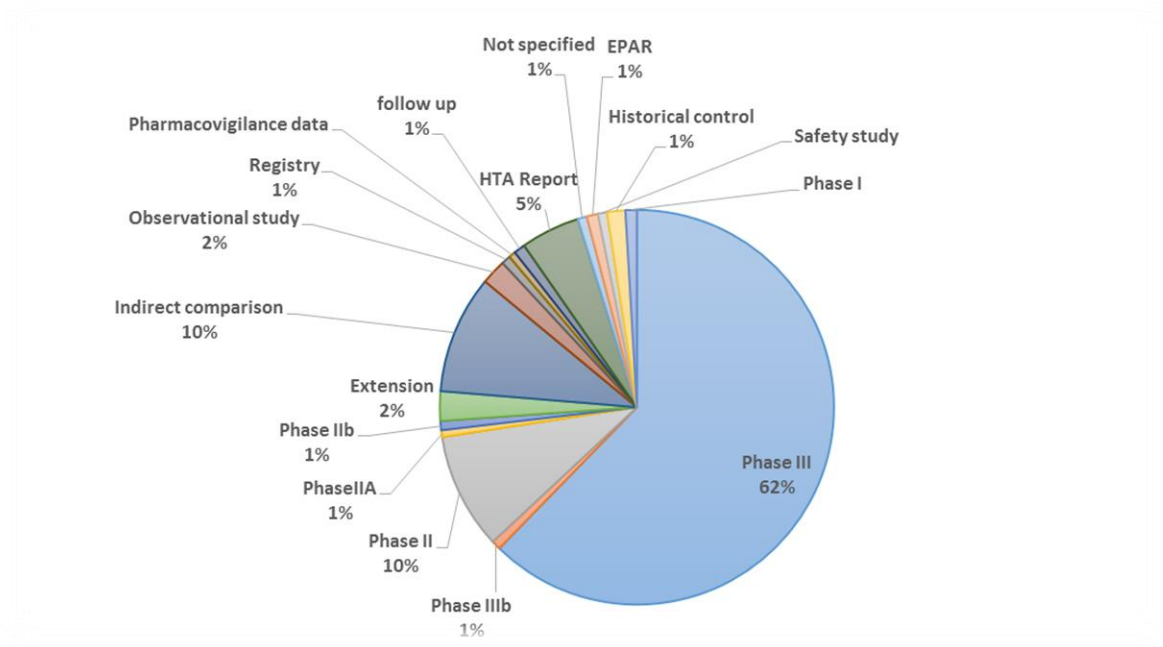


Figure 26: Percentage of clinical trials considered by agency- Pharmaceutical sample

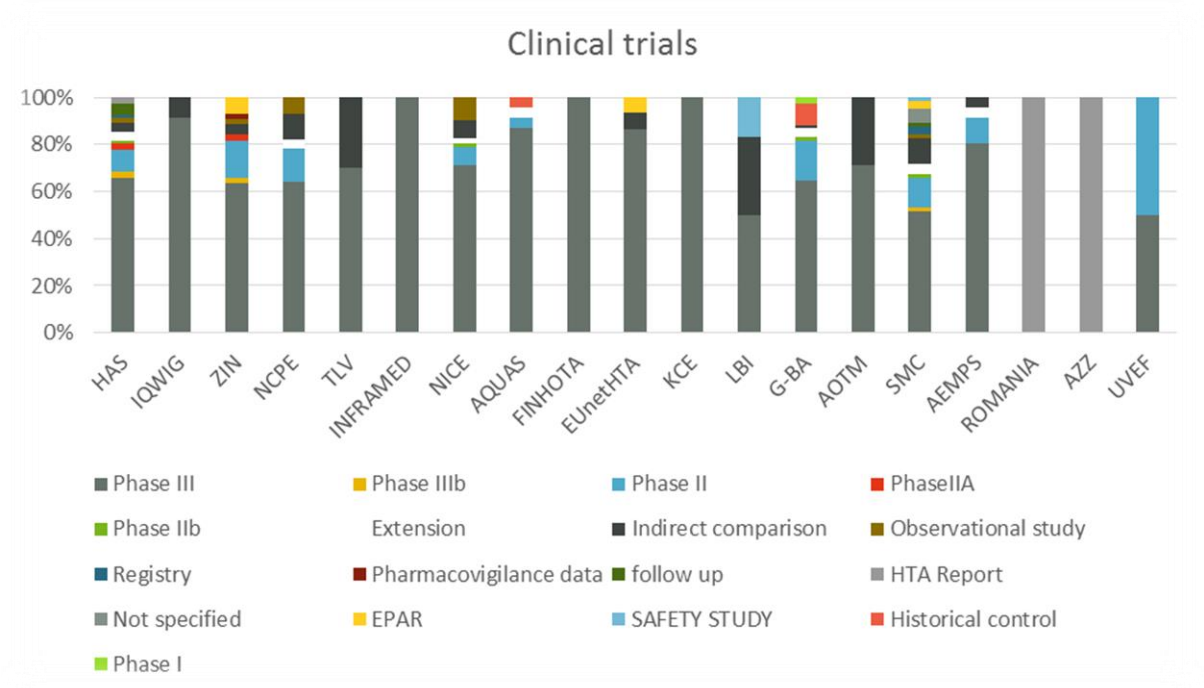
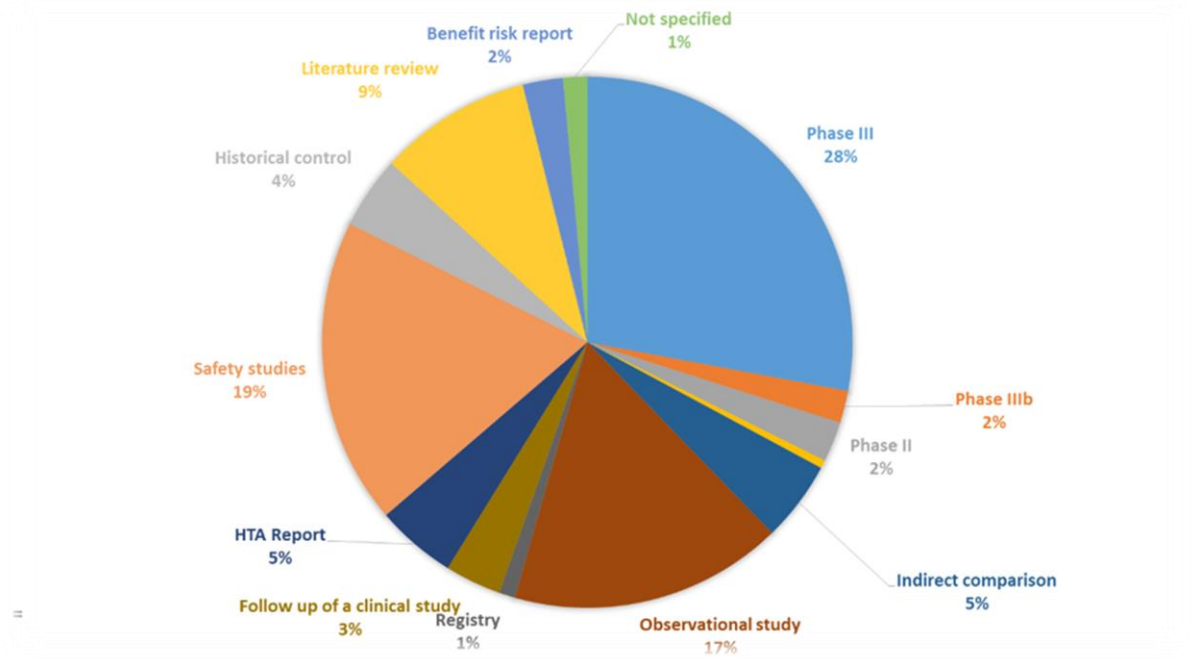


Figure 27: Type of clinical evidence Medical devices sample



7.1.9 Economic model

Not all countries assessed the clinical and cost-effectiveness of each study technology and the criteria in assessing them can vary considerably from country to country.

In the Pharmaceuticals sample, eight countries considered an economic evaluation in their assessment and, on average, 1.5 economic studies were considered for each Pharmaceutical product. Our findings show that, in general, a cost-utility analysis has been considered across all study drugs (in 85% of cases), followed by budget impact analysis (43% of cases). Only in a limited number of cases (6%), was a cost-minimization analysis adopted.

Considering the comparator presented, the most commonly used comparators were a direct comparator (86%). **Across the countries studied and in 68% of the cases, the comparator included was the same across HTA bodies**.

In the medical devices sample, eight countries considered economic evaluation with an average number of studies considered by agencies to be slightly higher, reaching 2.5 studies per technology. Looking at the type of economic evaluation, the trend was confirmed with mostly cost-utility studies (67%), followed by cost comparisons (21%).

In the 'Other Technologies' sample, seven countries considered an economic evaluation with 73% of the evaluations taking into account at least a cost utility analysis, followed by 45% of evaluations also taking into account a budget impact analysis.

7.1.10 Social value judgements

Due to the incomplete nature or the low quality of clinical and economic evidence, when evaluating health technologies, decision-makers are having to make judgements that may influence the decision process in dealing with uncertainty or accepting ICERs that are, strictly speaking, higher than national willingness to pay (WTP) thresholds. These judgments are commonly called 'social value judgements' (SVJs) and aim to interpret key elements related to the impact of the treatment on patients and society. As such,

SVJ have increasingly been included in HTA recommendations. For instance, NICE in England recognizes that special circumstances, such as disease severity, end-of-life situations, stakeholder interests and degree of innovation, are taken into consideration in addition to the cost per QALY (Quality-adjusted life year).

The aim of identifying these SVJ was to define whether they are captured, partly captured, or not captured by HTA bodies and their potential influence on the assessment. SVJs have been identified and coded across all appraisal reports, and classified into eleven main categories notably: (1) Significant innovation, (2) Life expectancy, (3) Small population, (4) Equality issues, (5) Wider societal benefit, (6) Impact on quality of life and daily activities, (7) Impact on the family and the carers, (8) Unmet need for treatments, (9) Rarity and/or (10) severity of the disease and (11) Other considerations, which may be related to the disease or the product in question.

Considering specific trends across different health technologies, the highest number of SVJs was identified in the Pharmaceuticals sample (n=304) followed by the medical devices sample (n=67). By contrast, in the 'Other Technology' sample, only four SVJs were considered.

Across the selected HTA bodies, only three HTA bodies have elicited/revealed their social value judgments in their guidelines: NICE in the context of end-of life (EoL) criteria, SMC with the so-called 'disease modifiers' and TLV with the 'human dignity, needs and solidarity' principle. However, the other HTA bodies take into account these values (albeit not in a consistent manner).

In the Pharmaceutical sample, the most common SVJ raised by all the agencies were about the improvement of quality of life for the patients and the carers (27% N=83) and the unmet need in specific disease areas and the treatment innovation (11% N=29). Eighty-two percent of SVJs identified provide considerations that favour the treatment. Interestingly, across the positive impacts on the quality of life, the administration and provision of the treatment is one of the most considered factors. This is probably connected to the important benefit gained by a Pharmaceutical product if it is administered orally, offering the possibility to take it home, and the positive effect that this could have on the organization of the health services and the public expense of health systems.

In the medical devices sample, only 67 SVJs were identified, mainly focused around a wider societal benefit arising from the introduction of the new technology in the health system (35%; n=23) and the severity of the disease (23%; n=15).

7.1.11 Concluding remarks on the evidence presented

An over-arching conclusion of this section is that, considering the evidence included in the different HTA reports, there appears to be a trend across HTA bodies studied for the same type of clinical and economic evidence. This may suggest a growing trend towards the homogenization of clinical and economic evaluation, at least in what concerns the primary evidence base that feeds into such evaluations.

In the case of Pharmaceuticals and in terms of the primary trial types considered by HTA bodies, a clear preference was shown for phase III clinical trials. This is hardly surprising, given this is considered to be the most robust type of evidence. The only exceptions were Croatia and Romania, which pursue a type of HTA referencing in the case of Pharmaceutical evaluations. AZZ in Croatia performs a literature review to collect the HTA decisions at the international level, whereas Romania consults the HTA decisions of European countries by employing a score-card system. The results show also that all the agencies prefer the inclusion of cost-utility analyses to evaluate the cost-effectiveness of new interventions.

In the case of medical technology, there are clear differences in comparison to Pharmaceutical products. The fragmentation of the sector is highlighted again in the evidence considered by HTA bodies. Despite a preference for RCTs, the clinical evidence considered varied significantly across the sample. This also raises questions regarding the preference for RCTs as the main evidence of HTA in the context of medical technologies. This might be related to absence of RCT data and the need of multiple sources of weaker evidence to proof the clinical effectiveness therefore raising also questions regarding the central role of RTCs in the evaluation of medical devices as the main evidence of HTA assessment. Primary data collection (interviews) and the literature suggest that, while long RCTs may be desirable from an evidence standpoint, they may not always be appropriate or feasible for medical technologies (33).

This is also confirmed also by the results from the SJVs, showing high variation across countries, showcasing how the quality of reports varies largely. Some important elements for patients, such as social value judgements, may not necessarily be considered on a routine basis.

Finally, the 'Other Technologies' sample shows a moderate level of agreement across countries and the use of a common methodology for retrieving and considering clinical and economic evidence.

7.1.12 Baseline costs

Thirty-three HTA bodies and 89 manufacturers provided responses to the cost part of the survey. All results were compiled in an excel spreadsheet and added to the relevant indicators. In order to standardize costs, we used historical national currency exchange rates to adjust to Euros. In the survey, four institutions classified themselves as HTA bodies, however they fell outside the scope of our research and therefore were excluded. Combining the results of the study by Julia Chamova with our results, we obtained data from 54 HTA bodies. However, the information was fragmented and incomplete. In order to overcome this limitation, HTA bodies were contacted again to obtain more specific information. Eight HTA bodies responded, giving a range of detailed costs information.

Of the 89 companies that responded to the survey, 76 were medical devices and 13 were Pharmaceutical companies.

The quality of the information received from the industry (both Pharmaceutical companies and medical devices companies) varies significantly. Although there is detailed information on staff numbers, there is partially complete information on permanent staff and consultant costs and almost no information on Full HTA and Early Dialogue unit costs.

In order to enhance the quantity of cost data further, contacts both with the industry and the HTA bodies were established. As detailed in the mitigating factors overviews, eight HTA bodies responded to a short request for further of information in order to fill some gaps in the cost data. The results were also presented in three different focus groups in order to test their reliability.

7.1.12.1 Baseline costs - HTA Bodies

In order to capture the different levels of spending of HTA bodies and according to their respective role (arm's length vs. integrated and advisory vs. regulatory vs. coordination), costs were categorized based on a taxonomy of HTA body types. Table 32 reports the average total annual number of REA, Single HTA and Multiple HTA by type of HTA body. Single HTA is a full HTA performed for a single indication for a single technology whereas Multiple HTA is an assessment which normally covers more than one technology, or one technology for more than one indication.

Table 32: Average number of total assessments - HTA bodies

Summary for HTA bodies	Arm's Length Body – Advisory	Arm's Length Body - Coordination	Arm's Length Body - Regulatory	HTA Function Integrated - Advisory	HTA Function Integrated - Regulatory	HTA Uncategorized
Countries	UK, Sweden, Hungary, Portugal, Ireland	Estonia, Belgium, Spain, Sweden	Sweden, Ireland, Finland, Slovenia	Belgium, Austria, Slovakia, Croatia, Estonia, Netherlands	Italy, Bulgaria, Slovenia, Latvia, Luxembourg, Hungary, Slovakia, Spain, Croatia, Malta, Lithuania	Austria, Latvia, Italy, Hungary, Cyprus, Czech Republic, Denmark, Estonia
Total Annual Number REA	105	29	N/A	N/A	7	149
Total Annual Number Single HTA	201	23	59	193	69	108
Total Annual Number Multiple HTA	4	11	2	5	4	26

The same categorisation based on a taxonomy of type of HTA bodies could not be done for the costs because the sample was too small. Indeed, due to the small sample size in

each category of HTA body reporting values, a broader categorisation based only on their integration within the governmental entities was applied.

Table 33: Categorisation of HTA bodies by integration into national governments*

CATEGORY	Number of agencies per category	Number of Agencies that perform REA	Number of Agencies with cost data on REA	Number of Agencies reporting costs on STA	REA costs (RANGES - MIN)	REA costs (RANGES-MAX)	STA costs (RANGES - MIN)	STA costs (RANGES-MAX)
Arms' Length Body	22	13	8	12	€4 000	€55 000	€4 000	€135 000
HTA Function Integrated	23	14	4	5	€6 820	€ 100 000	€16 000	€100 000
Other	5	5	3	4	€40 000	€40 000	€13 241	€80 000

STA: Single Technology Assessment (Full HTA); REA: Rapid Effectiveness Assessment * Average costs per output

Another classification was based on whether the HTA body is performing REA or not, and clustering by REA and STA spending, which is shown in

Table **34** and

Table **35**.The different classifications were adopted in order to capture both the possible influence on the costs of the type of body as well as the size of the body and how this can influence the number of agencies actively performing REA or STA.

Table 34: Categorisation of HTA bodies by REA activities and spending*

CATEGORY	Number of agencies per category performing REA	Number of Agencies that report cost on STA in the same category	REA costs (RANGES - MIN)	REA costs (RANGES-MAX)	STA costs (RANGES - MIN)	STA costs (RANGES-MAX)
Agencies with REA costs < EUR 20,000.00	6	5	€4 000	€20 000	€4 000	€51 000
Agencies with REA costs between 20,000.00 <REA costs < EUR 40,000.00	6	5	€22 580.65	€40 000	€45 000	€125 000
Agencies with REA costs>EUR 40,000.00	3	2	€55 000	€100 000	€60 000	€70 000

STA: Single Technology Assessment (Full HTA); REA: Rapid Effectiveness Assessment * Avarage costs per output

Table 35: Categorisation of HTA bodies by STA activities and spending*

CATEGORY	Number of agencies performing STA	Number of Agencies that report cost on REA in the same category	REA (RANGES-MIN)	REA (RANGES-MAX)	STA (RANGES-MIN)	STA (RANGES-MAX)
Agencies with 20,000.00 > STA costs	4	2	€4 000	€20 000	€4 000	€16 000

Agencies with STA costs between 20,000.00 <STA costs < 40,000.00	4	2	€6 820	€20 000	€20 461	€35 000
Agencies with STA costs>40,000.00	13	8	€20 000	€55 000	€45 000	€35 000

STA: Single Technology Assessment (Full HTA); REA: Rapid Effectiveness Assessment * Average costs per output

Out of the **52 HTA bodies considered, 32 are actively performing REA and 50 perform REA and economic assessment.** We received information on costs from **40 HTA bodies, from which four reported on cost data on REA and economic assessment, 21 on cost for Single HTA and 15 reported on cost data on REA**.

7.1.12.2 Baseline costs – Pharmaceutical Industry

For the baseline costs, 13 Pharmaceutical companies responded to the survey, providing data on costs in performing HTA. Descriptive results are shown in Table 36.

Table 36: Descriptive baseline costs - Pharmaceutical industry *

Summary for Pharmaceuticals Companies (**)	Value
% of Companies Engaging in Early Dialogue	**70% of companies (9/13)**
Average ED costs (Fees + Admin + Other) & HR resources (***)	**EUR 55 750.00; and 0.7 FTE**
ED Cost Reduction for general HTA activities	**No reported cost reduction**
Average PM working for general HTA submission activities	**11 PM/HTA**
Range of Cost per general HTA submission	**EUR 73 000 - EUR 1 700 000** (****) **(Average EUR 695 500)**
% of companies reporting costs of additional clinical evidence generation	**85% of companies**
Range of Cost of additional clinical evidence generation per HTA submission	**EUR 50,000 - EUR 20,000,000 depending on the type of evidence required**

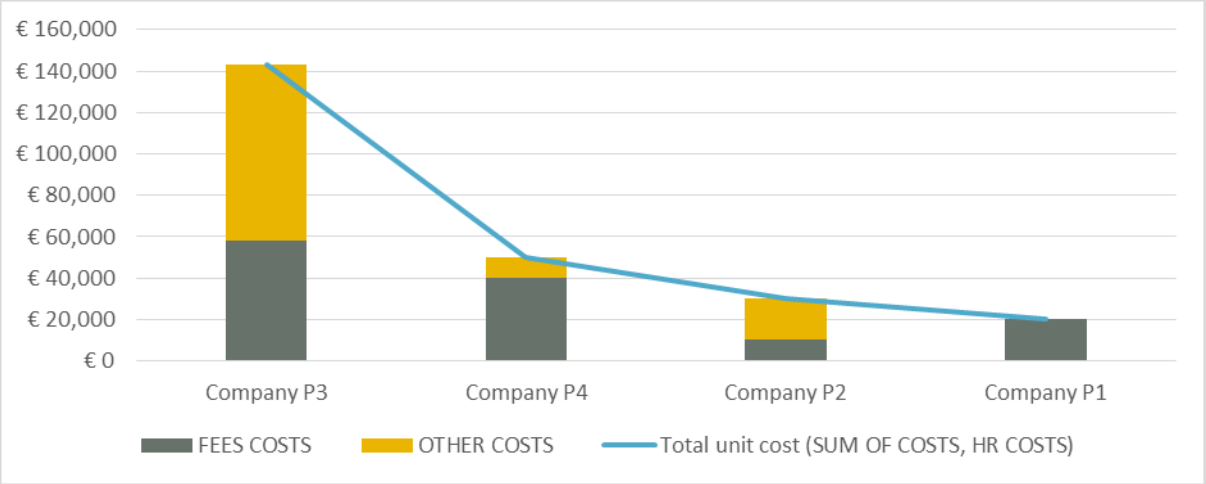
Notes: (*) All data refers to companies surveyed and therefore are not country specific. (**) Costs are not weighted due to the small sample size. (***) HR resources costs vary considerably due to different salary standards across Europe. (****) Ranges were rounded up for confidentiality reasons. (*****) Across the companies surveyed; ED: Early Dialogue PM: person per month. When averages are being calculated they are done so across all countries in which a company operates. If a company submits HTA in 10 countries, then the base will be 10. If they only report consultancy costs in 7 of 10 countries, the base remains 10, and the 3 countries in which they did not report fees are given a value of 0.

Looking at the descriptive results in Table 36, Pharmaceutical companies (70%) are actively engaging in Early Dialogues (ED) at an average cost of **EUR 55 750**. The cost related to ED includes ED fees, ED admin costs, and ED other costs and the human resource cost is reported as a Full Time Equivalent (FTE). In the survey, companies provided person per month (PM) per HTA figures in each country they operate and the value in Figure 28 represents the average across all countries in which a company operates. It is important to highlight that both the range and number of countries per company is highly variable. For all companies, it is assumed that this only includes country-level PM, and not global PM. This result may need to be interpreted with caution since only four companies reported information relevant to the sum of cost data, and only seven provided FTE data. Due to the low and variable number of companies and given the above assumptions, the averages provided here are unlikely to be representative of the spending across the Pharmaceutical Industry. However, the figures were considered reliable during a focus group with Pharmaceutical company representatives.

The number of staff employed on HTA varies significantly, depending on whether the country has an established HTA submission process or not.

Investigating the main drivers of the costs for Early Dialogue, it is clear that broad costs for Early Dialogue are related to submission fees. However, this can vary significantly by country setting due to the different regulations.

Figure 28: Drivers of costs in Early Dialogue- Pharmaceutical industry

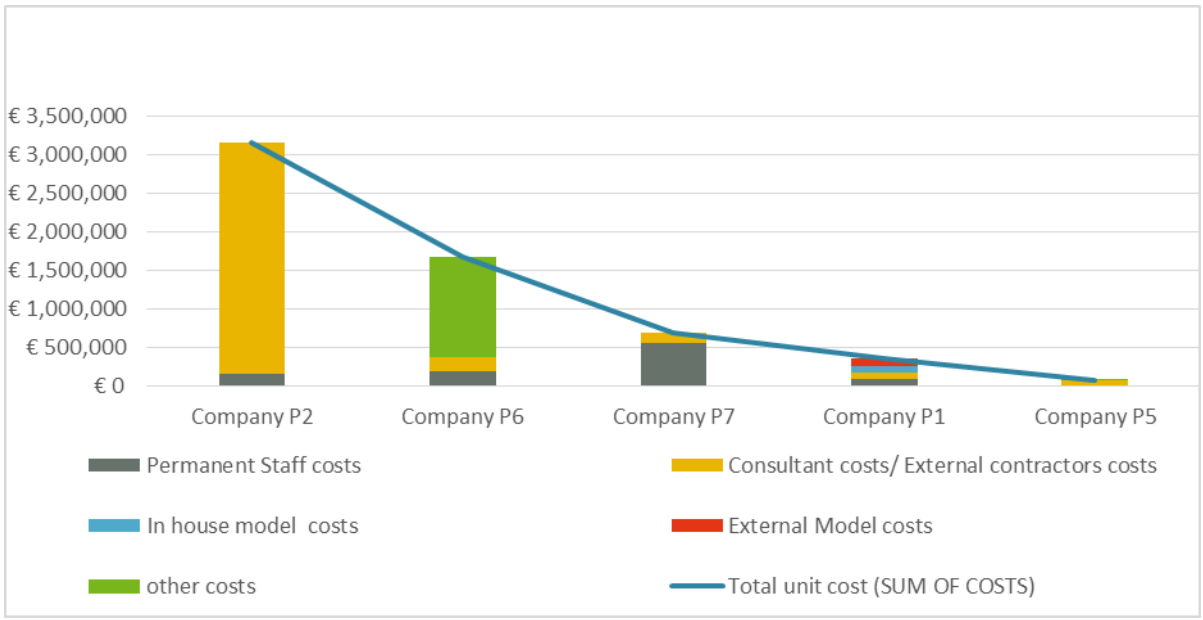


Fees depend on the country of submission. For some companies, the 'other costs' exceed 'fees costs' due to country setting. Company name were blinded for confidentiality

Looking at the figures relating to an **HTA submission reported in Table 36, the cost ranged from EUR 73 000 to EUR 1 700 000**. This value represents a sum of average costs per HTA submission per company. Companies reported staff costs, consultant costs, in-house model costs, external model costs, and other costs. These were provided by country of company operation. For staff costs, consultant costs, in-house costs, external model costs and other costs, an average was taken across all countries for each company. These average values were subsequently aggregated to arrive at the average cost estimate per HTA submission per company.

Investigating the main cost drivers of HTA submission, it appears that staff costs (internal and external) are the lead driver of expenditure (Figure 29).

Figure 29: Drivers of costs in general HTA activities - Pharmaceutical industry

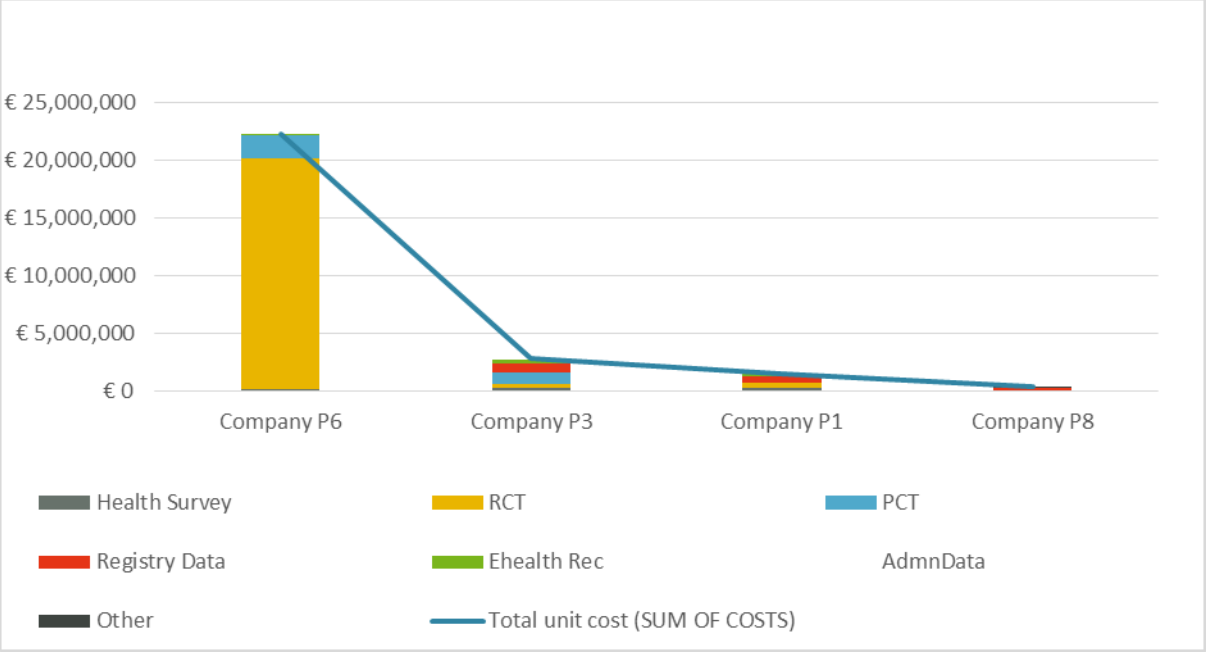


Two main limitations were identified regarding the data submitted by companies. First, in some cases it is unclear whether this value is in fact 'zero', or if a company simply did not report a value. This represents a limitation to the average cost data. However, it was deemed that keeping a consistent base for the average was necessary in order to avoid over-representation of the extent and impact of consulting costs and other costs, which do not necessarily occur in every setting.

A second limitation relates to how a summary of the HTA cost information should be presented. A sum of the various costs reported was chosen for simplicity, and this assumes that a sum of permanent staff costs, consultant costs, in house model, external model, and other costs is accurate for the average cost of a single submission.

Regarding average costs of additional evidence generation per HTA submission, within the survey data, companies were asked to provide average costs for health surveys, supplements to RCTs, practical clinical trials, registry data, electronic health records, administrative data, and other. The range of generating new evidence is very wide (from EUR 50 000 to EUR 20 000 000), and one company responding to the survey justified this high variability with a significant variation in the frequency of generating new evidence by country and by therapeutic area. Some of the additional evidence generation cannot be applied to single HTA submissions, but rather has implications for multiple countries and/or multiple submissions. For the purposes of this survey, we have assumed costs to be for individual HTAs. Eventually, averages cannot be interpreted as holding across disease or therapeutic areas, as there may be significant differences in evidence requirements according to therapeutic area.

Figure 30: Drivers of costs in further evidence generation - Pharmaceutical industry



Looking at the main costs afforded by generating new evidence, the highest expenditure is related to the generation of new randomized controlled trials (RCTs), followed by registry data. However, it is important to highlight that some of the additional evidence generation may not be applied to single HTA submissions, but rather has implications for multiple countries/multiple submissions.

7.1.12.3 Baseline costs – MedTech Industry

76 companies responded to the survey by providing information on the cost of performing HTA. However, costs reported by the same company but coming from affiliates operating in different countries were aggregated in order to have a consistent sample, leading to the identification of 46 MedTech companies.

Table 37: Descriptive costs baseline scenario- MedTech Industry *

Summary for MedTech & Diagnostic Companies	Value
% of Companies Engaging in Early Dialogue	**28% of companies (13/46)**
Average ED costs (Fees + Admin + Other) & HR resources (**)	**EUR 21 687.50; and 0.7 FTE**
ED Cost Reduction for General HTA activities	**6% of companies (1/13). No value given**
Average PM working on General HTA submission activities	**3 PM/HTA**
Range of cost per HTA submission	**EUR 1 000 – EUR 3 400 000 (Average EUR 410 358)**
% of companies reporting costs of additional clinical evidence generation (*****)	**37% of companies (17/46)**
Range of cost of additional clinical evidence generation per HTA submission	**EUR 17 000 - EUR 12 800 000** (***) **depending on the type of evidence required**

Notes: (*) All data refers to companies surveyed and therefore are not country specific (**) Costs are not weighted due to the small sample size (***) HR resources costs vary considerably due to different salary standards across Europe (****) Ranges were rounded up for confidentiality reasons (*****) Across the companies surveyed; ED: Early Dialogue PM: person per month. When averages are being calculated they are done so across all countries in which a company operates. If for instance a company submits HTA in 10 countries, then the base will be 10. If they only

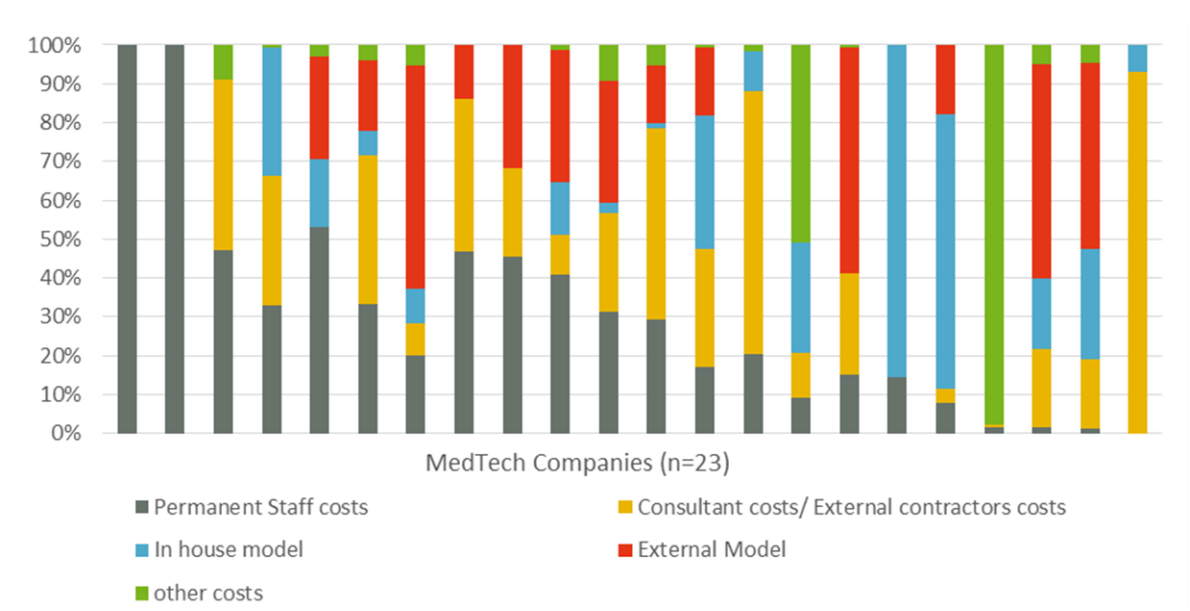
report consultancy costs in 7 of 10 countries, the base remains 10, and the 3 countries in which they did not report consultancy fees are given a value of 0.

Looking at the Early Dialogue results in Table 37, results show that only 28% of companies engage in Early Dialogue. The average cost of ED is EUR 21 687.5, including fees, admin costs, and other ED costs, with less than one person per month dedicated to it.

Considering the cost related to general HTA activities, the cost varies considerably, ranging from EUR 1 000 to EUR 3 400 000. As for the Pharmaceutical Industry, these values represent a sum of average costs per HTA submission per company comprising staff costs, consultant costs, in-house model cost, external model costs, and other costs through the survey. These were provided per country based upon the location a company operates. For each of staff costs, consultant costs, in-house costs, external model costs, and other costs, an average was taken across all countries for each company. These average values were then added to provide an average cost per HTA submission for each company.

Having investigated the distribution of the costs in performing HTA activities, our results show that the greatest proportion of costs relate to staff costs (permanent staff and consultants). Only in one case is the main cost driver classed as 'other costs'. However, the company in question did not specify the underlying reasons for this classification.

Figure 31: General HTA activities cost distribution (n=23 out of 46))* – MedTech Industry



*Companies did not answer to all the questions of the survey, leading to a smaller sample size.

The value for average costs of additional evidence generation per HTA submission comprise average costs for health surveys, supplements to RCTs, practical clinical trials, registry data, electronic health records, administrative data, and other.

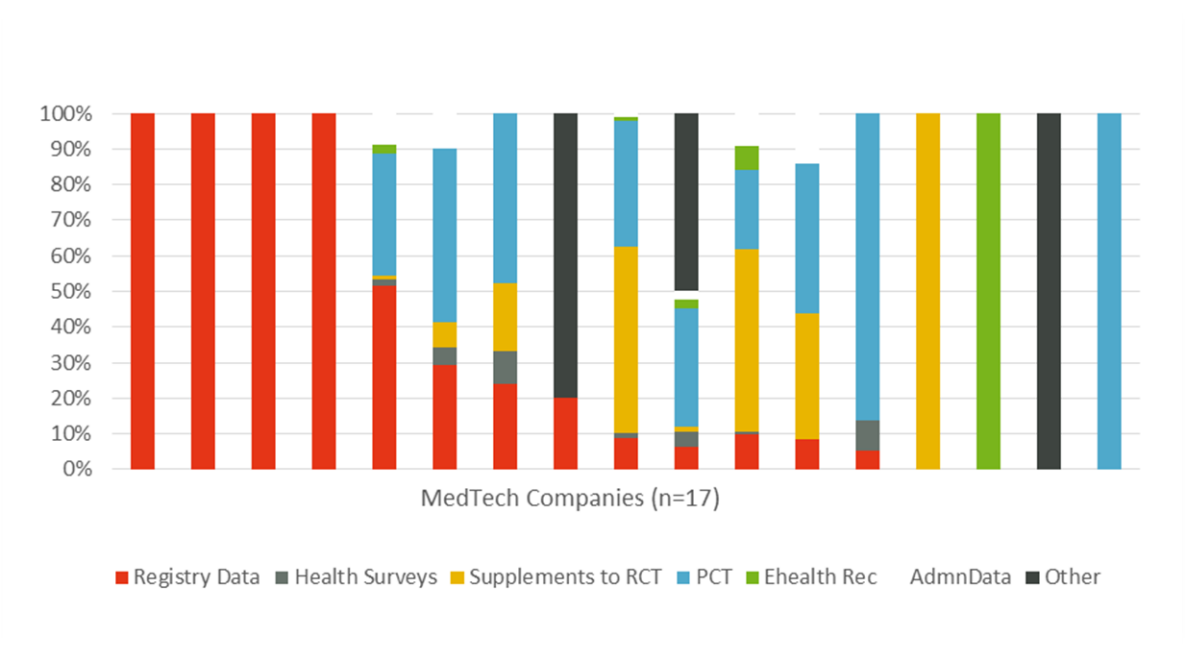
Similarly to Pharmaceutical Industry data, results show that there is a high variability in the cost of generating **further evidence, with costs ranging from EUR 17 000 to EUR 12 800 000**.

This high variability is confirmed by individual answers across medical device companies, which provide extremely large ranges (e.g. EUR 200 000 - EUR 3 000 000). As is the case for the Pharmaceutical sector, it is important to highlight that costs related to additional evidence generation vary significantly across type of evidence and country.

However, there are no data on the frequency with which these additional types of clinical evidence are generated.

This trend is confirmed by investigating the distribution of costs in further evidence generation, showing that there is no clear trend across MedTech companies. (Figure 32).

Figure 32: Distribution of cost of further evidence generation (n=17 out of 46)* – MedTech Industry



*Companies did not answer to all the questions of the survey, leading to a smaller sample size.

7.1.12.4 Concluding remarks on baseline costs

Data on the costs associated with the submission of HTA dossiers to HTA bodies, the conduct of HTAs or additional evidence generation have been obtained through the survey in order to capture different stakeholder perspectives (Pharmaceutical companies, medical device companies and HTA bodies). Industry focus group discussion confirmed the plausibility of these results.

First, the results of the survey show significant differences between the Pharmaceutical and the MedTech industries.

Second, for the Pharmaceutical sector, the survey results indicate a high variability in HTA spending (between EUR 73 000 and EUR 1 700 000 per HTA submission), and in additional evidence generation (between EUR 50 000 and EUR 20 000 000). The diversity in the figures reported may reflect the heterogeneity in evidence assessment across settings or the different needs for data generation and does not provide a clear picture of average spending across products or manufacturers. Furthermore, 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 the HTA circumstances prevailing in different countries.

Third, with regards to the MedTech industry, HTA submission figures revealed a range of EUR 1 000 – EUR 3 400 000, while additional evidence generation in the context of HTA submission had a range of EUR 17 000 - EUR 12 800 000. MedTech industry representatives argued that the current number of medical device assessments across countries

differs considerably, therefore constructing an average based on the above ranges would not be reliable.

Fourth, in terms of the identified cost evidence, it appears that in both the Pharmaceutical and the MedTech industry staff costs (internal and external) are the lead expenditure driver. However, focus group discussion showed that a key driver for HTA-related costs is (additional) evidence generation. It is mainly in the largest markets that companies perform additional evidence generation studies requested by HTA bodies. Alternatively, existing knowledge gaps may be often covered by post-marketing studies. The focus of additional evidence generation studies is predominantly in larger markets and requests for additional evidence generation by smaller countries can be disregarded due to the latter's market size.

Fifth, the Early Dialogue results indicate a completely different level of engagement between the Pharmaceutical and MedTech industries. The former actively engages in Early Dialogue (69% of responses) with an average cost of EUR 55 750 per case, the latter shows a low level of engagement (28% of responses) and a lower level of spending (EUR 21 687.50) per case. In focus group discussion, MedTech industry representatives confirmed that they do not engage routinely in Early Dialogue for medical devices.

Sixth, considering the cost evidence responses of HTA bodies, the differences in costs are highly influenced by factors such as the type of HTA process in place in different settings, the type of assessment performed and the level of integration of HTA bodies with government entities. In general, it appears that the cost of performing STA among 'arm's length bodies' is higher than among 'integrated' structures (the highest reported figure for STA was EUR 135 000 for arm's length bodies vs. EUR 100 000 for integrated structures), while the maximum reported figure for REA was EUR 55 000 for arm's length bodies and EUR 100 000 for integrated structures. However, as the data received in some cases had missing values, these estimates should be interpreted with caution.

7.1.13 Interview results

7.1.13.1 List of participants

The table below presents the manufacturers who participated in the interviews and the types of industry they represented. Eight Pharmaceutical companies and five medical devices companies participated in semi-structured interviews. Additionally, one Pharmaceutical Industry association and one medical device industry association were questioned during this process.

Table 38: List of Industry Interviews Performed

	Pharmaceuticals companies	Medical devices companies
Companies ranked in the top 10th by sales*	5	3
Companies ranked between top 11th and 20th by sales*	2	1
Companies ranked after the top 20th by sales*	1	1
Trade association	1	1

*For Pharmaceuticals: Pharmaceutical Executive. n.d. Top 50 global Pharmaceutical companies by prescription sales and R&D spending in 2016 (in billion U.S. dollars). Statista. Available from https://www.statista.com; For medical devices: Medical Design & Outsourcing annual 2016. Available from http://www.medicaldesignandoutsourcing.com

7.1.13.2 Pharmaceutical company results

Experience with EUnetHTA

Out of nine Pharmaceutical companies/associations interviewed, only four had directly participated in an EUnetHTA pilot. An additional four companies elected not to participate, either because they were not approached or because the pilots were seen as too resource-intensive. Comments from companies that did not participate directly were still taken into account. The IFPMA did not participate or comment on the EUnetHTA process. Insights were captured in terms of problems with EUnetHTA, potential solutions for future pilots, and additional feedback on EUnetHTA. The number of companies highlighting a problem, solution or additional insight is provided in brackets.

Table 39: Pharmaceutical company experience with EUnetHTA

Problems	Solutions	Additional feedback
Uptake of the EUnetHTA reports by MS was poor, and as a result the pilot became an additional barrier to work around. **(n=5)** EUnetHTA appears to have been largely an academic exercise thusfar, and it is unclear that the amount of rigor necessary was taken to have an impact at national, regional, or local level. **(n=4)** The EUnetHTA design was too top-level, resource-intensive for companies, and appeared arbitrary with some of the targets set. The expectations of EUnetHTA for evidence generation were not always realistic. **(n=3)** EUnetHTA assessments did not occur in a timeline that could help inform decision-making. **(n=3)** There wasn't always a consistent quality in the reviewer, particularly when the review took place in countries that were less sophisticated with HTA. This led to resistance from larger countries in accepting the assessments**. (n=2)**	Use/uptake of the reports should be mandatory by MS. **(n=5)** More work and consultation with local HTA is required in order to increase acceptability at MS level. Reports must be consistent and there must be predictability in how the evidence is looked and assessed. **(n=4)** Increased collaboration and discussion with industry would result in improved collaboration and a better design. **(n=3)** Assessments should take place in parallel with regulatory approval in order to provide speed of access and efficiency benefits. **(n=3)** There is a need for capacity building in some settings to ensure a consistently high standard of quality for all reports. **(n=2)**	EUnetHTA has a good methodology. It's not perfect, but overall it is good, open and extensive source of information. Establishing best practices has been one of the benefits of this scheme. **(n=2)** EUnetHTA missed an opportunity by not adding value from what is currently provided in the EMA EPA report. **(n=1)**

Impact of National Procedures on Pharmaceutical Manufacturers

Insights were captured in terms of problems associated with national procedures, potential solutions through EU collaboration or other means, and additional feedback on the impact of national procedures. The number of companies highlighting a problem, solution or additional insight is provided in brackets. All nine companies provided insights to varying extents.

Table 40: Impact of national procedures on Pharmaceutical manufacturers

Problems	Solutions	Additional feedback
HTA systems that are fragmented and complex are undesirable and present challenges in submissions (e.g. NICE, Nordics). **(n=4)** Frequentist HTA systems (e.g. IQWiG) tend to be narrow in scope in terms of the evidence they consider. This creates barriers to patient access. **(n=4)** There are substantial differences in the way in which countries deal with uncertainty, surrogate endpoints, and indirect comparisons. Evidence requirements vary across settings. This creates substantial costs for evidence development. **(n=4)** There are substantial costs associated with HTA submissions. Germany in particular has very stringent requirements and a resulting high cost. **(n=4)** Pharmacoeconomic based HTA systems tend to undervalue orphan products where health gains tend to be far in the future. **(n=1)**	Companies prefer that clinical evaluation and pricing negotiations are separate processes (E.g. Italy, Spain, France & Germany). **(n=4)** An EU HTA system should be open and expansive in terms of the information sources they consider (E.g. NICE). **(n=4)** Harmonization of evidence requirements could alleviate some of this burden, but will require compromise at MS level. **(n=4)** An EU-wide assessment, if accepted at MS level would help to reduce some of the costs and resources associated with HTA submissions. **(n=4)** Orphan drugs require special consideration or alternative pathways. **(n=1)**	NICE is a very complex system. They tend to focus too much on long-term uncertainty of a product, which makes little sense given the effective life cycle of products. **(n=4)** Many assessments, particularly for orphan products, often fail to include sufficient input from medical experts. **(n=1)** There are differences in the way countries value diseases. Countries often use their methodologies to justify their policies. **(n=1)** There are substantial differences in quality of assessment across countries. Smaller countries, particularly in Central and Eastern Europe tend to have greater issues, particularly when system reforms and political reforms interrupt the HTA process. **(n=1)** Timelines for assessment and access vary substantially across countries. Delays and lack of speed is a huge opportunity cost for industry and for patients. **(n=1)** Companies would prefer to present an argument on the value of a product across all patients, and let physicians decide rather than have HTA bodies restrict access to patient groups. **(n=1)**

Pharmaceutical manufacturers' experiences with Early Dialogue and rapid assessment

Seven out of nine Pharmaceutical companies/associations had participated directly in early scientific advice or Early Dialogue. One company had not participated in an Early Dialogue process. The IFPMA did not comment on Early Dialogue. Insights were captured in terms of problems associated with Early Dialogue and rapid assessment, potential solutions through EU collaboration or other means, and additional feedback on Early Dialogue/rapid assessment. The number of companies highlighting a problem, solution or additional insight is provided in brackets.

Table 41: Pharmaceutical manufacturers' experiences with Early Dialogue and rapid assessment

Problems	Solutions	Additional feedback
Scientific advice differs widely across agencies for a particular product. This presents challenges for development programmes. **(n=3)** Early Dialogue is less useful in settings that are too formulaic and fail to offer opportunity for discussion (e.g. Germany). **(n=2)**	A joint scientific advice, or consensus on evidence requirements would simplify development programmes. **(n=3)** Early Dialogue should be a cooperative and iterative process with opportunities for discussion. **(n=2)**	In general, Early Dialogue and early scientific advice is a very useful process. It improves transparency on evidence requirements. It helps to build a relationship and lowers the risk associated with a product. It can help answer important questions relating to clinical development and can help companies avoid common problems with submissions. **(n=7)** Rapid assessments are unlikely to speed up market access considerably. The biggest delay in access is during pricing negotiations and interpretation of the assessments. **(n=2)** Early Dialogue is an excellent tool in small companies. Internally it helps in negotiations on investment decisions on clinical development. **(n=1)** NICE in particular has a good system for Early Dialogue. It was very helpful in shaping clinical trial development. **(n=2)** Not all countries have the capacity and expertise to have conversations the company would like to have. Language is frequently an issue. Outputs can be highly variable. **(n=1)** Joint scientific advice platforms, where companies can receive regulatory and HTA advice at the same time, are very useful. **(n=3)**

Experience with evidence generation, resubmissions, and real world evidence

Insights were captured on current problems and potential problems through collaboration, potential solutions, and on additional feedback on evidence generation, resubmission and RWE (real world evidence). Only eight out of nine companies provided insights on evidence generation, resubmission and RWE. The number of companies highlighting a problem, solution or additional insight is provided in brackets.

Table 42: Pharmaceutical manufacturers' experience with evidence generation, resubmissions, and real world evidence

Problems	Solutions	Additional feedback
Divergent philosophies regarding the acceptability of different types of evidence across countries represent a substantial barrier to harmonization. Countries differ in the way they deal with comparators, indirect comparisons, crossover data, meta-analyses, and RWE. **(n=7)** Defining the appropriate comparator is a significant challenge for an EU HTA. There are a number of differences across countries in terms of standards of care. The current pace of science also means that the appropriate comparator can change frequently. **(n=8)** Given the heterogeneity of treatment and speed of science, we cannot always have perfect RCTs. In some cases, RCTs are unethical. **(n=3)** There are conflicting signals from regulators and HTA authorities on evidence generation. Regulators are promoting accelerated approval and patient access, while HTA bodies are delaying access due to uncertainty in the evidence. **(n=3)** Additional evidence generation may not be a commercially viable option for a company, particularly in settings where the outcome of resubmission is uncertain and where the price following resubmission is unlikely to rise. As a result, companies may elect to pull their product from the market. **(n=2)**	Compromises will be needed regarding evidence requirement and appropriate standards of care before any EU collaboration can be reached. **(n=7)** An EU HTA would likely need to wrap its hands around a large number of comparators to accommodate differences in standards of care across Europe. **(n=8)** There needs to be some recognition and acceptance of when it is appropriate for single-arm trials and indirect comparisons. **(n=3)** More harmonization is needed between regulators and HTA authorities. An EU collaboration on HTA, if accepted at MS level, could help to bridge the gap in evidence requirements. **(n=3)** Countries should be open to changes in price following resubmission or additional evidence generation, both upwards and downwards. More predictability in the result of resubmission would facilitate greater additional evidence generation. Harmonization would lower costs of evidence generation. **(n=2)**	There are several benefits to RWE. This includes facilitating conditional reimbursement, collection of additional safety data through registries, and the answering of additional questions about the product. **(n=5)** Conditional reimbursements requiring resubmission are associated with high workloads. Beyond costs of evidence generation, there submission workload is substantial. E.g. The submission for the new Cancer Drugs Fund was extensive, and must be repeated every 18 months. **(n=2)** The importance of RWE varies by disease area. RWE plays less of a role in diseases with long-term endpoints such as cystic fibrosis. It is more relevant in areas such as oncology. **(n=2).** There would be significant benefits to both industry and patients from methodological expansiveness in evidence types considered. Specifically, greater alignment on methodology surrounding crossovers would be useful in oncology. **(n=1)** There are incentive issues with sharing RWE. Access to data and data privacy are barriers to increasing use of RWE. **(n=1)**

Impact of HTA on innovation and predictability for Pharmaceutical manufacturers

Insights were captured in terms of problems with predictability and innovation, potential solutions through EU collaboration or other means, and additional feedback on innovation and predictability. Only eight out of nine Pharmaceutical companies provided feedback on innovation and predictability. The number of companies highlighting a problem, solution or additional insight is provided in brackets.

Table 43: Impact of HTA on innovation and predictability for Pharmaceutical manufacturers

Problems	Solutions	Additional feedback
Poor predictability, high complexity, poor transparency, and high fragmentation are barriers to health innovation and investments in development programmes. **(n=6)** There are tensions between regulators that promote accelerated access and reimbursement authorities that delay access owing to uncertainty of data. **(n=4)** Harmonizing HTA evidence requirements may result in convergence to the strictest requirements. This would create barriers to entry and discourage innovation/investment. **(n=1)** HTA systems tend to incentivize me-too products or 2nd, 3rd, 4th entrants, rather than the innovator. The first-mover tends to pave the road, and subsequent entrants have an easier time. **(n=1)** HTA systems based on cost-effectiveness (e.g. NICE) can punish innovation if the current comparator is a generic product. Demonstrating cost-effectiveness is very challenging, in settings where there has not been a new innovation in a long time. **(n=1)**	Harmonization of evidence requirements, if accompanied by MS acceptability, would facilitate easier investment decisions. **(n=6)** There should be greater consistency between regulators and reimbursement authorities on evidence requirements and the acceptability of indirect comparisons or single arm studies. **(n=4)** Harmonization must be informed by good and rational thinking. Some compromise is required in terms of evidence requirements. **(n=1)** Additional incentives are needed to sustain innovation. **(n=1)** Additional incentives are needed for truly innovative/transformative products. **(n=1)**	An EU HTA with a solid methodology would de-risk the submission process and help to eliminate arguments resulting from low quality assessments and misinterpretation of data. Greater consistency in HTA assessments would be very beneficial. **(n=3)** Innovation can be driven by early advice and greater clarity on payer expectations. This can help establish European priorities for innovation. **(n=1)** Clinical trial programmes are largely dominated by the FDA, due to the fragmented evidence requirements within Europe. Harmonization of evidence requirements would give the EU stronger influence on clinical trial development. **(n=1)** There is unlikely to be significant risk of a negative EU REA report if these products have made it through regulatory approval. Products with surrogate endpoints might be the exception. Other products would have already been removed from development prior to regulatory approval. **(n=1)**

Pharmaceutical manufacturers' thoughts on EC Policy Options

Insights were captured in terms of problems in collaboration, potential solutions, and additional feedback on the process of collaboration and on the impact of collaboration. The number of companies highlighting a problem, solution or additional insight is provided in brackets.

Table 44: Pharmaceutical manufacturers' thoughts on EC Policy Options

Problems	Solutions	Additional feedback
Economic value and Socioeconomic impact of products vary substantially across settings. **(n=6)** Identifying and fulfilling individual MS submission criteria requires a substantial amount of work. **(n=4)** If not designed and implemented properly, any form of EU HTA will simply represent an additional hurdle on top of current national requirements. **(n=3)** Defining the appropriate comparator is a key challenge for establishing any kind of EU HTA. **(n=8)** While universal agreement and acceptability on a methodology may be the ultimate goal, this is likely unachievable in the short term. **(n=1)**	Option 4.1 is the most appropriate solution put forth by the EC. Economic evaluation should remain a national process. **(n=6)** Establishing an EU HTA that evaluates clinical effectiveness may reduce some inefficiency and workload, although local teams will still be required for negotiations and market access. Local studies will still be required. **(n=4)** There must be some form of guaranteed acceptability and uptake of the EU HTA findings. The EU HTA should be demand- driven, from MS, rather than supply-driven from the EC. **(n=3)** The EU HTA will either have to wrap its hands around a large number of comparators or there will need to be some kind of compromise at MS level. **(n=8)** A short-term solution may be agreement on binding or semi-binding statements that we can build upon as outcomes of the European assessment. Over time, we would seek to reduce the differences in opinion on what is acceptable evidence. **(n=1)**	EU HTA is a substantial risk, as a negative n EU HTA outcome no prevents access from all EU countries. This ismight be exacerbated in the situation of false negative, where evidence is misinterpreted. **(n=6)** Harmonization must consider simple design, how many arms are required, appropriate comparators, length of trial, population size, indirect comparisons, and RWE vs clinical trial endpoints. Conversations about economic model, productivity, and indirect costs can remain at local level. **(n=7)** It is possible to do both clinical and economic assessment at EU level, however issues such as burden of disease and willingness to pay remain local issues. **(n=1)** An EU HTA report could improve upon the EMA EPA report by a) taking an iterative approach which does more over time and b) expands on the evidence types that inform the report by using indirect comparisons, sub-group analyses and meta-analyses. **(n=1)** Appropriate governance is required for any EU HTA. There must be some type of appeal process. **(n=1)** An EU HTA will not impact on market access. But it may help to improve consistency in evidence interpretation, reduce some duplication, and reduce delays from misinterpretation of evidence **(n=1)**

7.1.13.3 MedTech Industry results

Medical device company experience with EUnetHTA

Out of the six medical device companies/associations interviewed, only one company directly participated in EUnetHTA. Four companies had not directly participated in pilots, but provided some comments on EUnetHTA. MedTech also provided some insights. Insights were captured in terms of problems with EUnetHTA pilots, potential solutions, and additional feedback on the impact of EUnetHTA. The number of companies highlighting a problem, solution or additional insight is provided in brackets.

Table 45: Medical device company experience with EUnetHTA

Problems	Solutions	Additional feedback
EUnetHTA appears to be largely an academic exercise thus far; it is unclear that they have had any impact outside the level of academia. It has yet to have a commercial impact. **(n=4)** EUnetHTA may not have sufficiently understood the fundamental differences between Pharma and medical devices. Medical devices are much more integrated in the process of care. There is poor transferability of HTA across settings. The methodology did not sufficiently account for the fragmentation of decision-making. **(n=3)** There were problems with product selection and with company identification in the EUnetHTA pilots for medical device companies. **(n=1)** There were issues with timelines for submissions and a lack of understanding about how industry works in practice. The EUnetHTA requests did not acknowledge the smaller capacity of medical device teams relative to Pharma teams. It was very resource-intensive and the request was not made over a realistic timeline. **(n=1)** EUnetHTA did not recognize the difference between medical devices and in vitro diagnostics. (**n=1)**	Increased acceptability at MS level is required for pilots to provide value. **(n=4)** Design of HTA methodology for medical devices must be bottom-up and demand-driven, taking into account local information and decision-making needs. **(n=3)** Products selected for trials should be relevant to all EU markets. It is important that the assessments deliver valuable information, particularly if companies are expected to devote already limited resources towards the pilot. **(n=1)** Greater consultation with industry and appreciation of capacity would improve cooperation and participation. **(n=1)** A separate HTA methodology and template should be developed for in vitro diagnostics. **(n=1)**	Better resourcing and funding is required for EUnetHTA to have a more substantial impact. This would likely require moving past a model of voluntary cooperation. **(n=1)** The assessments performed by EUnetHTA have improved over time. The involvement of physicians in the process is encouraging. **(n=1)** EUnetHTA was beneficial when the focus was more on clinical uncertainty than on value or pricing. It provided clarity on the clinical pathway and on appropriate use of the product. **(n=1)** EUnetHTA implies additional risk. A 'no' at EU level excludes you from all European markets. **(n=1)**

Impact of national procedures on medical device manufacturers

Insights were captured in terms of problems associated with national procedures, potential solutions through EU collaboration or other means, and additional feedback on the impact of national procedures. The number of companies highlighting a problem, solution or additional insight is provided in brackets.

Table 46: Impact of national procedures on medical device manufacturers

Problems	Solutions	Additional feedback
HTA currently plays a minor role for medical devices in most settings. It is viewed largely as a barrier to access by medical device companies. It really only fits into access models to some extent for UK, France, Sweden, and Norway. **(n=5)** Medical devices far outnumber Pharmaceuticals. Many countries are starting to look at HTA for medical devices but lack the expertise and resources to do so properly. HTA is rarely used, typically access is through direct negotiation with health funds or hospitals. **(n=1)** Countries' are increasingly requesting national evidence. This is sometimes viewed as an artificial barrier and makes access pathways lengthy, quite costly, and lowers transparency. **(n=1)**	If framed as an opportunity to leverage the value of a product, through an EU HTA report, there may be more appetite for an EU HTA. **(n=5)** HTA is likely unsuitable for all medical devices, if HTA is to become more formalized, restrictions will be required on the types of devices that are assessed. **(n=1).** More agreement and flexibility on evidence requirements would be more appropriate in certain circumstances and would reduce unnecessary costs and barriers to market access. **(n=1)**	France has a national HTA framework for innovative medical devices, but this is largely a barrier to access and competition. In general, products are launched in France after other markets, and often at higher prices. A disproportionate amount of resources is used in France for market access. **(n=4)** There is extremely high fragmentation for market access in medical devices. This depends on local requirements that vary substantially. There are differences in methodology, frequency and transparency. Even within a country, there is significant fragmentation. **(n=5)** NICE assessment procedures are considered to be very transparent. **(n=2)** Regional health care systems such as Portugal, Spain, and Italy are more challenging for medical devices. You have regional officers running HTA, it becomes more complex, and you see differences in terms of how outcomes are dealt with and elicited. There are a lot of national specifics that make it difficult for companies to use any scaling effects **(n=1)** The medical device market is fundamentally different from the Pharmaceutical market. It is very dynamic and more open to competition. The effective life cycle of a medical device is much shorter than a Pharmaceutical, and patents are much easier to get around. **(n=1)**

Medical device manufacturers' experiences with Early Dialogue and rapid assessment

Out of the six companies interviewed, only two companies had participated directly in early scientific advice and Early Dialogue. Three companies had not participated but provided some comments. One company did not comment on Early Dialogue or rapid assessment. Insights were captured in terms of problems associated with Early Dialogue and rapid assessment, potential solutions through EU collaboration or other means, and additional feedback on Early Dialogue/rapid assessment. The number of companies highlighting a problem, solution or additional insight is provided in brackets. Only limited insights were collected for Early Dialogue and rapid assessment with medical device companies.

Table 47: Medical device manufacturers' experiences with Early Dialogue and rapid assessment

Problems	Solutions	Additional feedback
Early Dialogue across several countries suggests hugely fragmented and diverging views on evidence requirements and expectation. **(n=1)**	An EU collaboration could help harmonizing these diverging to some extent. This would simplify clinical development. **(n=1)**	Early Dialogue is a very useful process. All possible opportunities for engagement are used. It is useful to have a clear mandate from local authorities about what to do in terms evidence generation. **(n=2)** The value of rapid assessments is unclear for medical devices. Work is needed to establish what questions are being answered at local level and over what time frame. If this is not actively informing decisions, it simply becomes a hurdle. **(n=1)** Rapid HTAs may be acceptable as long as they are true assessments. Authorities need to recognize that all data may not be available at the time of rapid assessment. **(n=1)**

Medical device manufacturers' experience with evidence generation, resubmissions

Insights were captured on current problems and potential problems through collaboration, potential solutions, and on additional feedback on evidence generation, resubmission and RWE. Only five out of six companies provided insights on evidence generation, resubmissions and RWE.

Table 48: Medical device manufacturers' experience with evidence generation, resubmissions, and real world evidence

Problems	Solutions	Additional feedback
EU HTA in the context of medical devices would present a challenge for small companies in terms of fulfilling the evidence requirements. This would have significant impacts on the medical device market, where the majority of companies are SMEs. Currently, HTA is rarely used in the context of medical devices. An EU HTA would represent a significant barrier to entry for medical device companies. **(n=3)** Medical devices have a shorter life cycle than Pharmaceuticals. The market is much more competitive as patents are easier to get around for medical devices. While long RCTs may be desirable from an evidence standpoint, they may not always be appropriate or feasible for medical devices. **(n=3)** The number of medical devices far exceeds Pharmaceuticals. Performing HTA on all medical devices would be extremely resource-intensive for all stakeholders involved. **(n=1)** Reassessments can be problematic in the medical device sector given the level of competition. Following initial recommendations, competitors will enter the market and have an impact on the price of a product. This distorts cost-effectiveness models. **(n=1)** Brand-specific evidence generation is not always efficient, particularly in situations where the procedure is the same. **(n=1)**	Given the large proportion of small and medium medical device companies, any EU-wide HTA for medical devices ought to be cognizant of the resource constraints and impact on innovation and competition. **(n=3)** Evidence generation for medical devices likely requires greater use of RWE. **(n=3)** If HTA is applied to medical devices, it is likely only realistic to do so for a subset of devices. **(n=1).** HTA for medical devices must be cognizant of the short life cycle of medical devices and implications of competition. **(n=1)** HTA systems should try to identify situations in which there is a duplication of effort in evidence generation **(n=1)**	Countries vary substantially in how they define the appropriate comparator for a treatment. It is unclear how they will reach agreement at EU level. **(n=1)** An EU HTA would be a hurdle for medical device companies. Evidence requirements would still exist at the national and local levels. **(n=1)** HTA would be unlikely to solve any issues pertaining to recalls or the safety of medical devices. These problems typically emerge through long-term studies and would not be present at the time of HTA. **(n=1)** Increased awareness and acceptability of indirect comparisons are needed in the medical device sector. **(n=1)** A key challenge to more extensive use of RWE is the high cost of establishing registries. RWE can be leveraged by medical device companies to create barriers to entry for competitors. A smart company will offer evidence to decision-makers that competitors cannot match. **(n=2)** Value-based procurement will help to promote sustainable evidence generation. Managed entry agreements are an effective tool to promote increased RWE generation. **(n=1)**

Impact of HTA on innovation and predictability for medical device manufacturers

Insights were captured in terms of problems with predictability and innovation, potential solutions through EU collaboration or other means, and additional feedback on innovation and predictability. Only five out of six companies interviewed provided insights on innovation and predictability.

Table 49: Impact of HTA on innovation and predictability for medical device manufacturers

Problems	Solutions	Additional feedback
Evidence requirements tend to be strictest for the first-mover in a therapeutic area. HTA systems tend to incentivize me-too products or 2nd, 3rd, 4th entrants, rather than the innovator. The first-mover tend to pave the road, and subsequent entrants have an easier time. **(n=2)** HTA does not play a major role in the medical device market. Implementing EU HTA would represent a massive barrier to entry for SMEs, which make up the majority of the market. This would have significantly negative impacts on innovation and on prices of medical devices. **(n=3)** HTA designed from the top-down is likely to have a negative impact on diffusion of innovation as uptake will be poor. **(n=1)** Poor predictability, high complexity, poor transparency and high fragmentation are barriers to health innovation and investments in development programmes. **(n=1)**	Additional incentives are needed to sustain innovation. **(n=2)** HTA requirements for medical devices must be very low in order to avoid disrupting competition and create barriers to entry. **(n=3)** In order to provide value, HTA must be designed from the bottom-up and take into account the needs of local decision-makers. **(n=1)** Harmonization of evidence requirements, if accompanied by MS acceptability, would facilitate easier investment decisions. **(n=1)**	HTA is seen as a cost for medical device manufacturers, not a business opportunity. If it can be presented as an opportunity to move towards more of a value-based model, it may be more appealing. **(n=1)** Engaging in Early Dialogue can help improve predictability of submission outcomes. **(n=1)**

Medical device manufacturers' thoughts on EC Policy Options

Insights were captured in terms of problems in collaboration, potential solutions, and additional feedback on the process of collaboration and on the impact of collaboration. The number of companies highlighting a problem, solution or additional insight is provided in brackets.

Table 50: Medical device manufacturers' thoughts on EC Policy Options

Problems	Solutions	Additional feedback
Given the decentralized and fragmented nature of decision-making for medical devices, HTA at the European Union level does not make sense. **(n=4)** Differences in comparators, standards of care and patient population are significant barriers to harmonization. **(n=2)** An EU HTA would represent a barrier to access in the medical device field where the majority of companies are SMEs. These companies would be less able to finance evidence generation. This will reduce competition and raise prices. **(n=3)**	Academic discussion and sharing of best practices is useful, but 'evidence' on how HTA operates in European countries, specifically for medical devices, does not currently support implementation of HTA for medical devices at the European Union level. **(n=4)** Harmonization will require compromise at the MS level. Some standards would be required for evidence generation. **(n=2)** Any form of collaboration would need to be a bottom-up approach, starting at the hospital level and taking into account local decision-making needs. **(n=3)**	An EU HTA would not reduce much workload or eliminate much duplication. Work at local level would still be required, given the engrained nature of medical devices in the process of care. It would likely be a hurdle on top of national/local requirements. **(n=3)** An EU collaboration on HTA would be favourable under the following conditions: a) Conditional reimbursement; b) Outcomes to be licensed to rewards; c) Collaboration to address considerations of uncertainty; d) Agreement to evaluation to be done when evidence is available, especially for some particular technologies (e.g. 'disruptive technologies', big ticket items, etc.); and e) Agreement on the 'when' and 'what' to evaluate. 6. Need for national registries **(n=1)** In Pharma, an EU collaboration would potentially be replacing some activity and leading to efficiency gains. In medical devices, an EU collaboration would not be replacing activity, but rather, would represent new activity. Something quick and easy would not work in this context. More work is needed to identify and understand local contextual issues. **(n=2)** HTA is only useful in medical devices for technologies that a) address an unmet need, and b) require some form of organizational or structural reform for adoption. If we did have cooperation, it would need to be voluntary. **(n=1)**

7.1.13.5 Concluding remarks from interview results

Overall the interviews across both industries, Pharmaceuticals and medical devices, showed that the different national procedures have a different impact on HTA assessment, with national 'methodology' leading to substantial variations in the final outcome. Specifically, some HTA settings are driven by cost-per QALY and HTAs driven by clinical benefit show substantial variations in the way they value the same product. However, it is important to highlight that these differences are also influenced by the therapeutic areas in which the product fall.

Manufacturers highlighted that the current fragmented HTA system across EU MS requires companies to cater to a diversified range of demands and this might lead to difficulty in submitting reports or multiple re-submission to the same HTA bodies depending from the country setting. There is a consensus across the Pharmaceuticals industry respondents that EU collaboration on HTA may be possible for generating a relative effectiveness assessment, but decision-making and appraisals should remain a local process. Yet, Pharmaceutical Industry respondents envisaged that agreement on evidence requirements at EU level would offer substantial benefits, allowing a separation between clinical benefit and reimbursement. By contrast, manufacturers highlighted the heterogeneity and diversity of the Medical devices market in comparison with the Pharmaceutical product one. Manufacturer highlighted that HTA currently plays a minor role for medical devices in most settings due to the extremely fragmented market access of medical devices and therefore the current impact of HTA on their business is low.

Looking at the predictability of the process, the interviews agreed that it is a key element for investment and resourcing decisions, particularly for small and medium sized companies. It was commonly stated that the harmonization of process and evidence requirements would allow them to ensure there are no misunderstandings, and enhance the level of the predictability in the system.

Transparency of evidence requirements, consistency of methods, acceptability of indirect comparisons, and predictability of outcomes have been highlighted by several companies as desirable characteristics. Specifically, interviewees advocated for a better summary and inclusion of information on indirect comparison and secondary endpoints and a clear definition of the appropriate comparators, currently considered an issue in some country settings. By contrast, the Medical devices interviewees suggested that, while long RCTs may be desirable from an evidence standpoint, they may not always be appropriate, feasible or sufficient for medical devices

Finally, Early Dialogue and scientific advice are viewed as an extremely useful exercise and helps to increase transparency, suggesting that a system aligned to what is currently done with EMA would be beneficial. However, few respondents stated the importance of not introducing a double system where countries apply additional requirements.

7.1.14 Summary conclusion of the baseline scenario and related impacts

Currently, Health technology assessment (HTA) has been implemented in a growing number of European countries providing evidence-based information for both decision-making and policymaking regarding services and products to be made available as part of national health-care systems and/or for price negotiation. While HTA provides input for appraisals and pricing and reimbursement decisions, the study focuses on the assessment aspect, as in all Policy Options any subsequent appraisal and pricing and reimbursement decision for medical technologies, devices or Pharmaceuticals remain purely at national level.

The case studies conducted on 40 technologies for the baseline scenario aimed to give a clear picture on HTA in Europe through a comparative analysis of HTA recommendations

issued across MS. Results provide an understandable picture of these complex decision-making processes, differentiating by category of technologies considered.

For the Pharmaceutical sector, the current situation depicted by the study has different impacts:

- The average number of assessments per technology carried out in parallel by different HTA bodies is high across the sample (13.5 out of 19 agencies), showing a significant level of duplication. This is also confirmed by the Kappa score calculated and adjusted for proportions of agreement on the availability of reports showing that countries with established HTA bodies tend to assess the same Pharmaceutical products and the same drug-indication pairs. Yet the duplication is not homogenous. Results showed that agencies have a fair level of agreement in the assessment of Pharmaceutical products, but the number of assessments carried out is highly influenced by the type of HTA body and the level of HTA development in the country. This, in most cases, can be related to the selection criteria for Pharmaceutical products to be assessed. HTA bodies such as HAS, G-BA and AIFA due to their topic selection process (evaluating all the new Pharmaceuticals) showed a high level of agreement and so did HTA bodies such as TLV and NICE or INFARMED. Evidence also showed that agencies have different capacities for assessing technologies; only some well-developed systems can cover all the new Pharmaceuticals; others have topic selection processes in place enabling them to assess a proportion of newly launched Pharmaceuticals and some systems only assess a smaller number of technologies. Some countries are implementing HTA referencing.

- Looking at the recommendation level, the level of agreement across HTA bodies for the Pharmaceutical sample is generally low. Nevertheless, this should take into account the fact that in some cases HTA bodies perform assessments (the results of which could be transferrable across settings), while in other cases, HTA bodies perform appraisals, (which are context-specific and take into account factors and dimensions of value that are important in the setting concerned).

- A high degree of variability in the time of assessment of a Pharmaceutical product after MA was recorded, suggesting a general delay in assessment in a number of countries. This might lead to delays access by patients in some EU MS. However, it should be acknowledged that this difference might be related to other factors as well such as willingness to submit a report or delay a submission by the company, the different selection criteria in the choice of technologies to assess and the different role of the HTA body.

- Considering the evidence included in the different reports, a tendency in 'homogenization' across Europe is observed with a preference towards the same typologies of clinical and economic evidence. This suggests a growing trend towards the homogenization of clinical and economic evaluation. The primary trial types considered and the main economic evidence considered were generally of the same type, suggesting that there is a clear preference for phase III trials and cost-utility analysis.

- There is still not enough predictability in the system. Nonetheless, manufacturers highlighted that a key challenge is the agreement on evidence, highlighting that the preferences of national policy makers could have a high impact on the process and the fact that harmonization of evidence requirements is strongly favoured by the industry sector. SVJs are not routinely considered and where they are, significant variation was shown across MS, indicating how the HTA processes and the quality of the evidence considered vary quite significantly.

- Looking at the baseline costs for the Pharmaceutical industry the heterogeneity in the assessment of the evidence at national level can be associated with the non-feasibility to draw a clear average of the HTA spending across companies. Our results

showed a high variability in HTA spending (between EUR 73 000 and EUR 1 700 000 per HTA submission), as well as in the additional evidence generation (between EUR 50 000- 20 000 000). Interviews highlighted the wide heterogeneity in the level of acceptability of different types of evidence across countries representing an important driver of costs, impacting in some cases on their business decisions.

The landscape of **medical devices/technologies** clearly differs from that of Pharmaceutical products:

- Substantial inter-country variability in HTA recommendations across countries for medical devices sector was observed as well as a lower number of HTA per technology leading to a lower duplication of reports but to a difference in access across countries. The level of agreement in the availability of assessments showed by the Kappa score was mainly poor, showing that HTA is still underdeveloped in this sector. In line with the literature (32, 34), these results were also confirmed during interviews where manufacturers highlighted the heterogeneity and diversity of the medical technologies market including the market access process in comparison with the Pharmaceutical sector. This is propagated by the short life cycle of medical technologies (including fast development phase) and the limited requirements for clinical evidence, according to the current regulatory framework. Manufacturers highlighted that HTA currently plays a minor role in the market access process for medical devices in most settings due to the extremely fragmented market access of medical devices. Indeed, medical devices have a faster and dynamic life cycle than Pharmaceuticals and the market is much more competitive as patents are easier to obtain and the property rights are mildly enforced (35, 36).

- Regarding the processes of HTA in the medical device sample, the timing in evaluating the same category of medical devices varied significantly, probably related to the fragmented system in place for obtaining CE mark.

- The fragmentation of the MedTech sector was also shown in the evidence considered by the HTA bodies; despite a preference for RCTs, the other clinical evidence considered varied substantially across the sample. This might be related to absence of RCT data and the need for multiple sources of less strong evidence to prove the clinical effectiveness therefore raising also questions regarding the central role of RCTs in the evaluation of medical devices as the main evidence of HTA assessment. The interviews and the literature suggested that, while long RCTs may be desirable from an evidence standpoint, they may not always be appropriate, feasible or sufficient for medical devices (69). Confirming the literature, therefore, agreement on the best evidence and methodology for assessing medical devices is still lacking.

- With regards to baseline costs, the underdevelopment of the current role of HTA for medical devices, can be associated with the non-feasibility to draw a clear average of HTA spending across participating companies, the high variability in the HTA submission spending (EUR 17 000 - EUR 12 800 000) and in the generation on additional evidence for the purpose of HTA submission.

Finally, for **other technologies** the results generally showed:

- A low number of agencies actively engaging in HTA in this category of technology (n=14); in general, there is also a lack of publicly available reporting of country specifics in public health interventions for instance. There are large differences across MS in vaccinations programs due to different products considered and the different policies employed in implementing preventive programs, which do not allow clear conclusions to be drawn.

- Nonetheless, there seems to be some agreement in the use of a common methodology for retrieving and considering clinical and economic evidence and the

outcomes of HTA reports across countries. Further research in these types of intervention is needed.

Overall, the literature confirmed that there is a heterogeneity in the way health technologies are considered across EU MS. An analysis at micro-level of assessments performed by different HTA bodies, highlighted a tendency towards common methods in assessing products. Differences in health systems, political traditions, national income, and local practice patterns will continue to translate into different ways of appraising health technologies. Yet, a tendency towards homogenization in assessments is growing, leading to a duplication of assessments, specifically for the assessment of clinical and economic evidence. This is confirmed in the case of Pharmaceuticals, whereas for MedTech and other technologies the picture is still quite fragmented. There remains considerable room for improvement in moving HTA towards greater predictability and rationality. This will, of course, require resources as well as leadership, not only among governments, but also across industry stakeholders. The main goal should be to improve the science and to reduce uncertainty.

7.2 Costs of Policy Options

Information and calculations presented in this section should be considered with the underlying assumptions mentioned in the respective parts and associated limitations (see 6.2.2.6). They refer to a specific anticipated scenario and should not be considered in isolation, but rather in combination with other aspects, especially the social/health impacts of section 6.3, as many effects are not quantifiable but should be considered nonetheless. Figures presented are rough and rather conservative estimates.

7.2.1 Cost of implementation mechanisms for governance structures

This section displays the results of cost estimations for the implementation mechanisms. Indicated numbers are rounded estimates in thousand Euros per year.

The project-based cooperation includes estimates based on average salaries of EUnetHTA JA 3 and respective partners. The European staff regulations formed the basis for the cost calculations for the remaining four implementation mechanisms, i.e. the MS secretariat, the EU secretariat, the integration in an existing agency and establishment of a new EU agency.

The salary scheme for temporary agents working at EU institutions was used to calculate basic salaries. The salary scheme is comprised of 16 function groups and five steps within each function group. At first, qualification profiles were matched with applicable function groups and the average of the fiver steps of each function group were used for calculations. Moreover, basic allowances, like the dependent child allowance, assuming 1.58 ([47]) children per employee, and the household allowance, were included in salaries. Education allowance, pre-school allowance, expatriation or foreign residence allowances, installation allowance, daily subsistence allowance and additional pays, e.g. business travel costs, were not considered in the calculations, as they are particularly case-specific. Thus, calculated salaries are basic assumptions not accounting for specific characteristics of each case but include 13th and 14th salary.

The qualification profiles listed in Table 20 were matched with 16 function groups:

Table 51: Qualification profiles

Function group	Qualification profiles
AD 12+	Unit head
AD 9 (senior level)	Head
AD 7	Project manager, Scientific officer, Financial officer and IT officer
AST 3	Administrative assistants, Communication assistants

According to EU staff regulations, qualification profiles assigned to function group AD 12, AD 9 and AD 7 presume a university degree of four years of education or more, a university degree of three years and at least one year work experience in a relevant field, or equivalent training and professional experience. Classification in function group AST 3 necessitates post-secondary education, secondary education and a minimum of three years of relevant work experience or equivalent professional training and a minimum 3 years of relevant work experience.

([47]) Fertility rate in EU 28 according to Eurostat:
http://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&pcode=tsdde220&plugin=1

Other relevant costs for calculations were travel costs for the coordination team, one-time costs for sufficiently elaborated IT systems (data protection), expenditures for software licences and licences to access literature databases, premises costs and costs associated with the management board and the independent review process by the expert committee. Costs for the independent review process of the committee include fees payed to experts according to the expert fees of the EC and travel costs for respective meetings, i.e. either four times or eight times p.a. Due to the high number of anticipated assessments, online meetings seem more efficient. Finally, 15% overhead were included to account for other potential incidental costs. Cost calculations **do not include costs resulting from adaptation of existing facilities** or acquisition costs for new facilities. In the case of POs 1 to 4, i.e. project-based cooperation, a MS secretariat, an EU secretariat or integration in an existing agency, existing facilities might be used. Moreover, there are no special requirements like considering an extensive IT system as was the case for eu-LISA. Consequently, costs incurred by adapting existing facilities or acquiring new facilities were not considered as a major cost element for implementation cost calculations. Running costs of premises were considered for calculations. With respect to the different price levels of the MSs, staff costs and premise costs derived from the EU salary scheme required adjustment according to the salary indexation list ([48]). Three categories representing countries with a high price level (Category 1: Indices 113.8-141.8), a medium price level (Category 2: Indices 85.7-108) and a low price level (Category 3: Indices 51.1-80.6) account for respective differences. Moreover, premise costs were adjusted according to the salary indices to ensure comparability within the calculation.

Licences for IT software, including a strong firewall and literature databases, are necessary to provide state-of-the-art conditions to optimally support HTA assessments contracted to HTA bodies and ensure efficient processes within the coordination unit and between the coordination unit and contracted partners. Estimates on IT software licenses include only HTA-specific requirements (e.g. for maintaining the POP-database). General software licenses were not estimated because the costs depend on the location and existing licenses. It was assumed that these costs are covered by the overall EC budget/agency budget (as is the case for energy supply and basic internet connection). Licenses for literature databases are exclusive licenses, thus only available for the coordination team, for this a lump sum was estimated because costs depend on the number of databases and licenses.

The management board is mainly responsible for running the agency, and the expert committee provides scientific expertise.

Table 52 depicts an overview of estimations for the different implementation mechanisms in combination with the respective policy option presented in Table 7. Cost positions include running costs and implementation costs for respective outputs projected in Table 16 and Table 17, hence including 65 REAs.

([48]) Provided by EC services.

Table 52: Costs of running a central coordination body covering 40 EDs, 65 REAs and 11 Full HTA, costs are given in EUR 1 000 p.a.

Type of costs	Project-based cooperation (PO2)	MS secretariat (PO3a)	EU secretariat (PO3b)	Existing EU agency (PO 4.1)	Existing EU agency (PO 4.2)	New EU agency ([49]) (PO 5)
	Implementation Costs					
IT (implementation costs)	17 ([50])	Cost depend to a large extent of the 17,4situation in the premise (e.g. is there already an IT network established or not, are premised equipped with computers, are specific communication tools necessary, 'power' of firewall)				
	Running Costs					
Staff costs (Total costs) ([51])	785	1 871 (Cat 1) 1 417.7 (Cat 2) 963.9 (Cat 3)	1 463.8	2 954.9	3 264.3	4 170.2
Travel costs ([52])	132.6	42.5	42.5	42.5	42.5	42.5
IT software licenses ([53])	10	10	10	10	10	10
Licences for literature databases ([36])	20	20	20	20	20	20
Premises ([54])	254 (Cat 1) 192.5 (Cat 2) 130.9 (Cat 3)	295.5 (Cat 1) 224 (Cat 2) 152.3 (Cat 3)	231.3	512	573	753.6
Management Board ([55])	1 118.6([56])	205.3	205.3	63.7	308	308
ED Committee ([57])	N/R	723.6	723.6	241.2	723.6	723.6
REA Committee	N/R	N/R	N/R	732.6	2 197.8	2 197.8
Full HTA Committee	N/R	N/R	N/R	N/R	N/R	135.2
	Overhead for running costs (+15%)					
Total costs	2 685.2 (Cat 1) 2 614.5 (Cat 2) 2 543.6 (Cat 3)	3 642.8 (Cat 1) 3 039.5 (Cat 2) 2 435.2 (Cat 3)	3 100.9	5 263.4	8 210.1	9 615

N/A= Not applicable; all amounts are indicated in Euros (EUR); Cat 1=MS with high price level, Cat 2=MS with medium price level, Cat 3=Ms with low price level

([49]) Implementation costs not estimable within this study.
([50]) Based on EUnetHTA JA 3.
([51]) Based on respective qualification profile displayed in Table 51: Qualification profiles and EU staff regulations; adjusted to price levels if applicable.
([52]) Based on information of EUnetHTA JA 3 budget.
([53]) Based on EUnetHTA JA 3 budget and expert opinion.
([54]) Based on EMA premise costs; adjusted for price levels if applicable.
([55]) Based on 'Ramboll/Euréval/Matrix- Evaluation of the EU decentralised agencies in 2009'; PO 2 includes project-based participation rate.
([56]) Fees and travel costs.
([57]) Based on expert fees of EC, incl. travel costs.

When introducing project-based cooperation, one coordination team would be responsible for overall coordination. This may cause a minimum of 120 travels p.a. just for the coordinating team. Based on cost information available from previous EUnetHTA JAs, an average of EUR 850 per travel (including round-trip flights and one overnight stay at a hotel) is necessary. Relating to the other implementation mechanisms, meetings will be organised at the secretariat's or agency's location, thus a significant reduction of travel costs for the coordination team would be achieved, assuming a maximum of one third of the travel costs compared to project-based cooperation.

Moreover, the extensive management board foreseen for the project-based cooperation causes high costs compared to the Management Board of other implementation mechanisms' structures. Providing quarterly meetings for participating partners, the number of EUnetHTA partners of JA3 accounts for 79, represents a substantial cost burden. The introduction of a Management Board provides a leaner structure by organising quarterly meetings for representatives of each participating MS, even with the assumption of two additional meetings per year accounting for increased output production.

Taking that into account, after establishment of processes and structures, ideally 115 REAs in total should be performed (90 on Pharmaceuticals and 25 on medical devices). Cost estimates are presented in section 7.2.3.4.

7.2.2 Costs related to production of joint outputs

Table 53 to Table 55 depict relevant unit costs for outputs (Early Dialogues, REA and Full HTA) as far as available. Additionally, costs for the adaptation of joint products (in order to be applied at national level) have been estimated. It was also planned to take the costs of additional evidence generation requested by HTA bodies, which could be assumed to be decreased with the conduct of joint Early Dialogues, into consideration. However, this could not be incorporated because of missing data/information on the one hand and because very few of the survey respondents reported a reduction in HTA costs due to Early Dialogues (see Table 36 and Table 37). It may nonetheless be assumed that with mandatory options for REAs and full HTA, such cost reductions will become more likely due to harmonisation of MS requirements.

Costs are shown separately from the perspective of HTA bodies/MS and industry – specifically, the Pharmaceutical and medical devices industries.

Costs for joint outputs are given separately for EU level and industry.

Costs for REA, Full HTA and their adaptations have been estimated separately for reports done mainly by HTA bodies and reports/submissions done mainly by industry and reviewed by HTA bodies. It is assumed that costs to industry for HTA body-based reports are negligible.

It has proven very difficult to gather data on the costs for an industry HTA submission (see also 7.1.12). Cost estimates available for Pharmaceutical and medical devices' industry are highly variable and higher than that for HTA body-based reports. Moreover, costs for 'REA submission' and costs for 'Full HTA submission' cannot be distinguished between (although, according to estimates derived from Chamova 2017, economic considerations and calculations mostly have to be included within submissions at national level).

Even if all inputs are combined, it remains rather unclear what part of industry submission costs can be assumed to be replaced by joint assessment at MS level.

Therefore, it was assumed that the cost savings to industry may be estimated by the costs of one Joint Assessment (REA or Full HTA).

The following examples illustrate some further assumptions:

- A reduction of 40 HTA body-based **REAs** at national level leads to cost savings equivalent to the costs of 40 HTA body-based national REAs and the additional costs of the adaptions of 40 joint REAs in the national context. These savings and costs occur on the side of HTA bodies for, respectively, MS and their authorities.
- For **Full HTA** similar assumptions are made, despite that in systems with industry-based submissions it is assumed that HTA bodies/MS bear the costs for adapting the four REA domains in the national context and industry adapts the ECO domain, and if necessary, other domains.

Table 53: Unit costs per outputs, costs on the level of HTA bodies/MS (national outputs) and costs at EU level (joint assessments), cost in EUR 1 000 p.a.

	Current costs of HTA bodies/MS respectively EU (for Joint Assessments)					
	Performed at national level			Performed as Joint Assessments		
	Average	Min	Max	Average	Min	Max
Early Dialogue ([58])	€41.7	€19.4	€64.0	€45.9	€22.0	€70.4
	Assumptions: The final report of the SEED consortium reports 'fees for single HTA EDs'. Out of that information, UK costs were taken as an estimate for national costs, because 'this activity receives no public funding' and operates 'on a cost neutral basis'. They are given as a range within the report; the average has been calculated by the authors. These values should indicate total ED costs on the side of the HTA body, which may be paid by HTA bodies OR industry.			*Assumptions: A markup for additional administrative costs could be assumed (based on UK fees) for the production of joint ED, assumed to be 10%. EMA-fees for scientific advice amount to EUR 42 300 to EUR 84 700 (as given on the website). On the other hand, the costs for 11 SEED Early Dialogues were EUR 250 000 (22,727 pro ED; information provided by DG SANTE).*		
REA produced mainly **by HTA body** (with no or only some evidence/data submission provided by industry) ([59,60])	€35.0	€10.0	€100.0	€117.0 for Pharma €85.7 for MedTech	€58.5 for Pharma €42.9 for MedTech	€234.0 for Pharma €171.4 for MedTech
	Assumptions: For national products information sources were studied, and rounded values taken based mainly on survey data for REA vs. HTA.			*Assumptions: For joint output, a wide range of one half to double of the amount was assumed (being one third to threefold at national level).*		
REA produced **by industry** and reviewed by **HTA body** ([61])	€20.0	€5.0	€55.0	N/R		
	Assumptions: Out of the survey results, rounded values were taken for those MS that reported costs and have reports based on industry submission (cave: small sample of available data).			*Assumptions: Joint assessments are always done mainly by the HTA institutions being authors/reviewers and may include industry submissions as data input (see EUnetHTA JA2).*		
Full HTA produced **by HTA body** (with no or some evidence/data submission provided by industry) ([62])	€95.0	€20.0	€300.0	€228.9	€114.5	€457.8
	Assumptions: For national products information sources were studied, and rounded values taken based mainly on survey data for REA vs. HTA.			*Assumptions: For joint output, a wide range of one half to double of the amount was assumed (being less than one third to threefold at national level). It is assumed that the ECO domain of a Full HTA at EU level mainly includes literature review and basic collection of cost parameters for ECO domain.*		
Full HTA produced **by industry** and reviewed by **HTA body** ([63])	€40.0	€5.0	€100.0	N/R		
	Assumptions: Out of the survey results, rounded values were taken for those MS that reported costs and have reports based on industry submission (cave: small sample of available data).			*Assumptions: Joint assessments are always done mainly be the HTA institutions being authors/reviewers, but may include industry submissions as data input (see EUnetHTA JA2).*		
	National adaptation of a joint REA ([64])			€17.5	€5.0	€50.0
				Assumptions: It is assumed that HTA bodies always perform the adaptation of the Joint REA.		
	National adaptation of a joint Full HTA ([65]), done by **HTA body**			€47.5	€10.0	€150.0
				Assumptions: See Footnote		
	National adaptation of a joint Full HTA ([66]), done by **HTA body** and **industry**			€17.5	€5.0	€50.0
				Assumptions: See Footnote – It is assumed that HTA bodies do the necessary adaptation of REA domains.		

N/R=Not relevant. Sources are given in the Footnotes

([58]) Based on final study of the SEED consortium (UK costs p. 29); see also https://www.nice.org.uk/about/what-we-do/scientific-advice/frequently-asked-questions; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000327.jsp&mid=WC0b01ac0580024596
([59]) Based on ECORYS-study (p 30) and Survey results (national output).
([60]) Evaluation study JA2 (p 65) and estimations of the authors (joint output).
([61]) Based on Survey results and Chamova 2017.
([62]) Numbers are based on ECORYS-study (p 30) and Survey results (national output); Evaluation study JA2 (p 65) and estimations of the authors (joint output)
([63]) Numbers are based on Survey results and Chamova 2017
([64]) Estimations by authors: It is assumed that this mainly includes adaptation (if necessary) of CUR, TEC and epidemiological data plus translation of relevant parts into national language, maybe update of literature search.
([65]) Cost estimations by authors: It is assumed that this includes the adaptation of CUR, TEC and other domains, as described above for REA, plus part of the ECO domain (without literature review and basic collection of cost parameters), and, if relevant, parts of other domains.
([66]) Cost estimations by authors: It is assumed that this includes the adaptation of CUR, TEC and other domains, as described above for REA, plus part of the ECO domain (without literature review and basic collection of cost parameters), and, if relevant, parts of other domains.

Table 54: Unit costs for outputs, costs on the level of Pharmaceutical Industry, cost in EUR 1 000 p.a.

	Costs for Pharmaceutical Industry					
	Outputs performed at national level Total unit costs in EUR			**Outputs performed as Joint/Collaborative Assessment** Total unit costs in EUR		
	Average	Min	Max	Average	Min	Max
Early Dialogue ([67])	€55.8; 0.7 FTE	not feasible	not feasible	not feasible	€0.0; 0.6 FTE	€85.0; 2.0 FTE
	Assumptions: For national output report survey, results are shown (for more information see section on baseline costs, 7.1.12). Alternatively UK fees can be assumed as a proxy for industry costs (see Table 53), which cover not all, but probably the main part of industry costs for Early Dialogues (see 7.1.12.1).			*Assumptions: At the moment, EUnetHTA EDs are done without fees for industry (SEED-study, p 28). So out of the study survey results only reported staff and other costs (no fee costs, see section 7.1.12.1, figure 26) are shown here as an approximation. Alternatively, UK fees can be assumed (see above).*		
REA produced mainly **by HTA body** (with no or only some evidence/data submission provided by industry)	0	0	0	€139.1	€ 14.7	€334.2
	Assumptions: For national output, it is assumed that costs for inputs from industry are negligible			*Assumptions: For the costs to industry for joint output, no data or information are available. For calculation as a proxy, they have been assumed to be one fifth of submission costs as reported in the survey with according ranges from the sensitivity analysis.*		
REA produced **by industry** and reviewed by **HTA body** ([68])	€695.5	€73.4	€1,671.0	*Assumptions: Joint assessments are by definition done mainly be the HTA institutions being authors/reviewers and may include industry submissions as data input (see above).*		
	No distinction possible between REA and Full HTA, high range/variability and uncertainties.					
Full HTA produced **by HTA body** (with no or only some evidence/data submission provided by industry)	0	0	0	€173.9	€18.4	€417.7
	Assumptions: For national output, it is assumed that costs for inputs from industry are negligible.			*Assumptions: For the costs to industry for joint output, no data or information are available. For calculation as a proxy, they have been assumed to be one fourth of submission costs as reported in the survey with according ranges from the sensitivity analysis.*		
Full HTA produced **by industry** and reviewed by **HTA body** ([69])	€695.5	€73.4	€1,671.0	N/R		
	No distinction possible between REA and Full HTA, high range/variability and uncertainties			*Assumptions: Joint assessments are always done mainly by the HTA institutions being authors/reviewers, and may include industry submissions as data input (see EUnetHTA JA2).*		
National adaptation of a joint REA ([70])				*Assumed to be done by HTA body/MS*		
National adaptation of a joint Full HTA ([71])**,** done by **HTA body**				–		
National adaptation of a joint Full HTA ([72])**,** done by **HTA body** and **industry**				€30.0	€5.0	€100.0
				Assumptions: It is assumed that this, on the side of industry, includes the supplementary production of part of the ECO domain (without literature review and basic collection of cost parameters), and, if relevant, parts of other domains.		

FTE=full time equivalent, N/R=Not relevant Sources are given in Footnotes

([67]) Based on Survey results.
([68]) Based on Survey results.
([69]) Based on Survey results.
([70]) Estimates by authors: It is assumed that this mainly includes adaptation (if necessary) of CUR, TEC and epidemiological data plus translation of relevant parts into national language, maybe update of literature search.
([71]) Cost estimates by authors: It is assumed that this includes the adaptation of CUR, TEC and other domains, as described above for REA, plus part of the ECO domain (without literature review and basic collection of cost parameters), and, if relevant, parts of other domains.
([72]) Cost estimates by authors: It is assumed that this includes the adaptation of CUR, TEC and other domains, as described above for REA, plus part of the ECO domain (without literature review and basic collection of cost parameters), and, if relevant, parts of other domains.

Table 55: Unit costs for outputs, costs on the level of MedTech Industry, cost in EUR 1 000 p.a.

	Costs for MedTech Industry					
	Performed at national level Total unit costs in EUR			**Performed as joint/collaborative assessment** Total unit costs in EUR		
	Average	Min	Max	Average	Min	Max
Early Dialogue ([73])	€21.7; 0.7 FTE	not feasible	not feasible	€21.7; 0.7 FTE	not feasible	not feasible
	Assumptions: For national output report survey, results are shown (for more information see section on baseline costs, 7.1.12). Alternatively, UK fees can be assumed as a proxy for industry costs (see Table 53), which cover not all, but probably the main part of industry costs for Early Dialogues (see 7.1.12.2).			*Assumptions: Joint output: At the moment, EUnetHTA EDs are done without fees for industry (SEED-report, p 28). As also no fees have been reported in the survey, these reported costs and resources are taken to be staff and other costs. Alternatively UK fees can be assumed (see above).*		
REA produced mainly **by HTA body** (with no or only some evidence/data submission provided by industry)	N/R			€82.1	€0.2	€668.0
	Assumptions: For national output, it is assumed that costs for inputs from industry are negligible			*Assumptions: For the costs to industry for joint output, no data or information are available. For calculation as a proxy, they have been assumed to be one fifth of submission costs as reported in the survey with according ranges from the sensitivity analysis.*		
REA produced **by industry** and reviewed by **HTA body** ([74])	€410.4	€1.0	€3,340.0	N/R		
	No distinction possible between REA and Full HTA, high range / variability and uncertainties			*Assumptions: Joint assessments are always done mainly by the HTA institutions being authors/reviewers, and may include industry submissions as data input (see above)*		
Full HTA produced **by HTA body** (with no or some evidence/data submission provided by industry)	N/R			€102.6	€0.3	€835.0
	For national output, it is assumed that costs for inputs from industry are negligible			*Assumptions: For the costs to industry for joint output, no data or information are available. For calculation as a proxy, they have been assumed to be one fourth of submission costs as reported in the survey with according ranges for the sensitivity analysis.*		
Full HTA produced **by industry** and reviewed by **HTA body** ([75])	€410.4	€1.0	€3,340.0	N/R		
	No distinction possible between REA and Full HTA, high range/variability and uncertainties			*Assumptions: For the costs to industry for joint output, no data or information are available. For calculation as a proxy, they have been assumed to be one fifth of submission costs as reported in the survey with according ranges from the sensitivity analysis.*		
National adaptation of a joint REA ([76])				*Assumed to be done by HTA body / MS*		
National adaptation of a joint Full HTA ([77]), done by **HTA body**				–		
National adaptation of a joint Full HTA ([78]), done by **HTA body** and **industry**				€30.0	€5.0	€100.0
				Assumptions: It is assumed that this, on the side of industry, includes the supplementary production of part of the ECO domain (without literature review and basic collection of cost parameters), and, if relevant, parts of other domains.		

FTE=full time equivalent, N/A=Not applicable. Sources are given in Footnotes

([73]) Based on Survey results.
([74]) Based on Survey results.
([75]) Based on Survey results.
([76]) Estimates by authors: It is assumed that this mainly includes adaptation (if necessary) of CUR, TEC and epidemiological data plus translation of relevant parts into national language, maybe update of literature search.
([77]) Cost estimates by authors: It is assumed that this includes the adaptation of CUR, TEC and other domains, as described above for REA, plus part of the ECO domain (without literature review and basic collection of cost parameters), and, if relevant, parts of other domains.
([78]) Cost estimates by authors: I t is assumed that this includes the adaptation of CUR, TEC and other domains, as described above for REA, plus part of the ECO domain (without literature review and basic collection of cost parameters), and, if relevant, parts of other domains.

7.2.3 Cost prognosis 2020+

The following sections describe the results **on projected costs and/or savings for the different Policy Options arising at EU level and at national level (across countries)**. They are also grouped by stakeholders (EU, MS / HTA bodies and industry). This is based on the current allocation of costs across stakeholders (as described in the previous sections).
Section 7.2.3.1 describes total costs arising at EU level, that is, coordination costs depending on implementation mechanisms as well as costs for the production of joint outputs.
Section 7.2.3.2 shows total costs and/or savings that arise at MS and industry level, through a reduction in previous national outputs on the one hand and national adaptations of joint outputs (as well as industry costs for joint outputs) on the other hand.
Section 7.2.3.3 summarises all these costs within one table and adds additional items that may cause costs and/or savings, but cannot reliably be quantified. Differences in the results between stakeholder groups are discussed and analysed.
Section 7.2.3.4 provides an alternative calculation with a higher amount of joint outputs.
Section 0 gives an overview about the performed sensitivity analyses.

7.2.3.1 Total costs arising at EU level

Combining implementation mechanisms of respective Policy Options with costs of output production, Table 56 displays costs arising at EU level from the proposed business models. Not implementing a sustainable model at EU level for future cooperation in the field of HTA would lead to sunk costs as outcomes of previous cooperation within EUnetHTA JA-JA3 and previous cooperation in HTA would be lost.

The following table depicts total costs of implementation mechanisms when matching with direct costs of subcontracting (for the production of the joint outputs) for the respective Policy Options. Cost calculations do not examine potential fees for output production because implementation and the level of fees is out of the scope of this study.

Maintenance of common tools, templates and methodologies will be performed in the central coordination unit and is included in the costs for implementation mechanisms.

Joint Early Dialogue, joint REA (65 REAs in total for PO 4.2, PO 4.2 and PO 5, comprising 40 REAs on Pharmaceuticals and 25 REAs on medical technologies) and joint Full HTA are subcontracted to HTA bodies and represent subcontracting expenses.

According to Table 7, PO 3 includes two options for implementation mechanisms:

- A permanent secretariat hosted by a MS.
- A permanent secretariat hosted by the EC.

Hence, PO 3a represents cost estimates for a permanent secretariat hosted by a MS and accounting for different price levels for the MS. PO 3b shows the permanent secretariat hosted by the EC.

Table 56: Costs of Business models assuming output production of 40 EDs, 65 REAs and 11 joint Full HTA, cost in EUR 1 000 p.a.*

	Project-based co-operation (PO 2)	MS secretariat (PO 3a)	EU secretariat (PO 3b)	Existing EU agency (PO 4.1)	Existing EU agency (PO 4.2)	New EU agency (PO 5) ([79])
Costs for common tools, templates and methodologies (Maintenance) ([80])	210.0	included in implementation mechanism	included in implementation mechanism	included in implementation mechanism	included in implementation mechanism	included in implementation mechanism
Costs for common tools, templates and methodologies (Development) ([81])	300.0	300.0	300.0	300.0	300.0	300.0
Costs for joint Early Dialogues ([82])	596.3	1 834.8	1 834.8	1 834.8	1 834.8	1 834.8
Costs for joint REA ([83],[84])	1 598.3 (Pharma: 1 170 MedTech: 428)	N/R	N/R	6 821.6 (Pharma: 4 679 MedTech: 2 142)	6 821.6 (Pharma: 4 679 MedTech: 2 142)	6 821.6 (Pharma: 4 679 MedTech: 2 142)
Costs for joint Full HTA ([85])	N/R	N/R	N/R	N/R	N/R	2 479.9 (Pharma: 1 526 MedTech: 954)
Costs for implementation mechanism	2 685.2 (Cat 1)	3 642.8 (Cat 1)	3 100.9	5 263.4	8 210.1	9 615
	2 614.5 (Cat 2)	3 039.5 (Cat 2)				
	2 543.6 (Cat 3)	2 435.2 (Cat 3)				
Total costs ([86])	5 389 8 (Cat 1)	5 777.6 (Cat 1)	5 235.7	14 219.8	17 166.5	21 051.3
	5 319.1 (Cat 2)	5 174.3 (Cat 2)				
	5 248.2 (Cat 3)	4 570 (Cat 3)				

Cat 1: MS with high price level; Cat 2: MS with medium price level; Cat 3: MS with low price level

*PO2 includes 8-10 REAs Pharma and 3-5 REAs medtech

What becomes apparent looking at Table 56 is that PO 3a and 3b do not include production of joint REAs because the policy structure anticipates voluntary participation and voluntary uptake. Voluntary uptake means that if joint assessments would lead to unfavourable results, participants do not have to accept these, which would lead to inefficiency of processes. Hence, the combination of voluntary participation and voluntary uptake would not incentivise participation of stakeholder groups. This assumption aligns with the findings of the report survey and the additional follow-up. MedTech industry stakeholders pointed out that because PO 3 foresees a voluntary participation as well as voluntary uptake for joint REA, cooperation on joint REA production would not fulfil its purpose if participants are not tied to a mandatory uptake. Hence, industry stakeholders' interest in participation would be much lower compared to other options.

([79]) Implementation costs not estimable within this study.
([80]) Based on information of EUnetHTA JA 3 for PO 2; costs for PO 3a- PO 5 are included in costs for implementation mechanisms.
([81]) Assumption by study authors, development of new guideline not included as not quantifiable.
([82]) PO 2: 9 EDs on Pharmaceuticals, 4 on medical technologies; PO 3a - PO 5: 30 EDs on Pharmaceuticals and 10 on medical technologies.
([83]) Does not include costs arising to industry within the production of joint assessments (e.g. submission templates).
([84]) PO 2: 8-10 REAs Pharma, 3-5 REAs medtech; PO 4.1, PO 4.2 and PO5: 40 REAs Pharma, 25 medtech.
([85]) Does not include costs arising to industry within the production of joint assessments (e.g. submission templates); 7 joint full HTAs on Pharmaceuticals and 4 on medical technologies.
([86]) Including implementation costs; Overhead costs are included in the respective cost elements; not adjusted for inflation.

7.2.3.2 Total costs or savings arising at national level, across countries

Table 57 shows **the results of average additional costs or savings at national level from the perspective of the different stakeholder groups**. Figures in red (negative numbers) are savings and figures in black (positive numbers) additional costs.

These figures have been calculated with a **high number of assumptions** (as justified in sections 5.2.2 and 6.3.2) and a **high degree of underlying uncertainty**. They can therefore only be seen as **estimates** showing the general trend.

Table 57: Potential savings per policy option regarding the production of REAs and Full HTA for each stakeholder group related to different business models; cost in EUR 1 000 p.a.

Costs/savings from the **perspective of MS** (across countries)					
	Project-based co-operation (PO 2)	**MS/EU secretariat (PO 3)**	**Existing EU agency (PO4.1)**	**Existing EU agency (PO 4.2)**	**New EU agency (PO 5)**
Pharmaceutical products	-256	N/R	-1 567	-2 673	-3 801
Medical Technologies	-127	N/R	-1 186	-1 965	-2 594
Sum of costs/savings from the perspective of MS	-383	N/R	-2 753	-4 638	-6 395
Costs/savings from the **perspective of industry** (across countries)					
	Project-based co-operation (PO 2)	**MS/EU secretariat (PO 3)**	**Existing EU agency (PO 4.1)**	**Existing EU agency (PO 4.2)**	**New EU agency (PO 5)**
Pharmaceutical products	-3 744	N/R	-35 117	-63 833	-69 608
Medical Technologies	-92	N/R	-3 288	-6 797	-7 758
Sum of costs/savings from the perspective of industry	-3 836	N/R	-38 405	-70 629	-77 366

N/R=Not relevant

Comments: Results do not include costs (and savings) of ED due to a lack of reliable data.

There are no savings or costs given for PO 3, since in this policy option both production and uptake are defined to be voluntary and thus not included in the estimates. For the other POs, it can be seen that with regard to the production of REA and Full HTA savings (through the reduction of national output production) exceed costs (for adaptation of joint output and industry submissions for joint assessments) for both sectors, from the perspective of MS as well as from the perspective of industry.

Results clearly show that PO 4.1 and onward lead to a significant amount of savings, especially for the industry.

However, there are differences between the Pharmaceutical and the MedTech industry. Savings for the Pharmaceutical Industry, as presented in Table 57, are much higher than savings for MedTech industry. This has several drivers:

- Joint MedTech reports are assumed to be less costly than joint Pharma reports (based on JA 2).
- The amount of joint REAs for Pharmaceuticals is assumed to be much higher than the amount of joint REAs for medical devices (40 vs 25).
- The proportion of joint REAs that are assumed to be (topic) relevant for the national context are also assumed to be higher (an assumption that was made because of the higher heterogeneity of the medical device sector).
- Many more countries have a reimbursement system based on industry submission for the Pharmaceutical sector than those who do for the medical devices sector.
- Average annual numbers of reports within countries are in general higher for the Pharma sector than for the MedTech sector. The latter two have the biggest influence on the difference between Pharma and MedTech.

7.2.3.3 Total costs and savings

Table 58 provides an overview about the results of the cost prognosis for the future cooperations on HTA after 2020, displaying costs that arise due the creation of joint output and the governance structure necessary for facilitating HTA cooperation and the potential savings due to a reduction of duplication of HTA assessments, including related adaptation costs (from MS and industry perspective separately).

Table 58: Summary of potential costs and savings per policy option costs, EUR 1 000 p.a.

	Project-based co-operation (PO2)	MS/EU secretariat (PO3a)	EU secretariat (PO3b)	Existing EU agency (PO 4.1)	Existing EU agency (PO 4.2)	New EU agency (PO 5)
Sum of costs at EU level: joint output	2 705	2 29	2 542	9 465	9 465	12 046
Sum of costs at EU level: Implementation Mechanism	2 685.2 2 614.5 2 543.6	3 642.8 3 039.5 2 435.2	3 100.9	5 263.4	8 210.1	9 615
Sum of costs/savings from the perspective of MS	-383	N/R	N/R	-2 753	-4 638	-6 395
Sum of costs/savings from the perspective of industry	-3 836	N/R	N/R	-38 405	-70 629	-77 366

N/R=Not relevant

Results of the calculation show that, especially with PO 4.1, 4.2 and 5, overall savings can be expected and that these savings rise with each subsequent policy option.

However, several additional impact factors have to be taken into consideration additionally, which cannot reliably be quantified but may have an impact on overall costs/savings and may change, reverse or diminish some of the results into the opposite direction:

Non-quantifiable potential savings

- Avoided duplication of national assessments through an increased number of collaborative **(intergovernmental)** assessments (with tools being mandatory)
- Reduced amount of national activities related to **tools and methods**
- Reduced national Horizon Scanning costs plus potential collaborations can be identified quicker
- Reduced number of Early Dialogues done at national level
- Reduction in additional evidence generation requested by HTA bodies through the production of joint Early Dialogues

Non-quantifiable potential costs

- Implementation of the mandatory uptake of joint output within national procedures, laws and regulations
- Joint Early Dialogues may have to be adapted to the national context or may not be transferable (see SEED report)

Savings for industry as a whole are higher than savings from the perspective of MS. The main driver is the fact that it is assumed that industry gains more from the replacement of national submissions through joint assessments – gains are assumed to be just equivalent to the costs of the joint assessment (of around EUR 100 000 for REAs). For MS, savings from the replacement of national assessments with joint assessments amount to the costs of a national report (around EUR 35 000 for REAs). Additionally, the analysis assumes that national adaptations are mostly financed by MS.

Although costs of implementation mechanisms and business models increase by ascending policy option, potential savings for the respective stakeholders rise accordingly. In the long run, it seems vital that the number of joint assessments on Pharmaceuticals

supplements the number of centrally authorized new Pharmaceutical substances and new indications, ensuring comprehensive processes. To optimise processes, specifically those concerning the MedTech Industry, initial temporary workgroups including all stakeholders offer the potential to design the most efficient respective processes.

Finally, it must be considered that costs and savings from the perspective of the different stakeholders are based on current cost allocations and funding mechanisms.

7.2.3.4 Increasing joint output for Pharmaceutical products from 40 to 90 REA

It may be argued that a higher amount of joint assessments, especially for Pharmaceutical products, may be useful or that the amount of these joint assessments may be increased step by step. With respect to the total number of EMA decisions, an amount of 90 joint REAs for Pharmaceutical products might be a relevant alternative to the 40 assumed above.

Costs estimated for running a central coordination body with an output production of 40 EDs and/or 115 REAs (90 on Pharmaceuticals and 25 on medical technologies) and/or 11 Full HTAs are depicted in the table below.

Table 59: Increased output - Costs of Running a Central Coordination Body coordinating 40 EDs, 115 REAs and 11 Full HTA, cost in EUR 1 000 p.a.

Type of costs	Project-based co-operation (PO 2)	MS secretariat (PO 3a)	EU secretariat (PO 3b)	Existing EU agency (PO 4.1)	Existing EU agency (PO 4.2)	New EU agency (PO 5) ([87])
	Implementation Costs					
IT (implementation costs)	17 ([88])	Costs depend to a large extent on the situation in premise (e.g. is there already an IT network established, are premises equipped with computers, are specific communication tools necessary, 'power' of firewall?)				
	Running Costs					
Staff costs (Total costs) ([89])	785	1 871 (Cat 1) 1 417.7 (Cat 2) 963.9 (Cat 3)	1 463.8	3 595.1	4 095.1	5 001.9
Travel costs ([90])	132.6	42.5	42.5	42.5	42.5	42.5
IT software licenses ([91])	10	10	10	10	10	10
Licences for literature databases ([94])	20	20	20	20	20	20
Premises ([92])	254 (Cat 1) 192.5 (Cat 2) 130.9 (Cat 3)	295.5 (Cat 1) 224 (Cat 2) 152.3 (Cat 3)	231.3	628 9	724 9	905 4
Management Board ([93])	1 118.6 ([94])	205.3	205.3	63.7	328.4	328.4
ED Committee ([95])	N/R	723.6	723.6	241.2	723.6	723.6
REA Committee	N/R	N/R	N/R	1 238.6	3 715.8	3 715.8
Full HTA Committee	N/R	N/R	N/R	N/R	N/R	135.2
	Overhead for running costs (+15%)					
Total costs	2 685.2 (Cat 1) 2 614.5 (Cat 2) 2 543.6 (Cat 3)	3 642.8 (Cat 1) 3 039.5 (Cat 2) 2 435.2 (Cat 3)	3 100.9	6 716	11 109.3	12 515

N/R=Not relevant

([87]) Implementation costs not estimable within this study.
([88]) Based on EUnetHTA JA 3.
([89]) Based on respective qualification profile displayed in Table 51: Qualification profiles and EU staff regulations; adjusted to price levels if applicable.
([90]) Based on information of EUnetHTA JA 3 budget.
([91]) Based on EUnetHTA JA 3 budget and expert opinion.
([92]) Based on EMA premise costs; adjusted for price levels if applicable.
([93]) Based on 'Ramboll/Euréval/Matrix- Evaluation of the EU decentralised agencies in 2009'; PO 2 includes project-based participation rate.
([94]) Fees and travel costs.
([95]) Based on expert fees of European Commission, incl. travel costs.

Besides the cost estimates for a coordination unit, costs of the respective business models were adapted to the increase in REAs performed.

Table 60 shows an alternative calculation for the business models, including production of 115 REAs in total, including 90 REAs on centrally authorized new substances and new indications for Pharmaceuticals and 25 REAs on medical technologies

Table 60: Increased output - Business models; costs in thousands of Euro p.a. (Pharma and MedTech) for 40 EDs, 115 REAs and 11 joint Full HTA*

	Policy Option 2	Policy Option 3a	Policy Option 3b	Policy Option 4.1	Policy Option 4.2	Policy Option 5
Costs for Common tools, templates and methodologies (Maintenance) ([96])	210.0	included in implementation mechanism	included in implementa-tion mechanism	included in implementation mechanism	included in implementation mechanism	included in implementation mechanism
Costs for Common tools, templates and methodologies (Development) ([97])	300.0	300.0	300.0	300.0	300.0	300.0
Costs for Joint Early Dialogues ([98])	596.3	1 834.8	1 834.8	1 834.8	1 834.8	1 834.8
Costs for Joint REA ([99],[100])	1 598.3 (Pharma: 1 170 MedTech: 428)	N/R	N/R	12 669.8 (Pharma: 10 527.8 MedTech: 2 142)	12 669.8 (Pharma: 10 527.8 MedTech: 2 142)	12 669.8 (Pharma: 10 527.8 MedTech: 2 142)
Costs for Joint Full HTA ([101])	N/R	N/R	N/R	N/R	N/R	2 479.9 (Pharma: 1 526 MedTech: 954)
Costs for Implementation Mechanism	2 685.2 (Cat 1)	3 642.8 (Cat 1)	3 100.9	6 716	11 109.3	12 515
	2 614.5 (Cat 2)	3 039.5 (Cat 2)				
	2 543.6 (Cat 3)	2 435.2 (Cat 3)				
Total costs ([102])	5 389 8 (Cat 1)	5 777.6 (Cat 1)	5 235.7	21 520.6	25 913.9	29 799.5
	5 319.1 (Cat 2)	5 174.3 (Cat 2)				
	5 248.2 (Cat 3)	4 570 (Cat 3)				

*PO2 includes 8-10 REAs Pharma and 3-5 REAs medtech

Table 60 includes costs for the increased number of REAs on Pharmaceuticals and respective output-related staff increases. Presented estimates do not account for potential mixed funding mechanisms.

Table 61 depicts the quantitative results for that assumption. As this is only relevant for PO 4.1, 4.2 and 5, no changes apply for the other options.

([96]) Based on information of EUnetHTA JA 3for PO 2; costs for PO 3a- PO 5 are included in costs for implementation mecha-nisms.
([97]) Assumption by study authors, development of new guideline not included as not quantifiable.
([98]) PO 2: 9 EDs on Pharmaceuticals, 4 on medical technologies; PO 3a & PO 5: 30 EDs on Pharmaceuticals and 10 on medical technologies.
([99]) Does not include costs arising to industry within the production of joint assessments (e.g. submission templates).
([100]) PO 2: 8-10 REAs Pharma, 3-5 REAs medtech; PO 4.1, PO 4.2 and PO5: 40 REAs Pharma, 25 medtech.
([101]) Does not include costs arising to industry within the production of joint assessments (e.g. submission templates); 7 joint full HTAs on Pharmaceuticals and 4 on medical technologies.
([102]) Including implementation costs; Overhead costs are included in the respective cost elements; not adjusted for inflation.

Table 61: Increased output – Summary of potential costs and savings per policy option – results for 40 EDs, 115 REAs and 11 Joint Full HTAs

	Project-based co-operation (PO2)	MS/EU secretariat (PO3a)	EU secretariat (PO3b)	Existing EU agency (PO 4.1)	Existing EU agency (PO 4.2)	New EU agency (PO 5)
Sum of costs at EU level: joint output	2 411	2 051	2 051	14 721	14 721	17 201
Sum of costs at EU level: Implementation Mechanism	2 685	3 643	3 101	6 716	11 109	12 515
	2 544	3 040				
	2 603	2 435				
Sum of costs/savings from the perspective of MS	-383	N/R	N/R	-3 192 (*)	-5 388 (*)	-7 203 (*)
Sum of costs/savings from the perspective of industry	-3 836	N/R	N/R	-54 627 (*)	-103 213 (*)	-109 997 (*)

N/A=Not applicable

(*) For these calculations, the cut-off for the grouping of MS according to the volume of annual output had to be adapted. Again, a cut-off of 1.5 of the joint output volume was chosen.

Results clearly show that PO 4.1 & onwards lead to a significant amount of savings, especially for the industry, however these are only valid taking the underlying assumptions into account.

Sensitivity analysis

Uni- and multivariate sensitivity analyses have been done for the output cost prognosis through setting cost parameters at minimum and maximum values. Table 62 displays the major results.

Furthermore, assumptions on the amount of national output reduction (replacement of national through joint output) have been varied within plausible ranges (e.g. only half of joint Pharma assessments are relevant, even with mandatory uptake and group1 countries; or for mandatory uptake and group1 countries all MedTech joint assessments are relevant instead of one half as assumed now).

Table 62: Sensitivity analysis for results on potential savings related to REAs and Full HTA

Parameter(s)	Product sector	Direction and dimension of resulting changes in expected savings when setting the selected parameter at MIN/MAX values Blue: changes in MS expected savings Green: changes in industry expected savings Number of arrows shows the extent of change (*)	
		Parameter(s) set to MIN value	**Parameter(s) set to MAX value**
MS costs of national adaptations	Pharma products	↑↑↑	↓↓↓ No savings in all PO
	MedTech products	↑↑	↓↓ No savings in all PO
MS costs of national REA, Full HTA and national adaptations	Pharma products	↓↓	↑↑
	MedTech prouct s	↓↓	↑↑
MS costs of national REA, Full HTA and national adaptations	Pharma products	↓↓	↑↑
	MedTech prouct s	↓↓	↑↑
Industry cost of joint REA and Full HTA	Pharma products	↑	↓
	MedTech products	↑	↓↓ No savings in all PO
Industry savings due to reduction of national REA and Full HTA	Pharma products	↓↓↓	↑↑↑
	MedTech prouct s	↓↓↓ No savings in PO 2	↑↑↑
Industry savings due to reduction of national REA and Full HTA set to MIN + MS Costs of national adaptations set to MIN	Pharma products	Industry savings in PO 4.1, 4.2 and 5 reduced to around 200% of the amount of MS savings	
	MedTech prouct s	Industry savings in PO 4.1, 4.2 and 5 reduced to around 50% of the amount of MS savings	
Costs of joint assessments reduced by 30%	Pharma and MedTech products	Reduces overall costs at EU level for joint output production (common tools, Early Dialogues, REA, Full HTA) by 20% in PO 2 up to 25% in PO 5.	

Number of arrows indicating (in both directions): ↑↑↑=major changes; ↑↑=medium changes; ↑=small changes

(*) Setting the cost parameters to their minimum and maximum values normally affected all PO in roughly the same way, otherwise it is indicated. Sometimes savings were reduced to a degree that there were no savings anymore (costs exceeded savings), e.g. when MS costs of national adaptations were set to maximum.

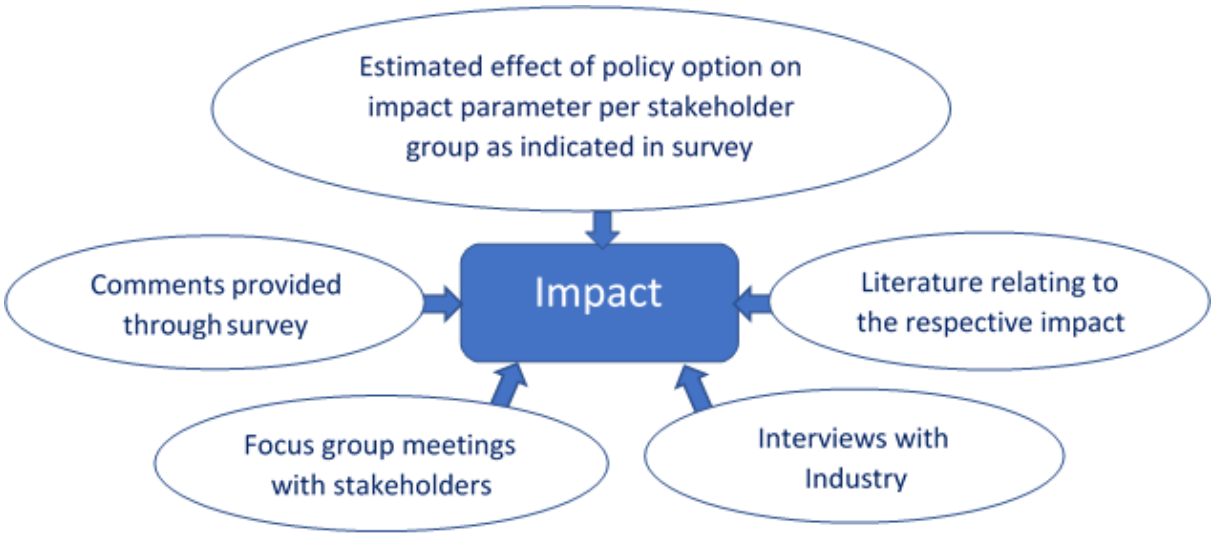
Higher replacement rates directly lead to higher savings and vice versa. Specifically expected industry savings are sensitive – in absolute numbers – to changes. Increasing/Decreasing opt-in rates for options with voluntary opt-in has a similar effect. Increasing opt-in rates in PO 4.1 brings results in the vicinity of PO 4.2 results (100% opt in, leading to the same quantitative results as mandatory opt-in). Reducing opt-in and uptake for Full HTA in PO 5 in the same way brings PO 5 results in the vicinity of those of PO 4.2 (except the additional production costs of the joint Full HTA).

7.3 Overall assessment of Policy Options

7.3.1 Outline

In this section, the potential effects of the different Policy Options (POs) under consideration are analysed for different impacts, thereby including multiple sources of information as depicted in Figure 33. Details on economic and social/health impacts can be found in 6.2.1.

Figure 33: Overview on gathered information for assessing impacts



In order to draw a full picture of the expected effects of the POs, information utilized for the overall assessment included:

- the **survey results**, which included quantitative elements (assessing stakeholders' perception of how the different POs might affect impacts measured by one or more indicators per impact) and qualitative elements (comments to the survey)
- relevant **literature** which was identified and selected by a literature review (chapter 5.1)
- information gathered via **focus group** meetings with Public Administration, Pharmaceutical and Medtech companies (section 5.3.4)
- information gathered via **interviews** with industry and patient groups (section 7.1.13)

Though the study team covered all impacts (except environment) defined in the EU 'Better Regulation Guideline', **only the most relevant for the different stakeholders are described and analysed** in the following sections. 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. Results of impacts not included in the main report can be found in Annex 24 for Public Administration, Annex 25 for Pharmaceutical Industry and Annex 26 for MedTech Industry.

Survey results are presented per impact (combining all indicators) as well as per specific indicator as the **mean value of responses per stakeholder group and Policy Option**. Results are displayed as line charts, however it is highlighted that impacts do not represent a continuous trend. Still responses per Policy Option are shown in one graph in order to allow for better comparison. Results of the subgroup analysis for SME and large companies are mentioned when significant differences were identified.

Key stakeholders addressed were from Public Administrations (HTA Bodies), the Pharmaceutical and MedTech industries, patients and health professionals. For the two latter groups, however, not enough responses to the survey were obtained, so they could not be assessed in great detail.

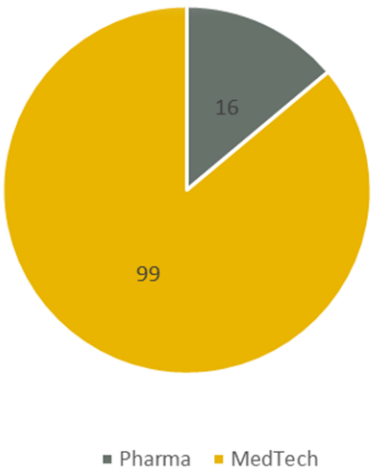
For all impacts described **additional information** is provided in footnotes on:

- Average responses: average number of responses per sub-question (for all POs)
- Response rate: average response rate as a percentage of number of responses persub-question of all answers taken into account for the analysis (e.g. for MedTech Industry 99 questionnaires were taken into account; if for one sub-question on average 90 answers were filled, the response rate is depicted with 90,9%)
- Average standard deviation: average standard deviation per sub-question (for all POs)
- No trend: percentage of answers showing no trend (value of Policy Option 5 less value of Policy Option 1 = zero)
- Negative trend: percentage of answers showing a positive trend (value of Policy Option 5 less value of Policy Option 1 > zero)
- Positive trend: percentage of answers showing a negative trend (value of Policy Option 5 less value of Policy Option 1 < zero)

Final data set for analysis

The number of responses to the survey used for analyses (among other input) differs from the total number of responses outlined in section 5.3.2 since not all respondents provided information on costs (Part 2 of the questionnaires) and impacts (Part 4 of the questionnaires) alike. Finally, 23 responses from **Public Administration and 115 responses by industry could be included.** Figure 34 provides an overview of the respondents by product scope.

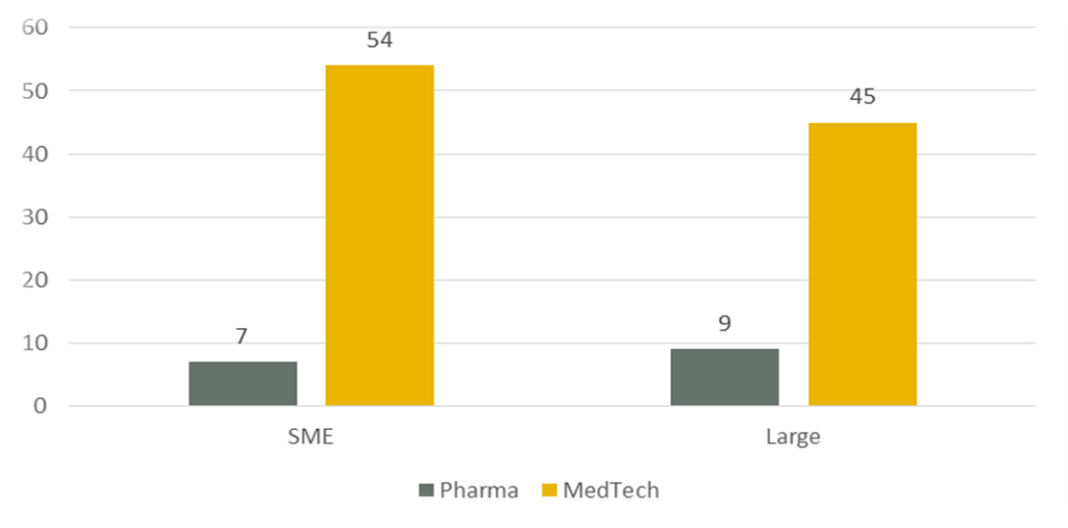
Figure 34: Survey - Industry response by Product Scope



Source: GÖ FP / LSE survey 2017

Companies or trade associations from the **medical technologies sector** provided **99 of 115** industry responses and **Pharmaceutical manufacturers** or trade associations **16 responses**. Regarding the company size, **7 out of 16 Pharmaceutical companies** were indicated to be a **SME** while nine were stated to be large-sized companies. For the **MedTech Industry, 54 respondents** were stated to be **SMEs**, while 45 were indicated to be large-sized companies.

Figure 35: Survey - Industry responses by product scope and company size



Source: GÖ FP / LSE survey 2017

7.3.2 Public Administration

7.3.2.1 Costs

For this impact, potential cost evolution was investigated in relation to Horizon Scanning, Early Dialogues, REA submissions, Full HTA submissions, and additional data requests by respective HTA organisations, personnel requirements and HTA reassessments.

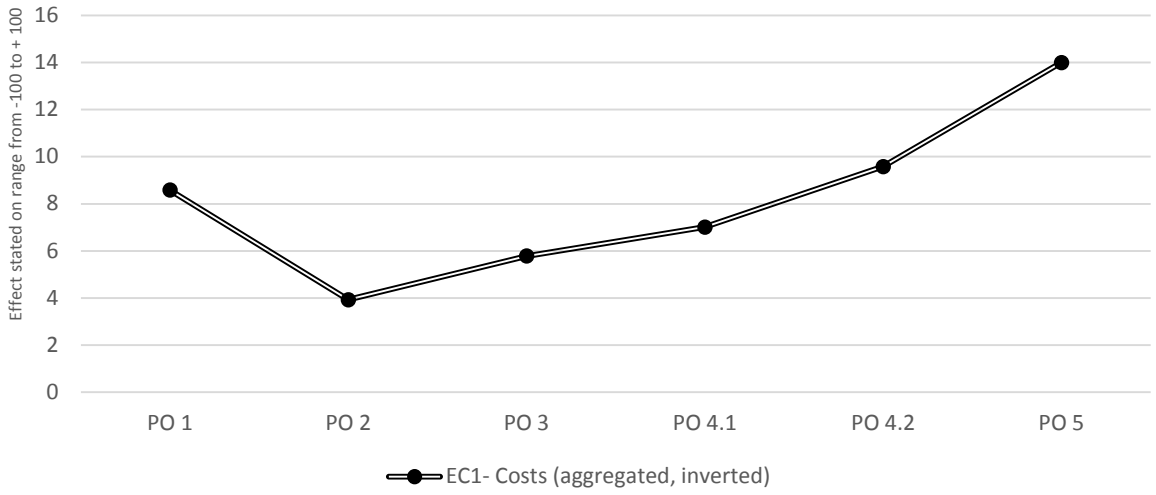
National Public Administrations perform HTA-related processes, at least to some extent, in most European countries with varying related expenses. When assessing Pharmaceuticals in the context of pricing and reimbursement, a study found that manufacturers are obliged to submit evidence-based applications to national Public Administrations in 36 European countries (37). In some European countries, Public Administrations produce the respective evidence reports completely or partly themselves (37), resulting in different costs as compared to reviewing input from industry. In both cases, an evaluation committee comprised of scientific personnel is needed, whose cost are usually covered by Public Administrations.

Currently, costs arising from HTA processes vary considerably across European countries as shown in the case study (7.1.12.1). This is driven by the overall economic situation of a country but also by the scope of HTA processes, the granularity of performed assessments as well as the institutional setting for the implemented HTA processes. When it comes to the potential costs of future development of HTA at EU level, the current state-of-play of HTA in a country is paramount.

Countries that have no or only little HTA related activities will most likely benefit more from joint output and central governance, as they (a) have not made major investments in building up national HTA systems and (b) are more open to use resources to adapt joint results for national decision-making purposes. Still, the data that were available to the study team did not allow the team to quantify the effects for the different systems.

In our survey, we asked respondents to provide estimates on cost development for several cost components from their perspective, trying to account for the potentially different perspectives based on the current system. Figure 36 displays the overall results of the eight surveyed cost indicators across all respondents from Public Administration.

Figure 36: Public Administration – survey results on perceived average effect of Policy Options on costs (aggregated) ([103],[104])



Source: GÖ FP / LSE survey 2017

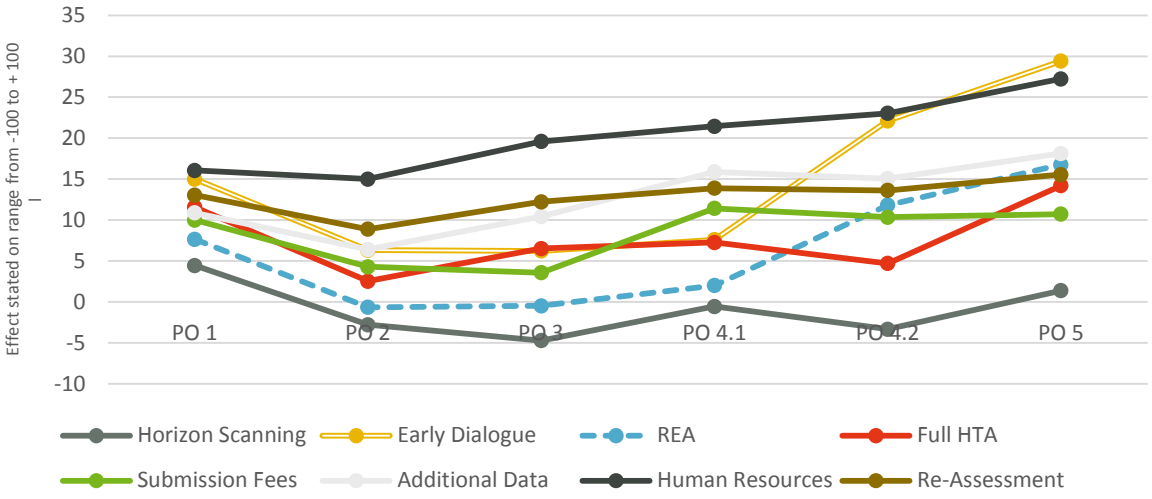
On an aggregate level responses show that experts from a representative number of countries and different types of HTA systems ([105]) do not expect major changes in their HTA-related costs irrespective of the future model.

Investigating cost indicators in detail (Figure 37), it becomes apparent that costs are expected to rise especially for REA and Early Dialogue for Policy Option 4.2 onwards. This might reflect the fact that both participation to and uptake of these joint outputs are mandatory for these POs, which is a very new situation for the countries and thus higher (initial) expenses are expected. The need for Human Resources also increases for all POs, especially from PO3 onwards.

([103]) Inverted data for submission fees
([104]) positive value indicates increase in costs, negative value indicates decrease in costs

([105]) For analysing the baseline costs for Public Administration a taxonomy was applied, differentiating HTA bodies based on their level of integration within governmental bodies and the function they are performing. Due to insufficient responses per type of system, no detailed analysis for the estimated costs per Policy Options was possible. However, at least one body per type of HTA system was included within the survey responses, thereby covering the scope of currently existing systems.

Figure 37: Public Administration – survey results on perceived average effect of Policy Options on cost indicators (unaggregated) ([106],[107])



Source: GÖ FP / LSE survey 2017

Discussions in the focus group with Public Administration revealed opposing views. Experts pointed out that stronger EU cooperation would lead to a cost decrease per product, rather than even a small increase. This mainly relates to reduced current duplication of efforts and increases in efficiency. Current experience suggests that work-sharing lowers the costs for agencies significantly (in one case, where only two agencies agreed to cooperate on clinical guidelines, they were able to save 30% each). Whilst there are higher overheads, particularly at the start of a cooperation, this is expected to be more than compensated by work-sharing arrangements.

For smaller agencies, which currently conduct only a limited number of HTA activities, cooperation could increase the scope of their activities with a relatively small investment. This could explain some of the answers, since this would increase costs. Looking at the direction of responses, it becomes apparent that expected cost increases and decreases are quite equally distributed across survey respondents, highlighting that some countries would rather profit in the sense of cost saving, while others expect higher costs.

Points discussed and highlighted within the focus group meeting are in line with **costs calculations** done within this study (see 7.2.3 for details). Since HTA systems are quite different in Europe, the potential effects of changes in HTA cooperation at EU level will differ between MS. Still, at an aggregate level, the cost prognosis indicates that (taking into account the underlying assumptions) savings (through the reduction of national output production) are likely to exceed costs (for adaptation of joint output and industry submissions for joint assessments) for all POs and for both industry sectors.

([106])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Horizon Scanning	18.0	78%	32.0	39%	39%	22%
Early Dialogue	17.5	76%	36.0	18%	35%	47%
REA	17.0	74%	40.6	6%	47%	47%
Full HTA	19.0	83%	40.1	0%	47%	53%
Submission Fees	14.2	62%	33.4	29%	36%	36%
Additional Data	16.3	71%	34.6	25%	31%	44%
Human Resources	19.0	83%	42.3	0%	47%	53%
Re-Assessment	18.0	78%	36.3	17%	33%	50%

([107]) positive value indicates increase in costs, negative value indicates decrease in costs.

These estimated savings will amplify with the extent to which joint outputs are covered within the cooperation. **Options comprising a permanent secretariat and higher joint output lead to substantially larger savings compared to the project-based cooperation** (below EUR 500 000 across all countries in PO2 versus over EUR 3 million across all countries in PO 4.1). Additional savings might arise through an increased amount of intergovernmental assessments as well as a reduced number of Early Dialogues done at national level (these could not be quantified within the calculations).

Summing up the findings derived from costs prognosis, focus group meetings and survey results, POs providing a legislative framework for HTA cooperation in Europe will potentially have a positive effect on cost evolution for national Public Administration across MS. While this result on a macro level might not directly translate to all countries, since potential cost evolutions are also related to the current situation and spending's for HTA processes in a specific country, an overall positive effect can still be expected.

7.3.2.2 Administrative burden

Administrative burden derived from HTA processes was understood in a broader sense in the study than in the Better Regulation Guidelines, where it refers to the costs as a result of administrative activities performed to comply with information obligations included in the European legislation. Thus, the following indicators were defined: overall administrative burden; number of HTA submissions for the same product across European countries; time needed for an HTA process and complexity of HTA assessment processes.

Literature indicates efficiency gains for HTA bodies when joint assessments are produced, since resources for national assessments can be replaced (38, 39), which is also related to a decrease in administrative burden for national assessments. While of course joint work also requires administrative processes, POs providing a sustainable central organisation have the potential to limit the associated administrative burden by providing adequate administrative support. Representatives of Public Administration commented that reacting to legislative demands is easier as compared to voluntary demands, emphasizing the value of a potential legislative framework.

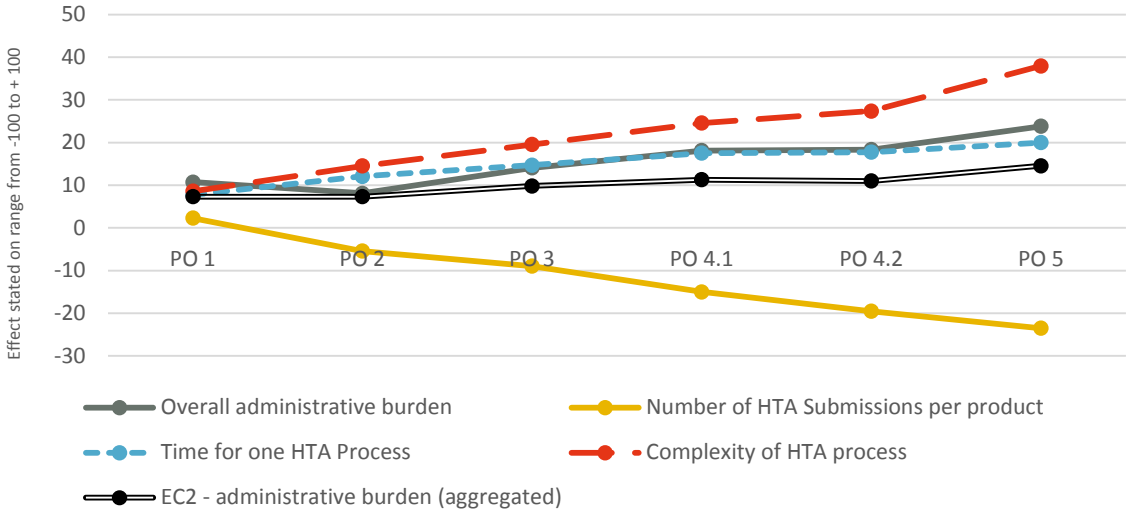
Moreover, time and resources were assessed as critical factors in the framework of establishing more efficient cooperation and outputs (40, 41), thus requiring optimised processes between different stakeholder groups. With respect to the time needed for performing an HTA, differences have been reported across European countries, but also within countries, based on the scope and the regulatory framework of the specific country settings (2). When it comes to joint assessment, time has therefore been identified as an important factor for national uptake and adaption of joint work on EU-level (38), which will be also true for future cooperation in the field of HTA.

Our analysis of agencies comparable with the outlined governance model of a new EU agency showed that **stronger governance,** enabled through a legislative framework as well as the establishment of a permanent secretariat**, might facilitate a faster assessment of more health technologies as compared to current joint work**. The same might be argued for the **mandatory uptake:** if joint outputs must be considered in a national setting, MS might put more focus on a swift proceeding and preparation as compared to entirely voluntary cooperation.

Another point influencing the time of a joint HTA process is the time needed to adapt joint reports for national settings (especially for POs with mandatory uptake). This again highlights the importance of having clear processes and common methodologies to minimize national adaptions and ensure efficient processes. In general, national adaption of reports might be less problematic and time-consuming for joint REAs as compared to joint Full HTA. This is because of the inclusion of more domains (e.g. costs and economic evaluation and ethical aspects) within full HTA, which need to be more country-specific to fulfil their purpose.

Survey responses from Public Administration (Figure 38) indicate that a rather slight increase of overall administrative burden is expected for the respective POs compared to the status quo.

Figure 38: Public Administration – survey results on perceived average effect of Policy Options on administrative burden ([108])



Source: GÖ FP / LSE survey 2017

The number of HTA submissions for the same product across Europe is expected to decline by each Policy Option, reflecting the increase in joint output production at EU level that potentially replaces national assessments, which is backed by input from focus groups. In contrast, a slight increase in complexity of HTA processes is expected from PO2 onwards, which becomes more pronounced for PO5. Full HTA, which is covered in this option, seems to have an explicit impact on the complexity of HTA processes. This was confirmed by representatives of Public Administration in the focus group: complexity increases when trying to reach a common agreement on economic aspects of HTA reports, because these aspects are more context- and country-specific.

Still, Public Administration representatives stressed that – despite administrative complexity potentially increases from Policy Option 1 to 5 – resources for research may be spent more efficiently, which ultimately would lead to a neutral effect. Experts highlighted that the administrative burden is likely to decrease for less-experienced countries, while it might grow initially for experienced countries (e.g. Germany, France) because major changes of established systems and resources for information sharing could be necessary. For example, most public bodies are legally bound to assess newly authorised Pharmaceuticals within 90 or respectively 180 days after public reimbursement is requested (38). Related processes might need to be adapted when legislation covering joint work on REA is installed.

([108])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Overall administrative burden	21.0	91%	35.4	14%	29%	57%
Number of HTA Submissions	22.0	96%	30.2	14%	64%	23%
Time for one HTA Process	22.7	99%	34.1	14%	24%	62%
Complexity of HTA process	21.5	93%	30.0	10%	10%	81%

7.3.2.3 Innovation and Research

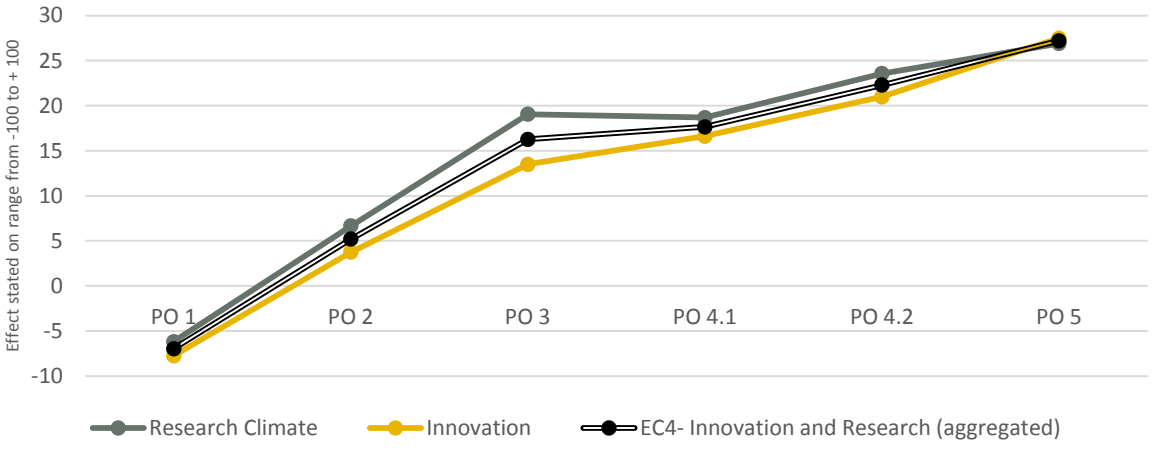
Here we assessed the effect of the various Policy Options on the research climate and innovation in the European Market. We linked our questions to the predictability of the market as well as the reduction of fragmentation as key factors for a favourable business climate that is meant to facilitate innovation to thrive.

When examining publications of scientific evidence in the context of HTA, its relevance becomes apparent since it represents the basis for decision-making processes in several European countries. Moreover, the diversity of methodologies applied for producing HTAs across Europe accentuates this. Different types of HTA organisations defined different evidence requirements for assessing the value of health technologies and different methodological approaches are applied for Pharmaceuticals, medical devices and other technologies (41, 42), showing the diversity in research in this academic area.

In general, the uncertainty surrounding the benefit and value of innovative products and innovative processes, and its wider impact on health systems and patients requires special attention (43). HTA is one approach for valuing innovation when informing the relative effectiveness of a treatment or health technology and a tool to increase efficiency in health-care (44, 45).

Challenges for innovation and research resulting from cooperation in HTA are, among others, to maintain local context, to ensure compatibility of methodologies (specifically for countries with well-established assessment processes) and to introduce transparent topic selection and prioritization (41, 46-48).

Figure 39: Public Administration – survey results on perceived average effect of Policy Options on innovation and research ([109])



Source: GÖ FP / LSE survey 2017

While an HTA assessment per se is not decisive for reimbursement or the price that can be achieved for a specific product, several EU countries (e.g. France and Sweden) have linked the evidence provided by HTA assessments to pricing and reimbursement decision (45). Even if the proposed Policy Options will not affect the autonomy of MS in setting

([109])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Research Climate	21.0	91%	22.0	5%	10%	86%
Innovation	20.0	87%	18.9	10%	5%	85%

prices for Pharmaceuticals and medical devices, a joint REA might provide recognizable evidence at EU level. This can be utilized especially in countries where no structured HTA process is yet in place, thus supporting these countries to make more efficient decisions.

Survey results show that no change for this impact is expected for PO1 and PO2 compared to the status quo (Figure 39). Other contrary, positive effects on innovation and research are expected for both indicators with an implementation of PO3, PO4 and PO5.

This is congruent with the expected increase of the predictability of the HTA systems and the expected decrease of fragmentation of the HTA system in Europe (see 7.3.2.8) ([110]). An estimated positive effect is therefore visible for all Policy Options that include a legislative framework and provide a more structured framework to European HTA cooperation.

Overall, these options (PO3-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 currently has a low priority.

7.3.2.4 Governance, participation and good administration

For assessing future effects on governance, participation and good administration the following indicators were surveyed:

- The involvement of different stakeholders in HTA processes;
- The responsibilities of Public Administrations and other organisations in the field of HTA at MS level;
- The uptake of joint outputs (e.g. HTA reports, Early Dialogues, developed tools, etc.)
- Resource efficiency of HTA processes in general; and
- The sustainability of European cooperation in the field of HTA.

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 and management (48), thus impacting the resource efficiency of a collaboration. When enforcing joint assessments, topic selection processes between stakeholders have been identified as key issues due to diverging national interests (38). Moreover, collaboration between different stakeholders requires sufficient political support in the first place to converge opposing interests (40). Strengthening the cooperation on HTA in Europe by introducing a legislative framework can provide positive impulses and support in this context.

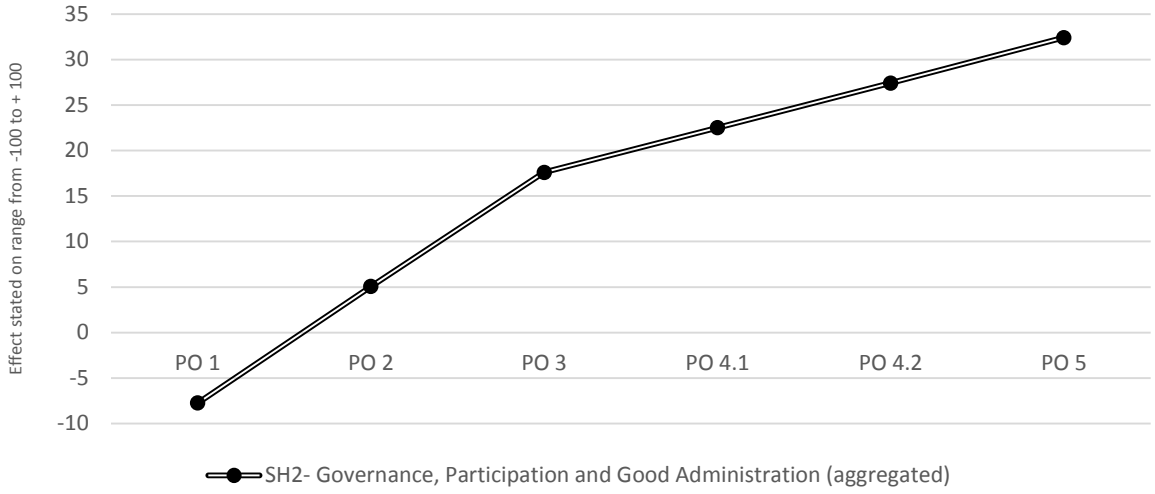
In order to assure consideration of all relevant stakeholder perspectives, studies suggest an inclusion of all relevant stakeholders in assessment processes, especially of those not regularly included in assessment processes so far. Positive developments were already achieved in increasing involvement 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 INAHTA agencies (49). However, the degree and scope in patient involvement still varies widely across Europe (50) and several points for improvement remain (51). These could be addressed by the establishment of a

([110]) Full question, as stated in the questionnaire for indicator innovation: 'To what extent do you expect each Policy Option to impact on the actual innovation for the European market? (i.e. focus on predictability and deduction of fragmentation as key factors for favourable business climate for industry facilitating innovation thrive)'.

permanent secretariat, which might facilitate such involvement processes (since they can be organised in a central way).

Beneficial effects when implementing PO3, PO4 and PO5 are perceived by survey respondents, while PO1 and PO2 seem to have a slightly negative or no effect, respectively (Figure 40).

Figure 40: Public Administration – perceived average effect of Policy Options on governance, participation and good administration (aggregated)

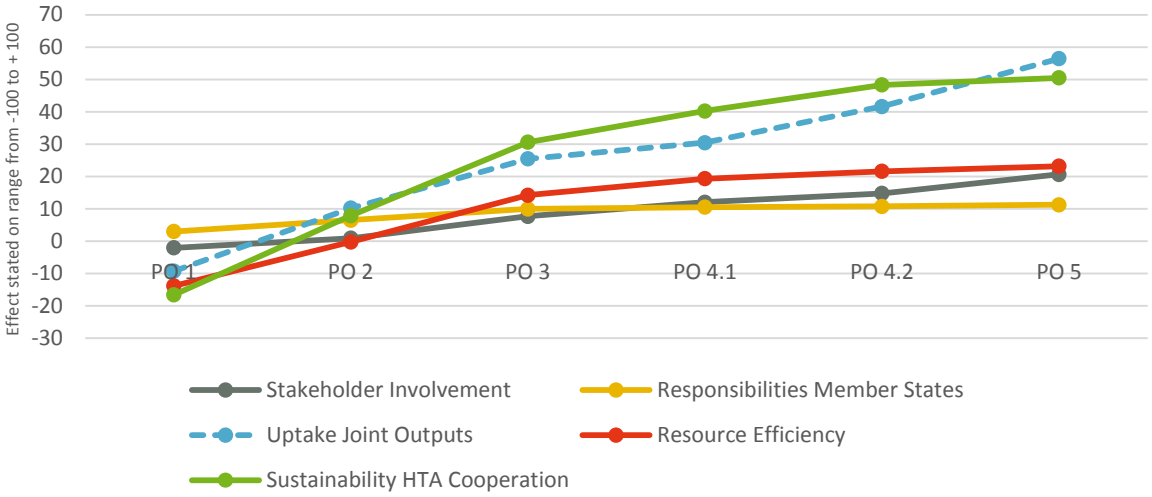


Source: GÖ FP / LSE survey 2017

This overall expectation is mainly driven by the positive assessment of Policy Options on the sustainability of HTA cooperation and the uptake of joint work from PO3 onwards. Uptake of joint work is an important factor, because it is a prerequisite for a functional system in which joint outputs are valued and used.

Survey responses indicate almost no effect from the different POs on the involvement of different stakeholders groups in HTA processes (Figure 41). Still, POs with a permanent secretariat can be assumed to have a positive effect on stakeholder involvement, since all organisational issues will be dealt from one instance.

Figure 41: Public Administration – survey results on perceived average effect of Policy Options on indicators for governance, participation and good administration (unaggregated survey results) ([111])



Source: GÖ FP / LSE survey 2017

No Policy Option is expected to impact on the responsibility of the MS, showing that none of the POs is seen to interfere with the autonomy of Public Administrations in this area. Resource efficiency is expected to be lowest for PO1 and to increase slightly with each subsequent Policy Option (Figure 41). Cost estimates and statements by representatives of Public Administration confirm this finding.

Hence, Policy Options covering a legislative framework will have a positive impact on the sustainability of HTA cooperation by providing a stable framework for joint work. Even if only common tools and templates are covered in a legislative framework (PO3) positive effects are perceived, which is in line with literature highlighting the importance of common tools and methodologies for joint work (52).

Increases in the uptake of joint outputs and the sustainability of the HTA cooperation, especially, have to be highlighted. Moreover, the potential to structure stakeholder involvement processes at EU level in an efficient way must be stressed, as this might improve the inclusion of patient perspectives within HTA assessments.

7.3.2.5 Access to social protection and health systems

In order to investigate the impact on 'access to social protection and health systems', the potential effect of Policy Options on the access to treatments that could be considered as 'innovative' was surveyed.

The addressed POs foresee that appraisal of technologies as well as pricing and reimbursement decisions remain at national level. However, even if Policy Options might

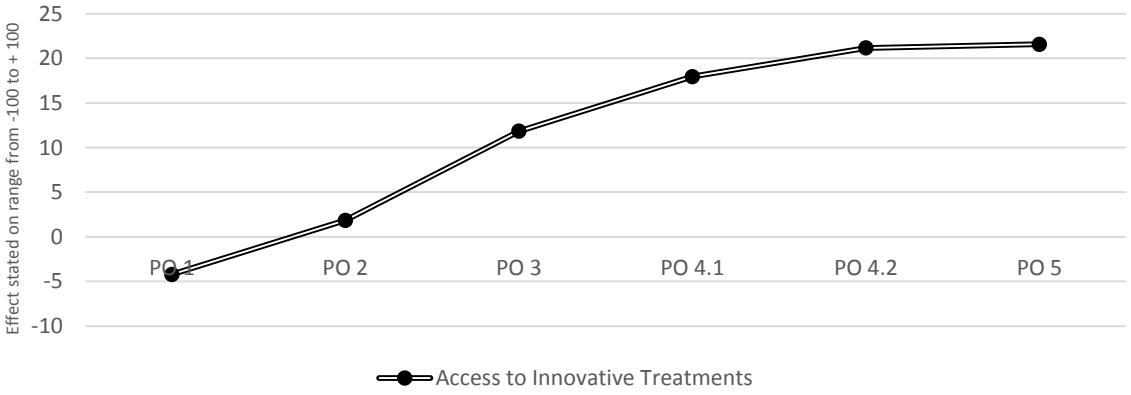
([111])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no trend	negative trend	positive trend
Stakeholder Involvement	22.0	96%	23.4	23%	18%	59%
Responsibilities Member States	20.0	87%	29.9	15%	45%	40%
Uptake Joint Outputs	21.0	91%	32.5	0%	10%	90%
Resource Efficiency	21.7	94%	36.5	0%	24%	76%
Sustainability HTA Cooperation	21.2	92%	28.9	5%	10%	86%

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 a country do not allow the assessment of all new technologies.**

Literature indicates that close collaboration between different stakeholders involved in this processes could improve access to and availability of health technologies on the market (47, 48). Ensuring access to innovative products is highly relevant for patients (7.3.5). Moreover, HTA is a valuable tool to support the use of products with higher additional value as compared to already marketed products. Survey results indicate that a positive effect on the access to innovative treatments is expected for PO3 which even increases for PO4 and PO5 (Figure 42), and no opposing statements were made in the focus group meetings with HTA-experts from academia and Public Administration.

Figure 42: Public Administration – survey results on perceived average effect of Policy Options on access to social protection and health systems[112]



Source: GÖ FP / LSE survey 2017

Reasons for this judgement are that closer collaborating HTA systems lead to a better selection of innovative products with high added value and increase the availability of relevant evidence for health technologies, as industry might adapt and refocus studies to assess outcomes that are more relevant for patients (e.g. quality of life) and payer's needs. Results for this impact match with a perceived increase in innovation as described in section 7.3.2.3.

As Public Administration are often responsible for assessing and/or appraising health technologies, **mandatory joint REA especially can provide significant input for decision-making across Europe.** This would also contribute to reduce a divergent evidence basis across Europe for medical technologies.

([112])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Access to Innovative Treatments	19.0	83%	16.9	26%	5%	68%

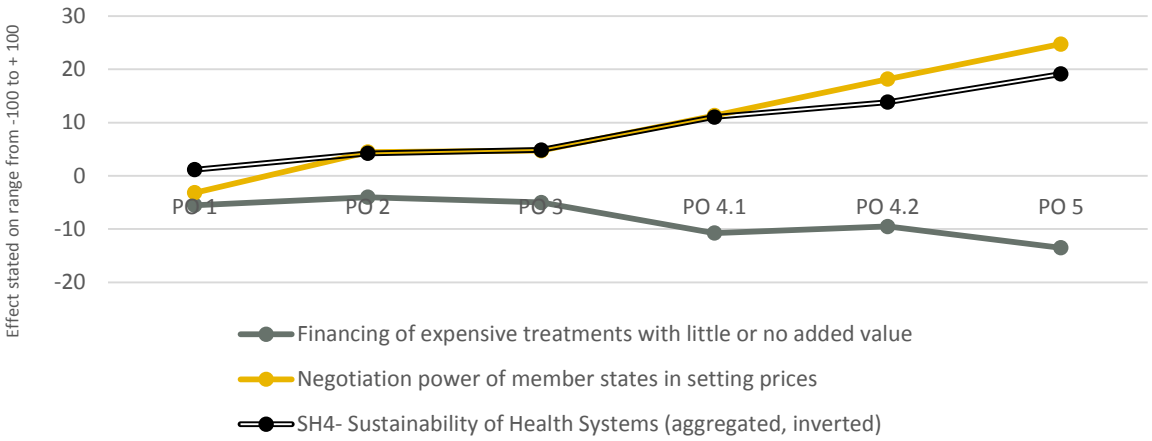
7.3.2.6 Sustainability of health systems

The sustainability of health systems was surveyed by the effect of the various Policy Options on the financing of expensive treatments with little or no added value and the negotiation power of MS in setting prices. These were chosen due to the tendency of rising public expenditures and increases in treatment costs in the Pharmaceutical and MedTech sectors linked to limited public funds. Especially investing in expensive treatments with little or no added value is questionable, since these resources might provide a higher benefit for the patients when used elsewhere.

Success factors like institutional capacity, timing, expertise and efficient processes have been identified to be decisive for improving cooperation in the field of HTA (40), thus affecting national health systems and its sustainability. Moreover, political support is important to improve the acceptance of cooperations and the benefits associated with them, especially in the light of conflicting interests and knowledge gains resulting from information exchange (40, 53, 54). Introducing a legislative framework for joint work on HTA could be seen as a sign for political support as it aims to enhance a more coordinated cooperation regarding HTA at EU level.

Studies indicate that a thorough examination of scientific evidence is needed for supporting health policy decision makers, as this can reduce the uncertainty in decision-making. Thereby it should be accounted for conflicting interests among different stakeholders and potentially biased publications should be identified (53, 55). This will be addressed by the introduction of MS expert committees when establishing permanent secretariats to organise the cooperation and the active involvement of national HTA bodies in output production. For goverance structures forseeing the establishment of a permanent secretariat (Po4 – PO5) this will be addressed by the introduction of MS expert committees, which will organise the cooperation and the active involvement of national HTA bodies in output production.

Figure 43: Public Administration – survey results on perceived average effect of Policy Options on sustainability of health systems[113]



Source: GÖ FP / LSE survey 2017

([113])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Financing of expensive treatments with little or no added value	20.0	87%	29.9	25%	55%	20%
Negotiation power of Member States in setting prices	19.0	83%	35.0	16%	21%	63%

Survey results for the effects of Policy Options on the sustainability of health systems indicate no changes for PO1, PO2 and PO3. For PO4.1, a small increase in the negotiating power of MS is expected, while the financing of expensive treatments with little or no added value is expected to slightly decrease (see Figure 43). For PO4.2 and PO5, estimated effects are more pronounced when it comes to the negotiating power of MS in setting prices, anticipating stronger standing based on joint output.

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 assessments of health technologies to provide support (39). As joint REAs are planned to be covered within the legislative framework from PO4.1 onwards, positive effects on the availability of assessments are reasonable to expect.

Public Administration representatives stressed that a joint perspective on the added value of a new technology, whether Pharmaceuticals, medical device or other technology, has the potential to improve sustainability in their health systems. Stronger cooperation would improve the negotiating power of MS and thus help to achieve lower prices for technologies with limited added value. Nonetheless, it would still be difficult to discontinue the financing of already marketed technologies since investment decisions are taken at national level and will remain so.

Overall, Policy Options with a legislative framework (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 expensive treatments with little or no added value. Also, all types of legal frameworks are enablers of sustainability. On the one hand, a legislative mandatory process helps Public Administrations to make more well-informed choices and, on the other hand, pricing and reimbursement processes might be accelerated due to the improved level of information.

7.3.2.7 Public Health

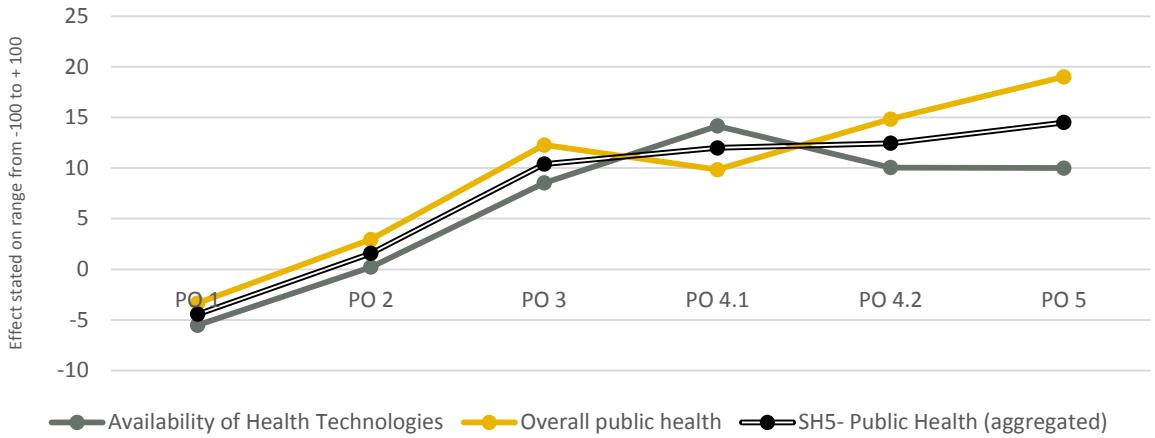
For assessing the effect of the Policy Options on Public Health the indicators 'overall public health' and 'availability of health technologies on the market' were surveyed and complemented by literature findings and expert input.

Public health puts a focus on health promotion, prevention of disease, epidemiology, innovative cures, patient access to Pharmaceuticals, safe Pharmaceuticals and efficacious treatments and thus aims to improve the health and well-being of patients. The national structures of health systems in the European Union reflect the needs of their population and aim to guarantee supply of required treatments. A study investigating the use of scientific evidence for pricing and reimbursement decisions in Germany showed a few years ago (56) that evidence supporting decisions on the availability of health technologies mainly originated from a few actors in the field and was often based on few studies. Moreover, the potential of evidence affecting national guidelines and decisions is high in some countries (57). Thus, evidence should be generated in a transparent manner by various stakeholders to avoid misinformation and information withheld (55) and to provide a solid evidence base for decision-makers (41) in order to ensure availability of health technologies and maintain public health. In the case of European collaboration, involvement of different stakeholders appears vital to account for different needs, interests and national structures (42, 46, 54).

Survey responses indicate no expected change for PO1 and PO2, while all subsequent Policy Options are expected to increase public health (Figure 44). Looking at the individual indicators on public health, the availability of health technologies is expected to be highest in PO 4.1, while this slightly decreases for the two subsequent Policy Options.

One important topic mentioned was that HTA has been slowly also used as tool to assess other health care issues, e.g. vaccination or screening programmes. This is considered to be of even more relevance in the future. Still, in the evidence generation done for the baseline scenario (see 7.1.3), only a little information could be found for assessment of such topics. One expert commented that the current HTA models are just in the process of adaptations to properly answer questions related to health promotion, rather than for a single medicinal product.

Figure 44: Public Administration – survey results on perceived average effect of Policy Options on public health ([114])



Source: GÖ FP / LSE survey 2017

The availability of technologies also depends on other factors, in particular the marketing authorisation or certification process as well as the national pricing and reimbursement systems. Therefore, the impact of HTA cooperation on this factor is difficult to quantify with precision. During the focus group meeting with Public Administration, it was considered that increased convergence of HTA methods would increase the availability of health technologies with added benefits, and as such benefit public health.

Overall, public health across MS might be positively affected. Specific stakeholder groups such as health professionals and patients could further benefit through transparent assessment processes and improved health technology monitoring.

7.3.2.8 Further impact

The study team also surveyed a few other parameters how Public Administrations could be affected by various Policy Options. The ones briefly outlined here showed only little relevance in our analysis. Detailed survey responses can be obtained from Annex 24.

Regarding '**employment**' we considered the number of personnel, including consultants, who are involved in HTA activities. The scope of HTA activities, both in terms of the specific expertise needed as well as the depth and scope of assessment, define the personal capacities needed to perform an HTA assessment. Across Europe, assessment groups within public bodies that include up to 30 members, depending on the scope of

([114])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Availability of Health Technologies	20.0	87%	29.9	25%	55%	20%
Overall public health	19.0	83%	35.0	16%	21%	63%

assessments, are usually in charge of determining the value of Pharmaceuticals ([37]). Therefore, assessment groups require expertise from different disciplines, e.g. the Pharmaceutical, epidemiological, mathematics, economics and medical fields (37). Moreover, specific requirements might relate to the assessment of a drug versus a medical device. A study found that there is considerable variance in the number of staff (full-time equivalents, or FTEs) dedicated to HTA activities in HTA organisations across EU countries and Norway: **between none to 604 FTEs who are permanently employed** were reported. Moreover, commissioning external experts to perform or contribute to HTA is done frequently independent of the size or scope of the mandate owned by the respective organisation (2).

HTA experts and Public Administration representatives see no changes in future overall employment levels for PO1, PO2 and PO3. From PO4.1 onwards, a slight increase in employed staff for HTA activities is expected by Public Administration. This corresponds with the foreseen increase in output production and its mandatory uptake for REA and Full HTA (only PO5), as these assessments have to be conducted by skilled staff. Comparing the results on employment level to the expected costs for human resources (see 7.3.2.17.3.3.1), the perceived developments are congruent across the different Policy Options.

For the impact **'Consumer and households',** we surveyed the number of health technologies assessed and the number of health technologies available on the European market, focusing on the availability of medical technologies for patients. HTA processes and systems differ between European countries regarding the capacity to conduct assessments (46) and not all HTA bodies can assess all new health technologies. A lack of comprehensive evidence-based information might hamper the process of decision-making, thus leading to delays in availability in health systems where a positive assessment required for reimbursment. Hence, joint work has the potential to increase the availability of new technologies in countries with less developed HTA systems (41).

Survey results for Public Administration indicate an expected increase in the number of health technologies assessed especially for PO4.2 and PO5. This corresponds with the foreseen mandatory nature of joint REAs for these Policy Options, which could increase the number of health technology assessments across Europe. No effect is expected for the number of available health technologies, which can be linked to the fact that pricing and reimbursement decisions will remain on national level.

For the impact on **'competitiveness of EU health technology sector',** two investigated indicators (competitiveness of SMEs and revenues) apply primarily to the industry sector since Public Bodies are usually financed mostly or exclusively via a dedicated budget ([2]). Still, the survey also aimed at gathering the expectations of HTA bodies as key players in the HTA sector for these indicators. The third indicator surveyed (predictability of HTA system in Europe) is also relevant for Public Administration.

We found an expected positive effect for the competitiveness of SME from PO3 onwards, while no effect is anticipated for PO1 and PO2. Revenues are not expected to be affected by any of the Policy Options under consideration, which most likely is a reflection of the above mentioned caveat regarding applicability of the indicator. **The predictability of the HTA system in Europe is expected to considerably increase for PO3 and the positive effect is amplified by each of the subsequent Policy Options.** This judgement is based on the legislative nature of PO3 to PO5. Public Administration representatives emphasized that predictability is also an important component for academic research institutions, and that stronger cooperation across Europe should lead to a significantly reduced fragmentation of HTA systems.

For the impact **'Functioning of the internal market and competition'**, the fragmentation of the HTA system in Europe, the convergence of HTA methodologies in Europe and the attractiveness of the European market for industry stakeholders, particularly

resulting from a lower fragmentation of HTA systems, were defined as indicators. While differences in HTA methods and processes across countries are not a disadvantage per se for the respective countries and their patients, the potential value and related efficiency gains of joint work has been recognised and lead to a number of international cooperation's, most notably EUnetHTA . Still, literature (2, 32, 58) and the case study (section 5.2) confirmed current differences in HTA processes and methods.

Survey responses and statements by Public Administration show an **expected decrease in the fragmentation of HTA systems across Europe from PO3 onwards,** corresponding to the increasing number of outputs by each Policy Option. **For PO1, an increase in fragmentation is expected, reflecting its entirely voluntary nature and the lack of a potential funding mechanism**. The convergence of HTA methodologies is expected to increase from PO3 onwards with each enhancement of covered outputs and has been highlighted as the most pronounced and influential effect of the Policy Options. Public Administration expects an increase regarding the attractiveness of the European market for industry stakeholder from Policy Options 3 onwards, in line with the decrease in fragmentation which was defined as key component for attractiveness within the survey. HTA outputs currently produced at EU level often require additional national adaption because national procedures differ from European standards, provided that endpoints included in the Joint Assessment are considered relevant at national level (41, 59, 60). Further convergence of HTA methodologies might reduce the need for national adaptation for some countries.

The impact '**International trade'** is not directly linked to Public Administration and altogether, the expected effect of the Policy Options on international trade across all respondents in this stakeholder group is relatively low, even though there is a slight increase in PO5. This might be related to the fact that Public Administrations are not directly affected and are thus hesitant to give estimates.

Results for the impact '**Macroeconomic environment'** show no major changes for PO1 to PO4.1 from the perspective of Public Administrations. For PO4.2 and PO5, overall a slightly positive effect is foreseen, which might be related to expected efficiency gains for policy options where both the participation and the uptake of joint REA is mandatory, thus impeding duplicated REAs across European countries.

7.3.2.9 Concluding remarks for Public Administration

Literature (41) and direct statements by various stakeholders indicate that HTA bodies have mixed opinions regarding the extent of collaboration: some representatives of HTA bodies prefer loose collaboration, merely exchanging information and developing common methodologies, while others prefer clear-cut cross-border assessments. Obviously the current situation of the country might influence the perception of current cooperation on HTA. As frequently highlighted, HTA systems in Europe differ from an organizational point of view and in other ways, and related agencies also differ in many dimensions. Still, different preferences and views regarding joint work are likely to also depend on the final arrangement and organisational details of a future cooperation on HTA.

Summarising, **no major effects with regard to HTA-related processes for PO1 and PO2 are expected** (as indicated in Table 63). With Policy Options comprising a legislative framework (PO3-PO5), slightly more **positive effects are perceived by Public Administration, amplified by each joint output that is covered by the cooperation.**

Table 63: Overview of relevant impacts for Public Administration

Impacts	Policy Option 1	Policy Option 2	Policy Option 3	Policy Option 4.1	Policy Option 4.2	Policy Option 5
Costs (EC1)*	0(-)	0(-)	0(-)	+	+	+
Administrative Burden (EC2)	0(-)	0(-)	0(-)	0(-)	0(-)	0(-)
Innovation and research (EC4)	0(-)	0(+)	+	+	+	+
Governance, Participation, good administration (SH2)	0(-)	0(+)	+	+	+	+
Access to social protection and health systems (SH3)	0(-)	0(+)	0(+)	+	+	+
Sustainability of Health systems (SH4)	0	0(+)	+	+	+	+
Public Health (SH5)	0(-)	0(+)	0(+)	0(+)	0(+)	0

(*) Inverted: - means that cost would go up, + means that cost would go down.
Legend: + positive effect, - negative effect, 0 neutral (+) or (–) representing the direction of results, as indication even if the expected effect is low)

This increase in positive effects with stronger central governance relates to the expectation that the **uptake of joint outputs** will increase with each subsequent Policy Option. Stricter regulation regarding uptake of joint outputs seems to be seen as a key element for sustainable and successful collaboration, since otherwise the impact of cooperation is limited. Moreover, agencies have different capacities for assessing technologies, therefore the number of evidence-based assessments can be increased with joint outputs and potentially more health technologies can be covered.

Positive effects are perceived for **innovation and the research.** This might relate to the expectation that HTA – as an approach for the identification of the added-value of one health technology compared to another – will be strengthened when a legislative framework is provided. Countries without structured HTA processes could especially profit from joint output, in particular from joint REAs.

Convergence of methodologies was emphasized to be a highly influential indicator by Public Administrations, as joint methodologies are a prerequisite for a successful and timely production of joint outputs. This important basic condition will be already fulfilled for PO3, since common tools, templates and methodologies are covered with mandatory participation and uptake. Moreover, increased cooperation is expected to improve the predictability of the HTA system in Europe, also due to an expected lower fragmentation of HTA systems.

No or slightly negative effects were expected by survey respondents across all Policy Options when it comes to the **costs** for HTA-related outputs as well as the administrative burden imposed on Public Administration. However, these results were mitigated by the focus group and the cost calculations performed within this study. Representatives of Public Administration expressed the expectation that, in fact, a closer collaboration would lead to a decrease in costs. Moreover, the cost calculations also indicate potential savings across MS especially from PO4.1 onwards. Administrative burden will most likely differ between MS, which was also highlighted in the focus group. While a decrease for less experienced countries is possible, administrative burden might increase for countries with an established HTA systems, since then more changes are necessary for adapting to a new situation.

Overall, all policy options covering a legislative framework entail positive effects on an aggregate level, although these might differ for the respective MS due to the current, varied landscape for HTA processes in Europe. A general secretariat is considered a potentially useful instrument to ensure stronger governance, which is needed to improve the number of outputs and the functioning of cooperation on HTA.

7.3.3 Pharmaceutical Industry

7.3.3.1 Costs

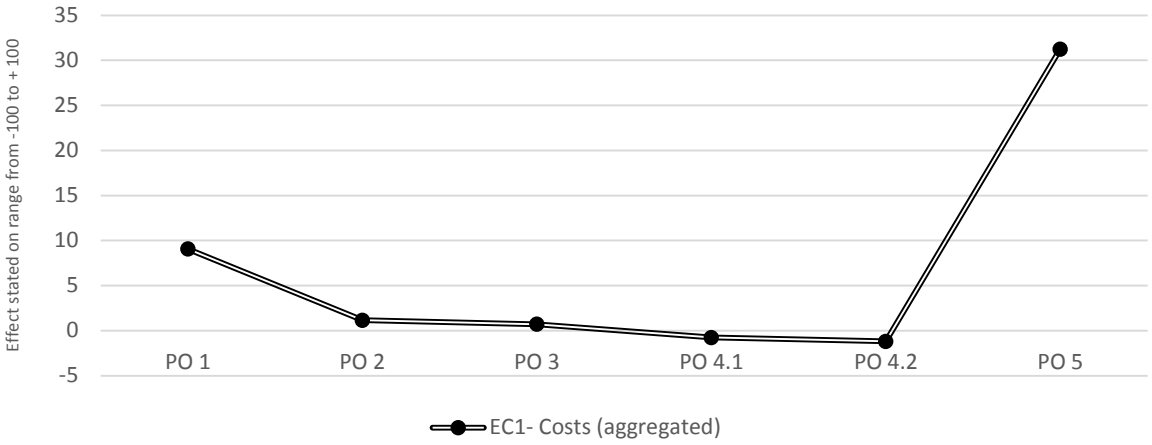
For this impact, potential cost evolution was investigated in relation to Horizon Scanning, Early Dialogues, REA submissions, Full HTA submissions, and additional data requests by respective HTA organisations, personnel requirements and HTA reassessments.

Costs for industry arise from providing specific data or reports for health technologies that are subject to an HTA process, especially when this has an obligatory nature within the specific country. The assessment of Pharmaceuticals in the field of HTA is quite common in a number of European countries, with structured processes in a number of settings. In several European countries, HTA is a part of the decision-making process regarding pricing and reimbursement for Pharmaceuticals (58, 61, 62). A recent study found that, for Pharmaceuticals, 23 EU countries and Norway use HTA for informing reimbursement decisions and 20 for pricing decisions (2). The high frequency of HTA processes indicates a higher level of experience as compared to the MedTech sector.

In general, the framework and extent of assessments performed, as well as the organisational structure at national and EU levels, are decisive for the costs connected to HTA processes. Specific country settings influence the related costs per industry, i.e. whether the manufacturer has to submit an evidence-based application or not, and the extent of such evidence requirements. This is also reflected in the costs per general HTA submission, which were found to vary quite widely in the case study. Pharmaceutical companies are directly affected by HTA processes in a number of European countries and particularly by costs for (additional) data generation, and human resources needed to deal with HTA submission were reported to be especially important in the case study. Therefore, expected changes for these cost components might be especially relevant.

When surveying the potential effects of the different Policy Options on costs, the respondents from Pharmaceutical Industry indicated overall a substantial increase in costs for Policy option 5. For all other Policy Options, almost no change in costs was estimated on an aggregate level (see Figure 45). Expected slight increases in costs for PO1 are mainly driven by SMEs, while large companies in fact don´t expect an increase in costs for PO1. The opposite trend was visible for PO5 when conducting this subgroup analysis: SMEs expect less increases in costs for PO5 than large companies. No differences between expected costs for SMEs and large companies were visible in subgroup analysis for PO2 through PO4.

Figure 45: Pharma Industry - survey results on perceived average effect of Policy Options on costs (aggregated)([115])

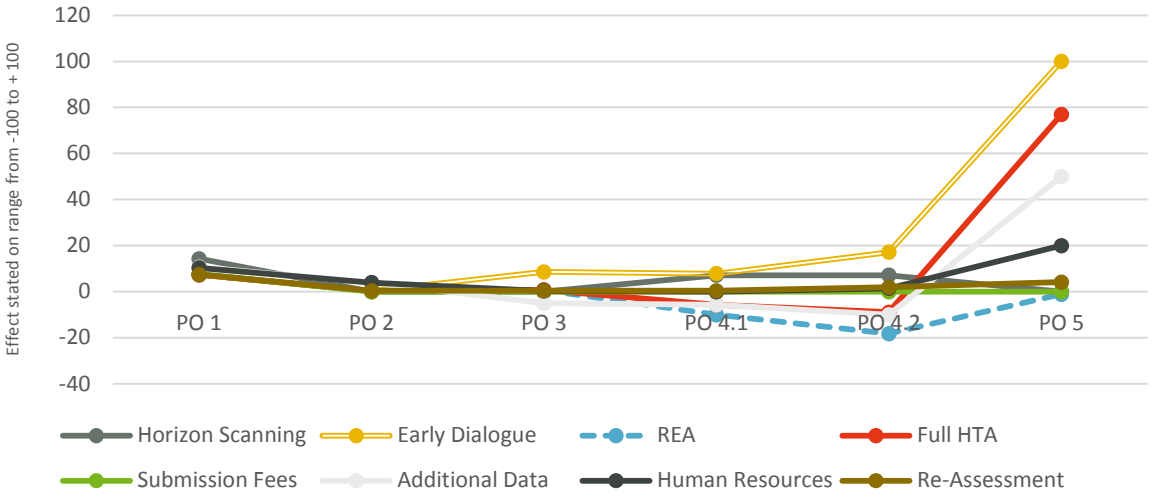


Source: GÖ FP / LSE survey 2017

Looking at the responses indicated for the respective sub questions, Figure 46 displays that the Pharmaceutical Industry expects an increase in costs, especially for Early Dialogues, Full HTAs and additional data requirements when implementing Policy Option 5. With regard to relative effectiveness assessments (REAs), a decrease in costs is expected for Policy Option 4.1 and 4.2, which probably reflect the fact that joint REAs are covered within the legislative framework for these options, potentially leading to a lower number of dossiers that need to be prepared across Europe.

([115]) positive value indicates increase in costs, negative value indicates decrease in costs

Figure 46: Pharma Industry - survey results on perceived average effect of Policy Options on cost indicators (unaggregated) ([116],[117])



Source: GÖ FP / LSE survey 2017

When discussing the results with representatives of the Pharmaceutical Industry, it was highlighted that overall no significant changes in their current costs are expected for PO2 to PO4. Possible increases and decreases of cost components are expected to level each other out. Giving some background information on the work processes in Pharmaceutical companies, it was explained that usually a central value dossier per product is prepared, which is used as a main source of input for the HTA submissions in different countries. One member mentioned that joint HTA reports at EU level could replace 20-25% of the HTA costs in local settings, since there are still e.g. epidemiological differences between countries that need to be addressed and companies still have to go through national reimbursement procedures. However, looking at the broader picture, it was also mentioned that overall consistency would increase with stronger cooperation on HTA in Europe, resulting in better business predictability and thus a positive effect on investment as well as research and innovation.

Costs prognosis (section 7.2.3) indicates that (taking into account the underlying assumptions) all Policy Options potentially lead to cost savings on the side of Pharmaceutical Industry. However, potential savings are considerably higher in POs that comprise both mandatory production and mandatory uptake of joint REAs (PO4.2 and PO5). Options comprising a permanent secretariat and higher joint output lead to substantially larger savings compared to project-based cooperation (in total nearly EUR 4 million across all countries in PO2, versus almost EUR 64 million in PO 4.2).

([116])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Horizon Scanning	6.3	40%	12.6	100%	0%	0%
Early Dialogue	14.0	88%	10.2	0%	0%	100%
REA	14.0	88%	12.7	0%	92%	8%
Full HTA	14.0	88%	16.3	7%	14%	79%
Submission Fees	12.0	75%	4.6	100%	0%	0%
Additional Data	14.0	88%	5.9	0%	7%	93%
Human Resources	14.0	88%	7.0	7%	7%	86%
Re-Assessment	13.0	81%	8.5	85%	8%	8%

([117]) positive value indicates increase in costs, negative value indicates decrease in costs

Moreover, additional evidence generation requested by national HTA bodies might be reduced when (mandatory) joint EDs and joint REAs are in place. This is a relevant factor for potential savings, but couldn´t be integrated into the cost calculations.

Overall, Policy Options providing a legislative framework for HTA cooperation in Europe will potentially have a positive effect on cost evolution for the Pharmaceutical Industry across MS. While survey results indicate no changes for the Pharmaceutical Industry, additional information from focus group and costs prognosis indicate potential savings from PO4 onwards.

7.3.3.2 Administrative burden

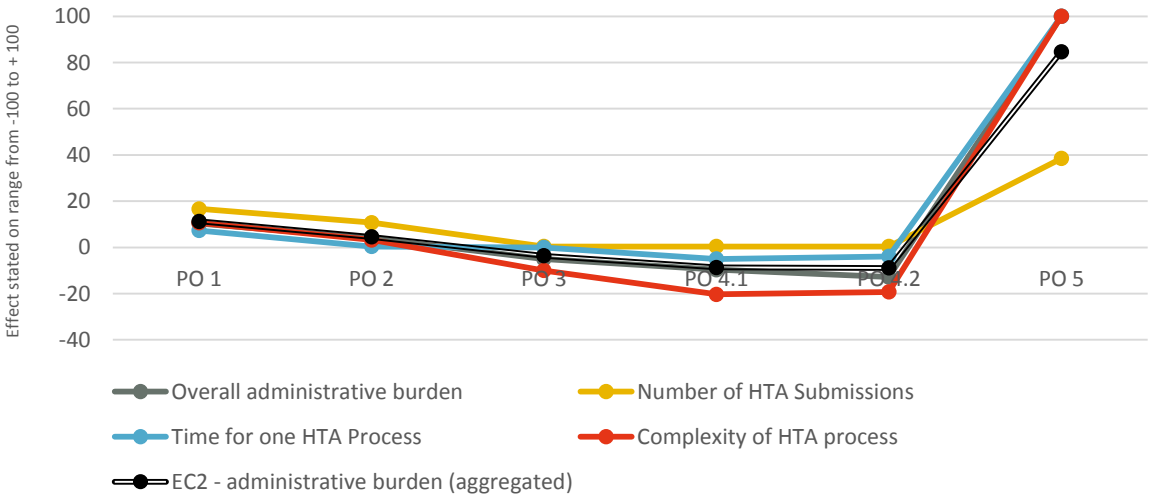
For assessing this impact, the following indicators were defined: overall administrative burden; number of HTA submissions for the same product across European countries; time needed for an HTA process and complexity of HTA assessment processes.

Literature and the case study investigating the baseline scenario indicate that currently the same products are assessed by a number of countries, irrespective of the type of HTA system (63). From an industry perspective, the number of HTA submissions required across Europe for the same product and indication is related to the administrative burden, especially for the Pharmaceutical Industry, since structured HTA processes are common across European countries in this sector.

Reducing duplication in submissions might lead to a decrease in administrative burden for industry, although the extent and effect is difficult to predict. It was reported that approximately 12 to 15 percent of European HTA products address the same technologies, which mainly include Pharmaceuticals or single technologies. A publication including four case studies from EUnetHTA Joint Action 1 showed that an overlap of 30 percent can be avoided if interventions for specific indications are bundled, illustrating the potential to reduce duplication (64).

Reviewing the survey responses from the Pharmaceutical Industry, Figure 47 depicts the results of the online survey, showing almost no expected change in the administrative burden (aggregated) for Policy Options 1 to 4 and a steep increase of expected administrative burden for Policy Option 5.

Figure 47: Pharma Industry - survey results on perceived average effect of Policy Options on administrative burden ([118])



Source: GÖ FP / LSE survey 2017

Examining the responses of the Pharmaceutical sector in detail, the complexity of the HTA process is expected to decrease especially for Policy Options 4.1 and 4.2 while an increase in complexity is estimated for Policy Option 5. With regard to the number of HTA submissions, no change is expected for Policy Options 3 and 4 as compared to the status quo, while for Policy Option 1 and 2, a slight increase in the number of HTA submissions for the same product and indication across European countries is expected. For PO5, a higher increase is expected with regard to the number of HTA submissions, and also the time for one HTA process is expected to increase. When looking at survey responses separately for SMEs and large companies, no differences between these two groups were visible for the Policy Options, expect for PO1. SMEs expect a higher administrative burden (+20) while no change is foreseen by large companies.

During the **focus group** meeting with respondents from the Pharmaceutical sector, it was highlighted that this expected increase in administrative burden for PO5 is largely triggered by the fact that this Policy Option also covers Full HTA, which includes an economic assessment. Joint economic assessments are considered especially complex, since these have to account for the specific country setting. Therefore, additional national submissions for the economic assessment were expected even if Full HTA is mandatory, which ultimately means more administrative burden for industry representatives.

Overall, **policy options 4.1 and 4.2 are favoured by the Pharma sector**, since they are expected to reduce the overall administrative burden, since joint REA with a mandatory uptake will lead to a reduction of the number of national HTA submissions. Moreover, the complexity of HTA processes is expected to decrease. This also becomes visible when summarizing the additional comments that were received within the survey. Respondents clearly stated that more divergent requirements across Europe are expected

([118])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Overall administrative burden	14.0	88%	5.8	0%	7%	93%
Number of HTA Submissions	14.0	88%	12.0	0%	0%	100%
Time for one HTA Process	14.0	88%	6.2	0%	7%	93%
Complexity of HTA process	14.0	88%	7.6	0%	7%	93%

for PO1 and PO2, which increases complexity from the perspective of the Pharmaceutical Industry.

7.3.3.3 Competitiveness of EU health technology sector

For assessing the competitiveness of EU health technology sector, the potential effect of Policy options on the predictability of HTA system in Europe, the competitiveness of small- and medium-sized companies and the revenues of health technology developers were surveyed.

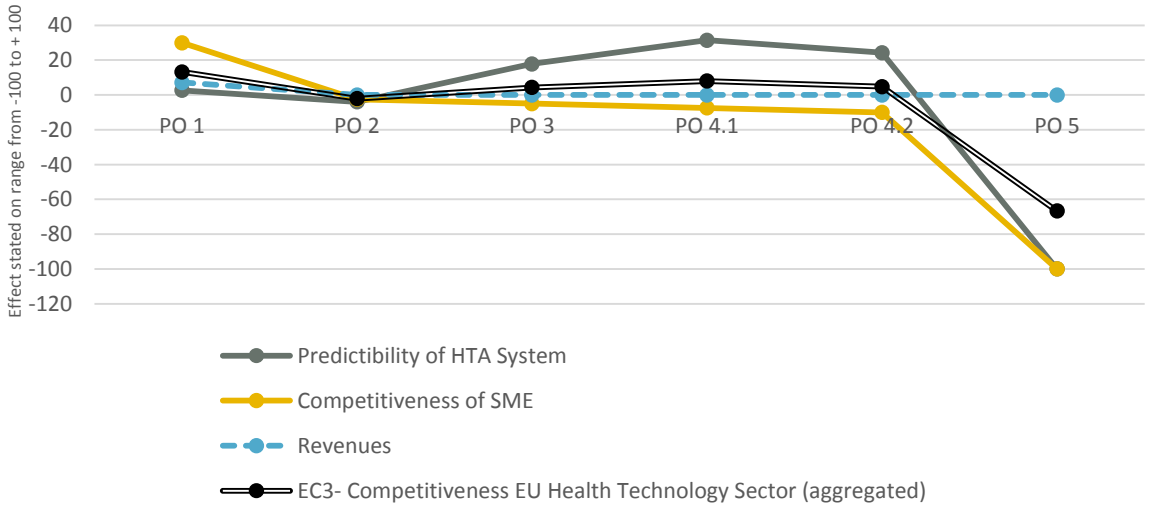
Representatives of Pharmaceutical Industry frequently highlighted the predictability of HTA system in Europe as very important impact. This was also reflected when rating the relevance of the different impacts in the online survey: on average, the respondents from Pharmaceutical Industry rated the importance of this impact to be 8 on a range from 0 (least important) to 10 (most important).

Currently, the predictability of the HTA landscape in Europe is low due to different national requirements regarding e.g. comparators or endpoints in HTA processes. Moreover, divergent outcomes derived from HTA assessments for the same Pharmaceutical and indication were frequently reported in country comparisons (23, 63) and these findings are confirmed by our case study (see section 7.1).

When it comes to the competitiveness of SMEs in relation to HTA processes, this is linked to the predictability of the HTA system as well as to the evidence requirements for HTA submissions, especially regarding additional data requirements on top of clinical data relevant for marketing authorisation. These additional data requirements in the course of an HTA submission might be harder to fulfil by SMEs because costs and organisational effort have a greater impact on them compared to larger companies that can easier attribute resources to this tasks (65). The current HTA landscape in Europe has direct or at least indirect influence on revenues for the industry in several EU countries as pricing and reimbursement decisions are informed by these assessments in a number of them.

Survey responses from the Pharmaceutical Industry show that no effect on any of the surveyed indicators for this impact is expected for PO2 (see Figure 48). For PO1, a positive effect on the competitiveness of SMEs is stated, while no effects from the other indicators are expected. For PO2, PO3 and both variants of PO4 a positive effect on the predictability of HTA system is expected. On the contrary, no changes for the other indicators are foreseen. For PO5, a negative effect regarding the predictability of HTA systems and the competitiveness of SME is expected. The perceived challenges regarding joint economic assessments, which lead to an increase in complexity, can serve as explanation (see 7.3.3.2 for detailed description). In general, no major effect on the revenues is expected across all Policy Options.

Figure 48: Pharma Industry - survey results on perceived average effect of Policy Options on competitiveness of EU health technology sector ([119])



Source: GÖ FP / LSE survey 2017

When discussing the expected neutral effect of all Policy Options on the revenues with the representatives of the Pharmaceutical Industry, it became apparent that the underlying reasons for these responses are twofold: on the one hand, they derive from the uncertainty of whether any of the POs will have a positive or negative effect on the revenues. Industry respondents stated that both directions can be plausible, depending on the specifications of the Policy Options. On the other hand, it was stated that no effect on pricing and reimbursement across Europe is expected, since the Policy Options are not linked to this. However, a more harmonized system could lead to faster market access if heterogeneity in assessment is reduced. This was also indicated during the interviews, stating that greater consistency in HTA assessments would be beneficial because it would de-risk the submission process (see 5.2.5), which can be attributed especially to PO 4.1 and 4.2, as these will cover REAs including an mandatory uptake, which was highlighted to be important by the Pharmaceutical Industry as well.

For Pharmaceutical Industry a positive effect on the competitiveness of EU health technology sector can be expected especially for PO 4.1 and 4.2. This is driven by the expected increase of predictability in HTA processes with regard to REA across Europe.

7.3.3.4 Innovation and research

The assessment of innovation and research, focused on the effect of the various Policy Options on: the research climate and innovation for the European Market.

HTA has been identified as a tool to increase efficiency in health-care and to steer innovation in the development of health technologies (44, 45). While an HTA assessment per se is not decisive for reimbursement or the price that can be achieved for the specific product, several countries across Europe (e.g. France and Sweden) have linked the

([119])

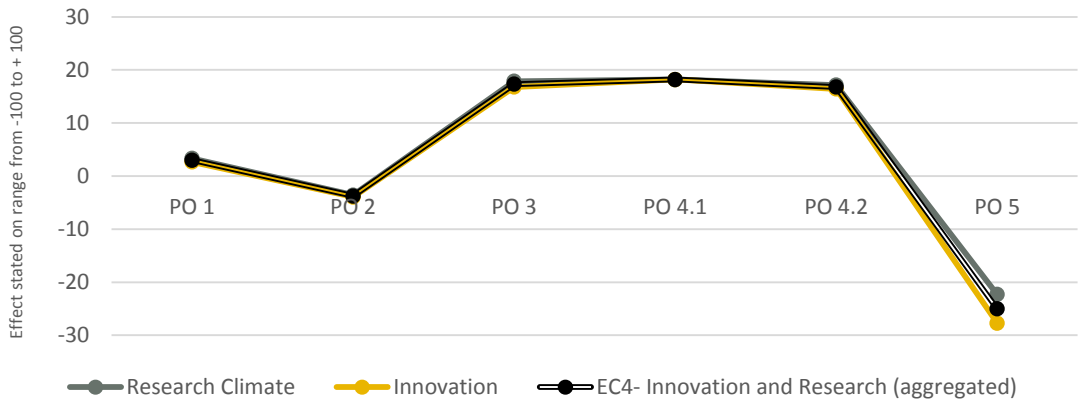
Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Predictability of HTA System	14.0	88%	10.3	0%	93%	7%
Competitiveness of SME	2.0	13%	-	80%	10%	10%
Revenues	13.0	81%	4.5	100%	0%	0%

evidence provided by this HTA assessments to pricing and reimbursement decision (45). A stable and predictable HTA system that values and rewards the innovative features of a health technology could incentivize the development of innovative products.

However, this system also needs to work for Industry, since currently industry stakeholders have reported perceiving requirements of HTA processes as a hurdle for patient access and innovation (54). Challenges for innovation and research resulting from cooperation in HTA are among other to maintain local context, to ensure compatibility of methodologies, specifically for countries with well-established assessment processes and to introduce transparent topic selection and prioritization (41, 46-48).

For the Pharmaceutical Industry, Figure 49 depicts the anticipated overall effect of the respective Policy Options on innovation and research. It shows an expected positive effect for Policy Options 3 to 4 but a negative effect for Policy Option 5. There is no expected effect of PO1 and PO2.

Figure 49: Pharma Industry - survey results on perceived average effect of Policy Options on innovation and research ([120])



Source: GÖ FP / LSE survey 2017

Results are in line with conclusions drawn from interviews with the Pharmaceutical sector. Interviewees highlighted that harmonization of evidence requirements are accompanied by MS acceptability and would facilitate easier investment decisions (see 7.1.12.1). Moreover, the predictability of the market was highlighted as a main driver for innovation by representatives of the Pharmaceutical sector. This is due to its contribution to a less risky environment which positively influences investment decisions. Hence, predictability of HTA systems and harmonization of evidence requirements are underlying drivers for innovation in the Pharmaceutical sector when it comes to the HTA landscape in Europe.

Underlying reasons for the expected decrease of PO5 are most likely due to the coverage of Full HTA within the legislative framework of this Policy Option. Comments to the survey and discussions during the focus group with respondents from the Pharmaceutical Industry revealed scepticism about the applicability of joint Full HTA across European countries.

([120])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Research Climate	14,0	88%	9,0	0%	100%	0%
Innovation	14,0	88%	11,9	0%	100%	0%

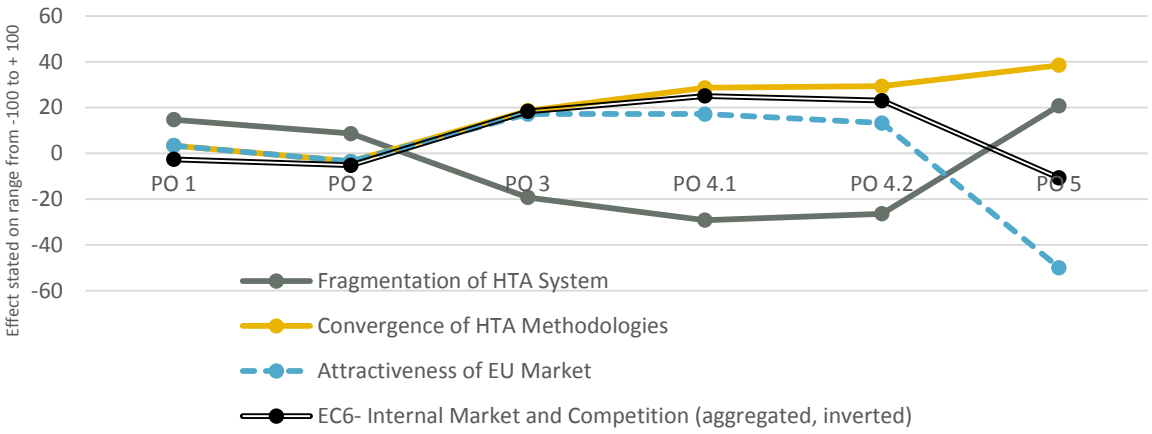
7.3.3.5 Functioning of the internal market and competition

Potential effects of the Policy Options on the functioning of the internal market and competition were assessed by investigating the fragmentation of the HTA system in Europe, convergence of HTA methodologies in Europe and the attractiveness of the European market for industry stakeholders, particularly resulting from a lower fragmentation of HTA systems.

Literature provides several examples illustrating the fragmentation of the HTA system and the level of convergence of HTA methodologies in Europe. Different methodological approaches can lead to varying pathways for pricing and reimbursement decisions, specifically for innovative products, thus imposing challenges on manufacturers (47) as also outlined in interviews with industry representatives. In general, the different steps of assessment, appraisal and pricing and reimbursement decisions are clearly separated in most EU countries and pricing and reimbursement decision are national or sometimes also local competences (66,37).

Analysing survey responses from Pharmaceutical stakeholders, Figure 50 displays the overall effect on the internal market and competition and the specific indicators.

Figure 50: Pharma Industry – survey results on perceived average effect of Policy Options on internal market and competition ([121])



Source: GÖ FP / LSE survey 2017

Overall, almost no change is expected for PO1 and PO2. On the contrary, positive effects are expected for PO 3, PO 4.1. and PO4.2: the fragmentation of HTA systems is expected to decline while the attractiveness of the EU market and the convergence of HTA methodologies increase, thus improving the conditions for the internal market and competition in Europe.

Differences between the specific indicators and the overall impact are visible for PO5. Pharmaceutical sector stakeholders expect the highest level of convergence of methodologies and simultaneously an increased fragmentation of methodologies, which might

([121]) Aggregation: inverted for fragmentation of HTA system

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Fragmentation of HTA System	14.0	88%	9.4	0%	0%	100%
Convergence of HTA Methodologies	14.0	88%	7.4	0%	0%	100%
Attractiveness of EU Market	14.0	88%	10.7	0%	100%	0%

seem counterintuitive. An explanation for this is the expectation of industry representatives that converged methodologies in economic assessment will not be able to fully replace national submission in this field. Thus, it was presumed that national submissions will still be necessary for PO5, which was pointed out in interviews as well as in comments to the online survey. The drop in the perceived attractiveness of the EU market for PO5 might relate to this issue as well.

7.3.3.6 Further impacts

Several impacts were surveyed but do not directly affect Pharmaceutical Industry, thus a quick summary for these impacts is displayed in this section while graphs for the respective survey results can be found in Annex 25.

For the impact **'consumer and households',** the number of health technologies assessed and the number of health technologies available on the European market, focusing on the availability of medical technologies for patients, were surveyed

Equal access to affordable Pharmaceuticals is an important aim across many OECD countries, including those in the European Union (23). An important factor regarding the availability of health technologies is the time to market. For this, differences are seen across EU countries when it comes to Pharmaceuticals (67). Increased collaboration at EU level could have a positive effect on this, but might also slow down availability due to national adaptation in countries with highly developed HTA system.

Overall, Pharmaceutical Industry respondents estimated that especially PO3, PO4.1 and PO4.2 have a slight positive effect on the availability of health technologies, whereas PO 5 is perceived to have a more pronounced and negative effect. This might be due to the expected longer timeframe for Full HTAs, which could prolong time to access for Pharmaceuticals or the fact that Full HTAs, which constitute more comprehensive assessments including, e.g., economic or social effects, are perceived to reduce the chances of a positive HTA outcome. Adddtionally, negative full HTAs at EU level might have further reaching consequences in terms of national HTA recommendations across Europe than joint REAs, as for these country-specific economic evaluations can still facilitate a positive outcome. In contrast, no change is expected in the number of health technologies assessed with the exception of PO5 for which a decrease is estimated.

For the impact **'International Trade'**, the survey aimed to assess the effect of the different Policy Options on international trade related to Pharmaceuticals and medical technologies, specifically the effect on related product import and export possibilities.

As five of the Top 10 Pharmaceutical markets worldwide (regarding sales in 2015) sre European countries (68), it is fair to say that for the Pharmaceutical Industry , Europe is an important market. Hence, possible effects of the current HTA system in Europe on the import and export of products were investigated.

Changes in HTA cooperation in Europe are not expected to impact on related product import and export possibilities from the Pharmaceutical Industry perspective, as indicated in the survey. An exception is Policy Option 5, where Pharmaceutical Industry expects a negative effect, which might relate to the overall perception that PO5 is too extensive.

For the impact **'macroeconomic environment'**, the survey aimed to assess the effect of the different Policy Options on the overall economic growth and labour market, the health care sector (including health care providers) and the health technology sector.

There are quite a number of factors influencing the macroeconomic environment of organisations, including changes in the legal framework organisations operate in. The need for national adaptation of collaborative European assessments, the differential methodologies applied at European, national or local level and associated legal re-

strictions (41) might limit the applicability of joint assessments in a national context. However, they still carry the potential to increase resource efficiency in the health technology sector and the health care sector. Early engagement between the different stakeholders (69) might lead to efficiency gains on both sides, the industry and Public Administrations and other organisations.

Overall, no major changes in the macroeconomic environment for the different Policy Options was expected with the exception of the MedTech industry which assumes a negative effect for all Policy Options with a legislative framework.

The impact **'Access to social protection and health systems'**, focused on access to innovative treatments. Especially for innovative treatments, hurdles to market access and reimbursement have been reported to be higher due to the uncertainty surrounding its value and potential barriers resulting from HTA requirements (43, 47). In general, the determination of a health technologies' value und communicating its value to other stakeholders has been described as vital for industry stakeholders to ensure timely patient access (70).

For the Pharmaceutical sector, the results of the online survey indicate that PO3 to PO4 are expected to increase the availability of innovative products, while PO5 is expected to have a negative impact. This is in line with the results of the indicator 'innovation and research' and related explanations apply (section 7.3.3.4).

For the impact **'employment'**, the survey aimed to assess the effect of the different Policy Options on number of personnel employed, including consultants, who are involved in HTA activities. Employees dealing with THA processes from the industry side need an understanding about the methods and requirements defined by the assessing body in order to successfully prepare these assessments. Additional to the scope of activities, the organizational capacity is decisive for performing HTA activities in-house or contracting consultants, both for HTA bodies as well as manufacturers.

In the Pharmaceutical sector, submissions related to HTA are quite common across Europe and organizational entities handling submissions are set up at least within larger companies. This both addresses people employed to deal with HTA-related issues at the specific company sites in European countries but also at EU-Level.

The expected effect of the different Policy Options on the number of staff employed for HTA-related activities indicates that no substantial change regarding the number of personnel employed is foreseen by the respondents of the Pharmaceutical sector. Given that quite a number of responses were given from a European perspective (e.g. market access manager at EU level), this might indicate that, across European countries, the staff level remains stable, even if more HTA activities are organized at EU level, which was confirmed by representatives of the Pharmaceutical Industry. It was moreover highlighted that the basis for HTA-related activities (e.g. evidence generation/value dossiers) is often performed at EU level and adapted afterwards in specific countries in Europe. Thus, the number of staff might not change, but the allocation of employed personnel across countries might change.

The **'sustainability of health systems'**, was surveyed by assessing the effect of the various Policy Options on the financing of expensive treatments with little or no added value and the negotiating power of MS in setting prices. All Policy Options are expected to have almost no effect on these indicators from the perspective of Pharmaceutical Industry except for PO1. Reasons underlying these results may be the fact that the POs do not address pricing and reimbursement decisions because these remain the competency of national authorities. This is in line with the results regarding the revenues with no anticipated effect of the Pharmaceutical Industry (see 7.3.3.3).

For the impact **'Public Health'**, the estimated effect of the Policy Options on two indicators (overall public health and the availability of health technologies on the market)

was investigated. Pharmaceutical Industry expects a negative effect of Policy Option 5 regarding Public Health, while there is no effect expected for Policy Option 2 and an increase for all other Policy Options. The availability of health technologies is expected to be highest for Policy Options 3 and 4.

For the impact **'Governance, participation and good administration'**, how the Policy Options affect the involvement of different stakeholders in HTA processes, the responsibilities of Public Administrations in the field of HTA at MS level, the uptake of joint outputs, the resource efficiency of HTA processes in general and the sustainability of European cooperation in the field of HTA was surveyed.

Over all indicators, a slightly positive effect of PO3, PO4.1 and PO4.2 is expected by Pharmaceutical Industry, while the Policy Options (PO1 and PO2) and PO 5 are expected to have a negative effect. This is mainly driven the expectation of a strong negative effect regarding the sustainability of the HTA cooperation PO1, PO2 and PO5, which can be related to the entirely voluntary nature of cooperation for PO1 and PO2 and the absence of a legislative framework. For PO5 the expected negative effect might relate to the high level of agreement that would be necessary for joint economic evaluations, which could be assumed to hamper sustainability of cooperation. On the contrary, respondents from the Pharmaceutical Industry do not expect any effect on the responsibilities of MS when assessing the different Policy Options. A slight increase is expected in the number of uptakes for joint outputs for PO4 and PO5. No change is foreseen for resource efficiency with the exception of PO5, for which a decrease is indicated. The expectation of additional national submission can serve as an explanation for this.

7.3.3.7 Concluding remarks for Pharmaceutical Industry

For **Pharmaceutical Industry,** overall results indicate positive effects for Policy Options including a joint work on REA at EU level. This especially relates to positive effects for innovation and research, functioning of the internal market and access to innovative treatments as displayed in Table 64. However, industry expects negative effects for PO 5, which includes a strictly mandatory and binding HTA process also covering Full HTA in Europe. **The highest number of positive effects across all impacts is seen with PO 4.1 and 4.2.**

Table 64: Overview of relevant impacts for Pharmaceutical Industry

Impacts	Policy Option 1	Policy Option 2	Policy Option 3	Policy Option 4.1	Policy Option 4.2	Policy Option 5
Costs (EC 1)	0(-)	0(-)	0(-)	+	+	-
Administrative Burden (EC2)	0(-)	0(-)	0(+)	+	+	--
Competitiveness of EU health technology sector (EC 3)	0(-)	0(-)	0(+)	+	+	--
Innovation and research (EC 4)	0(+)	0(-)	++	++	++	--
Functioning of the internal market and competition (EC6)	0(-)	0(-)	+	+	+	0 (-)

(*) Inverted: - means that cost would go up, + means that cost would go down.

Legend: + positive effect, - negative effect, 0 neutral (+) or (–) representing the direction of results, as indication even if the expected effect is low)

Underlying reasons for a negative expectation for PO5 were indicated during the interviews as well as in comments to the survey and in the focus group with Pharmaceutical companies. It was emphasized that mandatory joint economic evaluations as foreseen in Policy Option 5 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. However, joint work on REA has been indicated to potentially reduce inefficiencies and workload for the Pharmaceutical sector.

One important positive impact for the Pharmaceutical Industry relates to the expected increase in the predictability of HTA related processes in Europe, which is especially the case for joint REAs. The positive impact can be linked to less administrative burden due to the reduction of multiple submission for the same Pharmaceutical across Europe. Predictability of processes and evidence requirements has been mentioned to be a very important factor in the interviews with industry representatives as well as in comments provided to the survey, also facilitating innovation drive due to easier investment decisions.

Subgroup analysis showed that perceptions of the Policy Options are quite similar for SMEs and large companies, except for PO1, where SMEs indicated a more positive assessment across most impacts compared to large companies. No additional analysis could be done for HTA-experienced companies as all responding Pharmaceutical manufacturers had at least some experience with HTA.

With regard to costs for HTA processes, no major changes are expected by the respondents of the Pharmaceutical sector. According to discussions within the focus group meeting this is because possible increases and decreases of cost components are expected to level each other out. Results of cost calculations within this study, however, indicate that potentially savings due to a reduction in duplicated assessments can be achieved for the Pharmaceutical Industry across Europe for all Policy Options. However, potential savings calculated in the cost prognosis are considerably higher in POs that comprise both a mandatory production and mandatory uptake of joint REAs (PO4.2 and PO5). Options comprising a permanent secretariat and higher joint output lead to substantially larger savings as compared to the project-based cooperation (EUR 3.7 million in PO2 versus more than EUR 60 million in PO 4.2). Moreover, it has to be 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 but couldn't be integrated into the cost calculations.

7.3.4 MedTech Industry

7.3.4.1 Costs

For this impact, potential cost evolution was investigated in relation to: Horizon Scanning, Early Dialogues, REA submissions, Full HTA submissions, additional data requests by respective HTA organisations, personnel requirements and HTA reassessments.

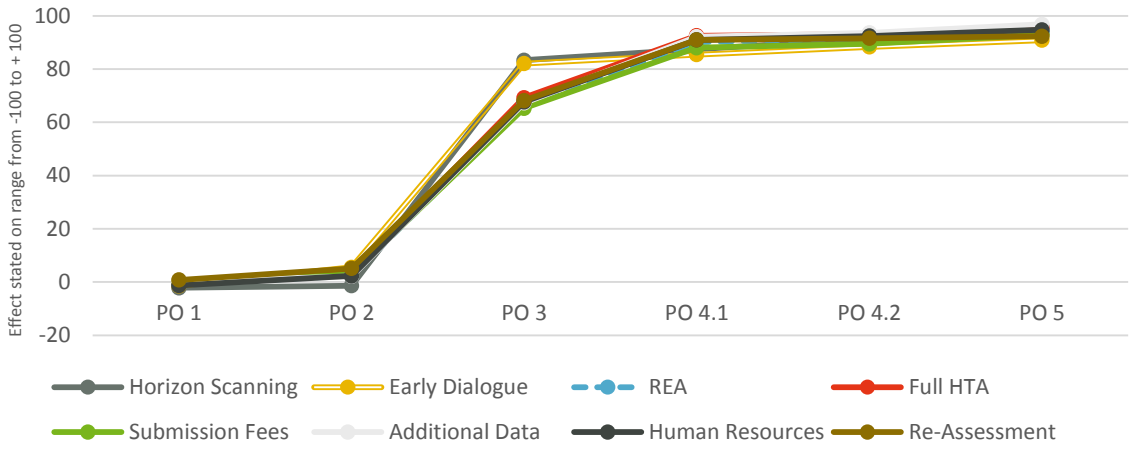
Currently, few countries in Europe have formal HTA processes for assessing Medical technologies, which is unlikely to change completely until 2020, when the current Joint action on HTA ends. Moreover, the pricing and reimbursement system for medical technologies is substantially different from that for Pharmaceutical products because decisions are more often based on regional level and the scope of products is very broad.

In the survey, MedTech Industry expected a substantial cost increase (see Figure 51) for all POs with a legislative framework (PO3 to PO5), which is in contradiction to our cost-prognosis. The latter indicates that the MedTech industry might benefit in terms of savings from options with stronger governance and regulations in the long run as the current duplication of dossiers will be strongly reduced and economy of scale would apply. These potential savings would increase for POs with a legislative framework and mandatory participation and uptake (PO4.1, 4.2 and 5).

But, initial investments to build up capacity for HTA in the MedTech sector are needed and have not yet occurred right now, giving a proper explanation for results of the survey shown below. MedTech representatives also explained that any legal requirements in addition to the two new regulations in the field are considered as drivers of cost. This explains why PO3 is expected to increase cost much stronger as PO 2 with mandatory

uptake of REA (where there is no real experience so far in many MedTech companies). Also, MedTech expect a legal system to significantly increase HTA activities in and across MS in the field of medical devices and IVDs at the time of the market launch of the product, where currently there are limited activities (if at all).

Figure 51: MedTech Industry - survey results on perceived average effect of Policy Options on cost indicators from survey (unaggregated) ([122,123])



Source: GÖ FP / LSE survey 2017

Another simple reason for the expected high increase in costs is that many medical device companies have only very limited experiences with HTA and thus might have a less realistic perception of the related cost. This assessment is true for both SMEs and other companies. Generation of evidence is considered a key cost-driver. Companies noted that efficacy data is not currently required (in the revised regulation it will only be required for a limited number of technologies). Costs for regulatory and HTA data generation differ; HTA evidence generation is estimated to be four times more expensive. Also discussed was that, for products requiring additional clinical data, it may be beneficial to align requirements if possible to maximise use of data and reduce duplication.

7.3.4.2 Administrative burden

For assessing this impact, the following indicators were defined: overall administrative burden; number of HTA submissions for the same product across European countries; time needed for an HTA process and complexity of HTA assessment processes.

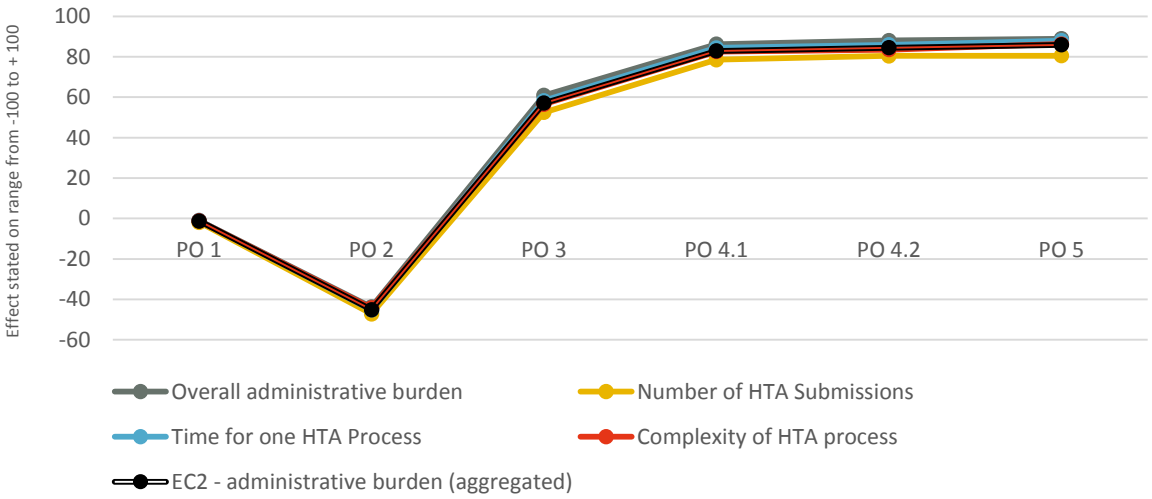
Since development pathways for medical technologies and market-access requirements differ from those of Pharmaceuticals, some issues have to be accounted for when it comes to the potential administrative burden of HTA processes, including timing issues.

([122])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Horizon Scanning	92.7	94%	25.0	0%	2%	98%
Early Dialogue	91.8	93%	27.4	2%	1%	97%
REA	91.7	93%	20.9	1%	0%	99%
Full HTA	90.7	92%	19.4	0%	0%	100%
Submission Fees	89.3	90%	21.9	7%	0%	93%
Additional Data	90.2	91%	18.1	1%	0%	99%
Human Resources	91.2	92%	20.4	0%	1%	99%
Re-Assessment	90.2	91%	24.4	5%	1%	94%

([123]) positive value indicates increase in costs, negative value indicates decrease in costs

Figure 52: MedTech Industry - survey results on perceived average effect of Policy Options on administrative burden ([124])



Source: GÖ FP / LSE survey 2017

Survey results indicate that respondents from the medical technologies industry expect a decrease in administrative burden for Policy Option 2, turning to an expected increase with Policy Option 3 and onwards (see Figure 52).

Separating the responses for each indicator, the expected effects align. This is also the case when looking at the subgroups of SMEs and large companies, which stated almost the same effect.

While discussing the results with MedTech representatives, it became apparent what reasons caused the sharp expected increase in administrative burden for PO3. Industry representatives explained, that a legally mandated REA at the time of launch (PO3) substantially increases HTA activities in MS, and might fundamentally change the business model even without mandatory uptake. At the same time, once evidence needs to be generated for HTA, there is little difference in terms of administrative burden, if additional data should focus on effectiveness or on economic aspects. This accounts for the relative stability of the curve from Policy Option 3 to 5.

When asked about the level of the figures given within the survey (which are quite high for PO4 and PO3), it was highlighted that this impact is quite important to the MedTech sector. This is in line with the ranking respondents provided in the survey (9 out of 10, while 10 represents high priority, see section 7.3.6). With regard to PO2, it was mentioned that common templates will reduce the administrative burden as it simplifies collaboration.

For the medical technologies industry, Policy Option 2 is most favourable, becuase it does not entail a legislative framework. Setting up new processes for HTA in the medical technologies sector would increase the administrative burden from the stakeholders'

([124])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Overall administrative burden	91.0	92%	33.7	0%	2%	98%
Number of HTA Submissions	90.8	92%	41.0	2%	7%	91%
Time for one HTA Process	90.5	91%	35.2	0%	3%	97%
Complexity of HTA process	90.5	91%	38.0	2%	6%	92%

perspective. However, this only holds true for the establishment phase. Once established, processes will be standardised and not impose a considerable burden any more. According to our judgement findings indicate that **Policy Options with stronger governance and at least the use of common tools, standards and methodologies in evidence generation and outputs** would be beneficial for the sector, since redundancies as observed in the Pharmaceutical sectors could be avoided to some extent.

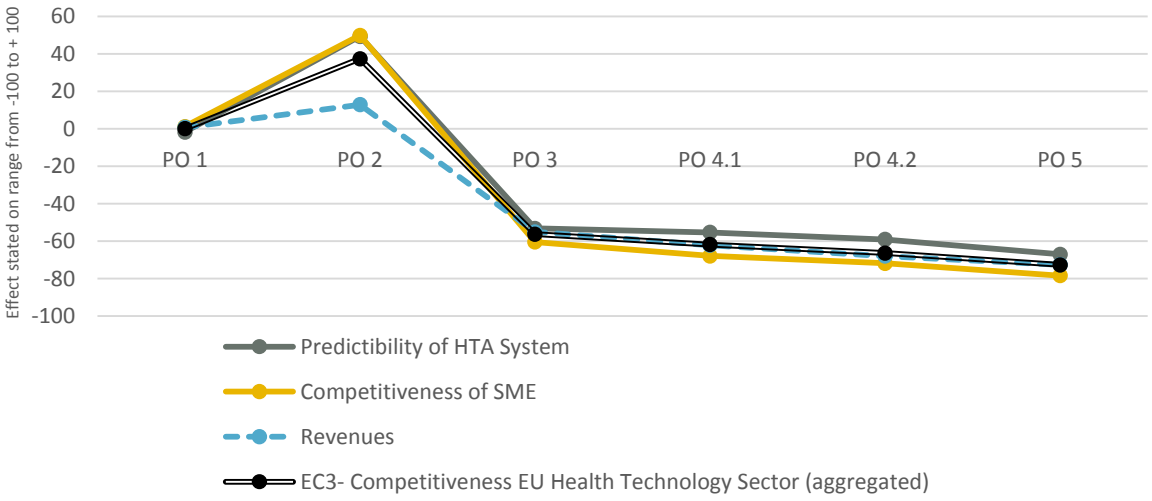
7.3.4.3 Competitiveness of EU health technology sector

For assessing the competitiveness of the EU health technology sector, the potential effect of Policy Options on the predictability of the HTA system in Europe, the competitiveness of small- and medium-sized companies and the revenues of health technology developers were surveyed.

When it comes to the competitiveness of SMEs in relation to HTA processes, this is linked to the predictability of the HTA system as well as to the evidence requirements for HTA submissions, especially regarding additional data requirements on top of clinical data relevant for marketing authorisation. These additional data requirements in the course of an HTA submission might be tougher to fulfil by SMEs, since costs and organisational effort have a greater impact on them compared to larger companies that can more easily attribute resources to these tasks. This is especially relevant for the Medical technologies sector, since many companies in the sector are SMEs (39, 71).

For the Medical technologies sector, survey results regarding the predictability of HTA systems and the competitiveness of SMEs show no effect for PO1, a perceived positive effect for PO2 and a perceived negative effect for PO3 onwards. This negative effect remains stable for PO4 and PO5. Given that HTA processes are currently not as common for medical technologies as they are for Pharmaceuticals, the survey results might reflect the uncertainty linked to new structures that will arise when a legislative process is established (39, 65).

Figure 53: MedTech Industry - survey results on perceived average effect of Policy Options on competitiveness of EU health technology sector ([125])



Source: GÖ FP / LSE survey 2017

A relevant aspect arising during discussions with the MedTech **focus group** relates to the time of assessment. When HTA is conducted at the time of market launch, the first company needs to generate comprehensive evidence. This might be used by an early follower, creating a considerable disadvantage for the first mover. In the view of participants, this could explain the sharp expected decline for these impacts from a completely voluntary cooperation (PO2) to an at least partly mandatory one (PO3-PO5).

Another point stressed by MedTech representatives is that increased harmonisation might delay first revenues. This can be challenging, since a quick access to market is highly important especially, but not only, for SMEs. Even if harmonization means access to more countries, losing the quick access to the first market (which is currently easy to access) might override the advantage of accessing more countries. Moreover, concerns were expressed with regard to a possible increase in evidence requirements when a new EU system is in place. This could be challenging especially for SMEs.

When it comes to medical technologies, policy option 2 appears to be the most favourable from the perspective of this sector because it offers the opportunity of joint output production without the undesired legal binding. However, voluntary cooperation has the disadvantages of less efficient processes and low target orientation. Thus, scarce resources in the health care sector should be used with caution and ensure efficient and sustainable cooperation.

7.3.4.4 Innovation and research

Here we investigated the current climate for research and innovation in Europe. In general HTA has been identified as a tool to increase efficiency in health-care and to steer innovation in the development of health technologies (44, 45). However, for

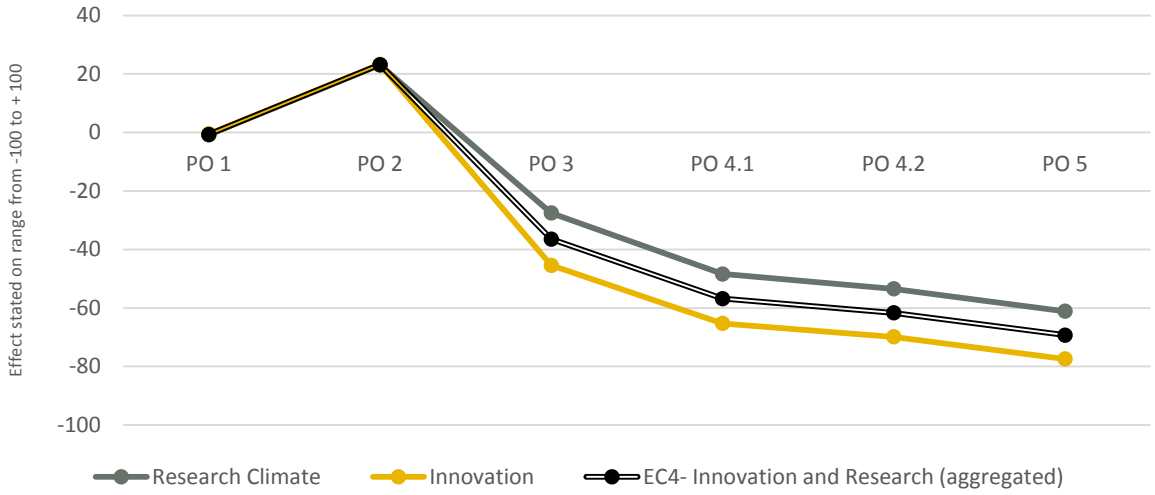
([125])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Predictability of HTA System	90.8	92%	41.0	2%	84%	14%
Competitiveness of SME	91.8	93%	32.8	1%	93%	6%
Revenues	90.5	91%	34.3	3%	90%	7%

Medical Technologies HTA-related processes are not as common and methodologies are still less developed compared to Pharmaceuticals. Moreover, the research cycles for Medical Devices are a bit different as compared to Pharmaceutical Industry as the scope of products is even more technology driven, resulting in shorter life-cycles, e.g. for medical software.

Survey responses show that a slight positive effect for innovation and research is anticipated for Policy Option 2 while negative effects are estimated for Policy Options 3 to 5. The most pronounced effect is expected when implementing Policy Option 5.

Figure 54: MedTech Industry - survey results on perceived average effect of Policy Options on innovation and research ([126])



Source: GÖ FP / LSE survey 2017

Reviewing the effect on innovation and research for the two specific indicators investigated, a more pronounced negative effect is expected for innovation as compared to the indicator research climate (see Figure 54).

An explanation for this expected deterioration of the innovation and research climate can be related to the shorter life cycle of medical devices. This among others impact the conduct of long RCTs while evidence-based on such studies is currently viewed as high-level evidence 45. As explained in the previous section (7.3.3.3), MedTech representatives argued that evidence requirements for new innovative products will increase with strengthened HTA cooperation in Europe. Representatives of the medical device industry explained, that when HTA is conducted at the time of market launch the first company needs to generate comprehensive evidence which then might be used by an early follower, creating a considerable disadvantage for the first mover. This point was also highlighted in Interviews with representatives of Medical device companies in the course of the case study (7.1.13.2). Expected increases in study requirements can therefore serve as underlying explanation of the expected sharp decline in innovation from a voluntary cooperation in PO1 and PO2 to a mandatory one in PO3 and onwards.

([126])

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Research Climate	91,0	92%	26,0	2%	91%	7%
Innovation	90,3	91%	29,7	2%	93%	5%

7.3.4.5 Functioning of the internal market and competition

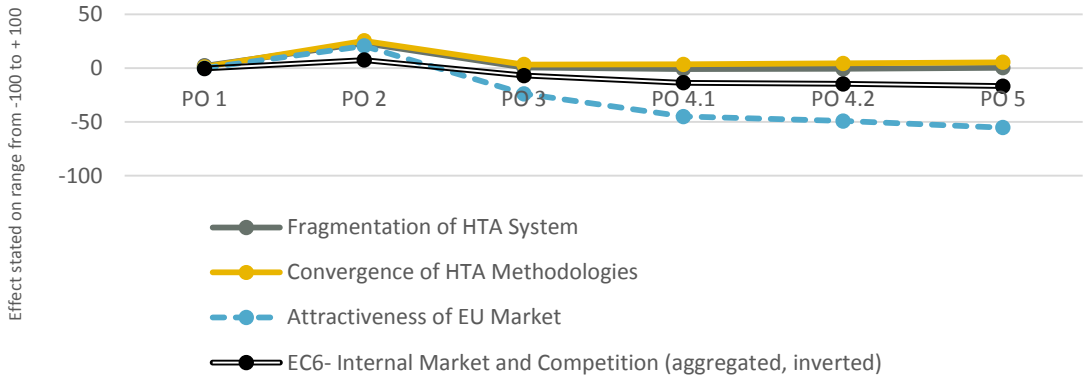
Potential effects of the Policy Options on the functioning of the internal market and competition were assessed by investigating the fragmentation of the HTA system in Europe, convergence of HTA methodologies in Europe and the attractiveness of the European market for industry stakeholders, particularly resulting from a lower fragmentation of HTA systems.

Literature provides several examples illustrating the fragmentation of the HTA system and the level of convergence of HTA methodologies in Europe which were confirmed by results of the case study. For example, the definition of medical devices and, therefore, the associated structures, procedures and applied methodologies for HTA processes differ between governmental institutions among Europe (58). Different types of public organisations engage in assessing medical devices. Depending on the organisation, the scope differs: either new medical devices or other technologies, only those used in the outpatient sector, or other technologies for specific purposes are assessed (32, 58).

Different methodological approaches can lead to varying pathways to pricing and reimbursement decisions for medical technologies, specifically for innovative products, thus imposing challenges on manufacturers (47). In general, the different steps of assessment, appraisal and pricing and reimbursement decisions are clearly separated in most EU countries and pricing and reimbursement decision are national or sometimes also local competences (66, 37). This is especially true for Medical Technologies, on which different pricing and reimbursement processes apply as compared to Pharmaceuticals.

When assessing input from the medical technologies industry a slightly negative effect is perceived from PO3 onwards, which is mainly due to a considerable decrease in their estimated attractiveness of the EU market (see Figure 55).

Figure 55: MedTech Industry – survey results on perceived average effect of Policy Options on internal market and competition ([127])



Source: GÖ FP / LSE survey 2017

([127]) Aggregation: inverted values for fragmentation of HTA system

Additional information as described in 7.3.1	av. responses	response rate	av. std. dev	no effect	negative effect	positive effect
Fragmentation of HTA System	88.0	89%	21.3	84%	9%	7%
Convergence of HTA Methodologies	88.0	89%	21.2	86%	2%	11%
Attractiveness of EU Market	89.2	90%	28.1	6%	87%	7%

MedTech stakeholders do not expect changes for PO1 compared to the status quo. Looking at PO2, respondents indicated a slight increase of fragmentation of HTA systems, convergence of methodologies and attractiveness of EU market. The attractiveness of the EU market is expected to go down, reaching its bottom for PO5. MedTech experts emphasised in the **focus group** that the reason for the expected unattractiveness is the fear of slower market access in particular for first movers/innovators and due to the fact that the legislation is not linked to pricing and reimbursement. Hence, it might impose additional work without resulting in a monetary benefit.

7.3.4.6 Further impacts

The study team also surveyed a few other parameters on how MedTech Industry could be affected by the various Policy Options. Those judged as less relevant are summarised in this section; detailed survey results can be found in Annex 26.

For the impact **'consumer and households'**, the number of health technologies assessed and the number of health technologies available on the European market, focusing on the availability of medical technologies for patients, were surveyed. Overall, MedTech indicated that PO1 and PO2 will not affect the number of health technologies assessed and available compared to the status quo to a great extent. For PO3 to 5 stakeholders expected a slight increase in the number of health technologies assessed, but with little variance compared to the status quo. Turning to the number of health technologies available, representatives of the medical technologies' sector expect availability to decrease for all options including a legislative framework (PO3-PO5). This might relate to an expectation of joint processes increasing the time s to market access.

For the impact **'International Trade'**, the survey aimed to assess the effect of the different Policy Options on international trade related to Pharmaceuticals and medical technologies, specifically the effect on the related import and export possibilities for products. With regard to medical technologies, Europe is one of the biggest markets, comprising of over 500,000 different registered products and showing an increased number of MD patent applications since 2004 (58). Responses by the medical device sector indicate that all options from PO3 onwards are expected to have a negative effect on international trade, while for PO1 and PO2 no effect is anticipated. This corresponds to the stated assumption that all options from PO3 onwards are considered to raise the level of utilization regarding HTA in Europe when it comes to Medical Technologies, which is seen as an additional burden by the MedTech sector. According to our analysis, a potential legislation in the field will, however, be of less relevance for investors than the two new EU regulations that are basically preparing the ground for more HTA processes in Europe since they also call for more evidence generation.

Regarding **'employment'**, the effect of the different Policy Options on the number of personnel employed, including consultants who are involved in HTA activities was assessed. Skilled staff are needed for all industry sectors, thus also MedTech to prepare value / submission dossiers. Industry experts in charge of HTA need an understanding about the methods and requirements defined by the assessing bodies in order to successfully prepare the evidence and dossiers needed. Additional to the scope of activities, the organisational capacity is decisive for performing HTA activities in-house or contracting consultants, both for HTA bodies as well as manufacturers.

Survey results indicate a slight increase in employed personnel for PO2, while the level of employment is expected to decrease from PO3 onwards. This was explained by the expectation of MedTech representatives that more tasks will be done at a central level which is in line with other fields where a centrally organised process reduced the capacities needed at regional or local levels. Still, it is possible that the type of expertise

needed will change (e.g. more communication expertise or behavioural science for Early Dialogues) to account for new developments in HTA for Medical Technologies.

However, we do not agree with this expectation as HTA activities are not very common in the MedTech sector yet. Therefore, the number of people dealing with HTA-related activities should rather increase across Policy Options especially since more joint activities in the field of medical devices and IVD are foreseen from PO4 onwards.

For the impact **'macroeconomic environment'**, we aimed to assess the effect of the different Policy Options on economic growth and labour market, the health care sector including health care providers and the health technology sector.

No changes for the macroeconomic environment are expected for PO 1 compared to the status quo while for PO2 a positive effect is stated. On the contrary, negative effects are expected from PO 3 onwards with PO 5 seemingly to have the most negative effect. This might relate to the establishment of a legislative framework from PO3 onwards and the increase of mandatory elements for joint cooperation, which are generally speaking not preferred by MedTech. Despite thorough literature search and expert interviews, we could not find enough evidence to verify or falsify the assessment of MedTech sector representatives.

The **'sustainability of health systems'** was surveyed by assessing the effect of the various Policy Options on the financing of expensive treatments with little or no added value and the negotiating power of MS in setting prices. With respect to the sustainability of health systems, respondents from the MedTech industry expect the negotiating power of MS in setting prices to remain unchanged. On the contrary, they responded that less expensive treatments with little or no added value are funded from PO3 onwards; a statement that we challenged. Following that, industry representatives responded that, due to the weak link between health technology assessments and pricing and reimbursement decisions for medical technologies, the changes in the HTA processes would not affect the negotiating power or the funding of technologies. We argued against that, e.g. strengthening HTA research and developing common tools in this field are likely to have an impact on national reimbursement procedures, as the example of the Pharmaceutical market shows.

For the impact on **'Public Health'**, the estimated effect of the Policy Options on two indicators (overall public health and the availability of health technologies on the market) was investigated. Relating to the effects of the POs on public health from the perspective of the medical device industry, a negative effect is estimated for all Policy Options featuring a legislative framework, while for Policy Option 2 assessments of MedTech go in the opposite direction. These effects are mainly driven by the estimated negative effect for the availability of health technologies while no impact on overall public health is foreseen. The latter finding is challenged by us because more stringent assessment procedures will definitely have a positive impact on the quality and safety of medical devices and IVD, which furthermore is also one of the objectives of new regulations in this field.

On the subject of **'Governance, participation and good administration'**, we looked how the POs might affect the involvement of different stakeholders in HTA processes, the responsibilities of Public Administrations in the field of HTA at MS level, the uptake of joint outputs, the resource efficiency of HTA processes in general and the sustainability of European cooperation in the field of HTA.

Survey results from the Medical Device industry indicate a positive effect for PO2 and negative effects for the subsequent Policy Options, as is the case for most options. Almost no change is foreseen with regard to the responsibilities of MS when it comes to PO3 to PO5, while an increase is expected for PO2. The other indicators were rated similarly, with a perceived increase for PO2 per indicator and an expected decrease from PO3 on. From the perspective of the MedTech industry, only the introduction of PO2 would result in positive effects, while negative effects are expected from PO3 onwards, thus including all Options that cover a legislative framework. **No explanation was given, but it seems that all 'legislative' options were downgraded by MedTech industry.**

The impact **'Access to social protection and health systems'**, focused on access to innovative treatments. Responses given by the MedTech industry indicate that PO3, PO4 and PO5 are perceived to have a negative effect on access to innovative treatments, which increases in magnitude from PO3 to PO5. On the contrary, almost no effect is expected for PO1 and PO2. The anticipated hurdles for the medical device industry and uncertainty about future evidence requirements might play a role in this context.

7.3.4.7 Concluding remarks for MedTech Industry

Results for MedTech Industry are very different compared to the Pharmaceutical Industry. All data collected point towards a negative effect of all Policy Options with the exception of Policy Option 2 (Table 65) for this sector.

In many discussions, by interview and in the focus group meeting, MedTech representatives explained some of the facts they gave. Policy Options covering a legislative framework are expected to function as a driver for further increase of HTA activities in MS, which industry perceived as a very important element of unpredictable change and a major driver of cost.

Table 65: Overview of relevant impacts for MedTech Industry

Impacts	Policy Option 1	Policy Option 2	Policy Option 3	Policy Option 4.1	Policy Option 4.2	Policy Option 5
Costs (EC 1)*	0(+)	0(-)	--	-	-	-
Administrative Burden (EC2)	0(+)	+	-	--	--	--
Competitiveness of EU health technology sector (EC 3)	0	+	--	--	--	--
Innovation and research (EC 4)	0(-)	+	--	-	--	--
Functioning of the internal market and competition (EC 6)	0	0(+)	0(-)	0	-	-

(*) Inverted: - means that cost would go up, + means that cost would go down.

Legend: + positive effect, - negative effect, 0 neutral (+) or (–) representing the direction of results, as indication even if the expected effect is low)

Since HTA activities currently do not play a major role in the medical technologies' market access path, any change is expected to increase burden on MedTech companies. This subsequently could also reduce the attractiveness of the European market and potential delays in first revenues are feared because currently there are only very few pre-market obligations in place. One key impact is the expected decrease in competitiveness and innovation. According to the focus group and the interviews, this is due to the perceived unpredictable change in the market access path

(also attributed to the two new EU Regulations on Medical Devices) ([128]), resulting in yet an additional new administrative hurdle, which are typically the strictest for the first movers (innovators).

Summarising, Med Tech respondents expect **any – from their perspective additional - regulatory approach and mandatory uptake at EU level to increase the costs and reduce the predictability of the market for medical device and IVD companies**. This relates to the fact that standardised HTA processes are far less common for Medical devices (or currently only being developed) and is also linked to some uncertainties companies expect with the implementation of the new Medical Devices Regulations.

A particularly important aspect is the expected increase in costs for PO3 to PO5 driven by additional evidence generation, which however needs to be challenged. In our opinion, this could be largely overestimated by the respondents, due the low level of HTA experience in the MedTech Industry. Moreover, our cost calculations did not show a major cost increase for MedTech Industry on a unit base in the long run, provided that the number of joint outputs will increase. It, on the contrary, indicated that the MedTech industry might also benefit from the POs under consideration when it comes to costs (aggregated across Europe). Potential savings are especially noticeable for the POs with a legislative framework (PO 4.1, 4.2 and 5).

We concluded that the underlying negative association of yet another new legislative framework was subsequently leading to negative expectations for a number of indicators. This is why some of the results, e.g. the negative impact on costs, could be overestimated. Subgroup analysis was performed comparing SMEs to large companies, but no noticeable differences were identified in results across all impacts and POs. It has to be mentioned that the actual level of experience with HTA for the respondents from the MedTech sector is considerably lower than for the respondents from Pharmaceutical Industry. Whereas Pharmaceutical products have a well-established pathway from marketing authorisation to HTA evaluation, followed by appraisal and an established HTA process in a large number of European countries, medical devices and other technologies follow heterogeneous rules or processes regarding their evaluation. Follow-up questions were distributed to respondents from the MedTech survey, trying to capture the level of experience of survey respondents. However, only 31 out of 99 survey respondents replied to these follow-up questions, with 22 of these stated to have experience with HTA submissions and 9 declared to have no experience in this field. For those few companies, we saw no significant differences in their position.

Summarising, it seems obvious that **Med Tech needs another approach than Pharmaceuticals because of the peculiarities of the sector**. Option 4.1 and up appear currently not applicable, but the **further development and use of methods and common tools that would enable the same or similar level of assessment for MDs around Europe would surely be beneficial from a Public Health perspective**. Still, the time horizon for introducing the same standards for medical devices and other technologies should be longer than for Pharmaceuticals. A phased approach on the development and implementation of legislation seems more promising.

7.3.5 Patients and patient organisations

The stakeholder groups of patients and patient organisations are heterogeneous and their involvement in HTA processes remains limited so far, taking place mainly in the appraisal

([128]) https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/revision_en

phase (51). Information presented here is derived from literature and expert talks as the participation in the survey was far too low to be analysed by MCA.

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 of public health research, which includes research in HTA, is limited (72). Although HTA is a transparent method to support decision-making processes in public health, HTA research on, for example, prevention programmes or vaccinations tend not to reach decision-makers (73). The lack of information exchange and focus on HTA imposes additional barriers for patients. To be better acknowledged by decision-makers, HTA methods should include other outcomes such as differences in access to health care or effects on patients' social environment, which are important factors from a patient perspective (74). Moreover, accelerated HTA processes would lead to faster patient access (34) in case of favourable assessments.

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 processes regarding reimbursement. On the other hand, HTA is a tool to limit continued use of health technologies with little or no added value (43). Thereby it also restricts access to health technologies but improves quality of care and the efficient use of health care resources (43). Furthermore, involvement of patients in health policy processes is important and potential related benefits resulting from increased involvement could top related risks caused by an insufficient level stakeholder involvement (75).

The importance of HTA from a patient perspective and its impact on patient access is illustrated by the observation that patients tend to experience greater disadvantages from losing access to health technologies (e.g., caused by delisting) compared to denying access to health technologies (43). Concluding, HTA has an indirect effect on patients which should be considered in future cooperation models in the field of HTA.

In order to assure consideration of all relevant stakeholder perspectives, studies suggest an inclusion of all relevant stakeholders in assessment processes, especially of those not regularly included in assessment processes so far. Positive developments were already 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 INAHTA agencies (49). However, patient involvement in general and the scope of patient involvement still varies widely across Europe (50) and several points for improvement remain (51). Especially, a clear definition of the role of patient involvement in HTA (51) is necessary to increase the efficiency of such processes.

Relating to the survey first, respondents indicated following aspects for consideration:

- 'Co-operation would increase the reliability of HTA assessments and safety of new technologies'. (general stakeholder comment)
- 'EU cooperation on HTA is needed also for hospital-based HTA, rehabilitation and prevention programmes, disease management programmes, organisational and supportive procedures (including surgeries) as well as ethical use of health technologies (e.g. with respect to end of life, assisted reproduction, prenatal diagnosis, health data) and, comparisons between Pharmaceutical and non- Pharmaceutical interventions'. (general stakeholder comment)
- Predictability of HTA systems is a key issue; full integration will strongly influence predictability.
- Policy option 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.
- Anticipated structures, i.e. PO 1 to 5, could limit the number of technologies available but the health care sector would be more harmonized and uniform, thus supporting availability of safer and more efficient technologies

Second, stakeholders contacted in the follow-up provided additional information on the current situation of patient involvement in HTA processes and key points for future involvement. Interview partners indicated that patient involvement in HTA varies considerably between countries (see also Scott and Wale, 2017) (51). Countries with more advanced HTA systems are more engaged to increase patient involvement and include their perspective adequately. Besides specific countries, patient involvement in the EUnetHTA JA 3 aims to improve patient involvement, but faces restrictions due to limited financial resources. Overall, there are clear signals to improve patient involvement in HTA processes throughout Europe (see also Scott and Wale, 2017) (51).

Stakeholders mentioned the following key points for future cooperation in HTA:

- Conflict of interest: The independence of HTA processes must be ensured and the influence of stakeholder groups should be limited; thus, future cooperation in the field of HTA should be mainly funded through public sources;
- Improving the transparency of HTA processes;
- Ensure patient involvement, including development of best practice design;
- Matching patients with respective topics most expedient;
- Patient involvement in Early Dialogues (enhances predictability);
- Inclusion of patient relevant outcomes including well-being.

From the consumer perspective, any stronger, more binding collaboration between MS will reduce duplication of work, increase the number of outputs and transparency of results and thus is likely to be beneficial for European patients.

Patient representatives indicated that **EMA and future HTA cooperative models should closely work together, but in an independent and thus separate way.** The development of common methodology, which needs to meet ethical requirements, is vital to include all relevant aspects. Implementation of a life-cycle approach would support evidence generation throughout the whole life cycle of a health technology, specifically whenever additional evidence is required. Regardless of the specific characteristics of the implementation structure, sufficient funding and investments were highlighted as necessary to adapt sustainable and transparent HTA processes.

We see a number of indications that **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, specifically for innovative treatments. Uncertainty surrounding the prescription of (innovative) products would be lower and support health professionals to ensure appropriate and secure use of health technologies. Moreover, health risks for patients would be lower through improving access to assessed (innovative) health technologies.

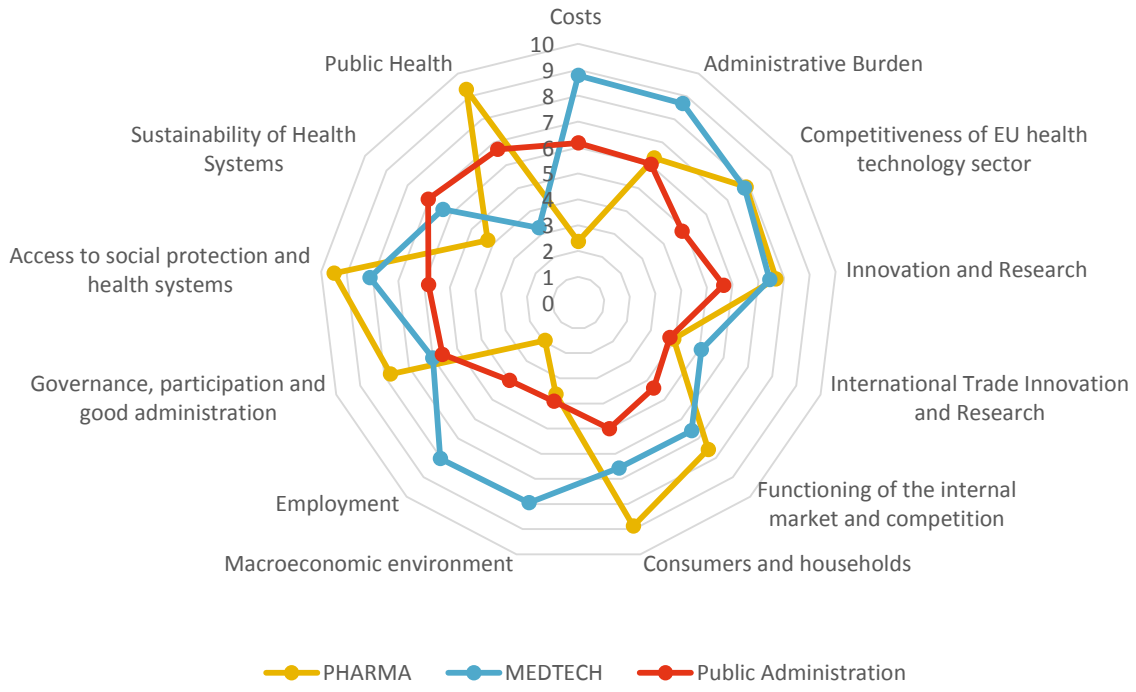
Overall, increased patient empowerment might affect public health in a positive manner. Specific stakeholder groups such as health professionals and patients could further benefit through transparent assessment processes and improved monitoring of health technologies. Therefore, all relevant stakeholder perspectives should be considered for final assessments of Policy Options. Irrespective of assessment results, a **mandatory legislative framework offers the opportunity to reduce selective assessment of health technologies and guarantee transparent processes as well as easier transferability to national systems**. Due to the currently low involvement of patients and scarce publicly available information regarding HTA results, this framework has the potential to permit patients to follow current developments. Continuous consultation of patients in health policy processes might not only optimise respective processes, but also result in greater understanding of different stakeholder groups positions (75), i.e. patients get better insights in decision-making processes and vice versa.

7.3.6 Rating on the relevance of impacts

Within the online survey, respondents were asked to rank the relevance they attribute to the impacts on HTA cooperation after 2020 on a scale from 0 to 10 (Q1 in Part 4 within the questionnaire, see Annex 3 and 4).

Figure 56 displays the result of this exercise for each impact, split into Public Administration, Pharma and MedTech Industry, which illustrates that the **relevance of the respective impacts is divergent between the stakeholder groups.** This is especially apparent for Costs, which is considered to be very relevant by MedTech companies, while Pharma companies only attribute a low relevance to the effect of this impact.

Figure 56: Relevance of impacts by respondent group



Source: GÖ FP / LSE survey 2017

7.3.7 Data plausibility check

An additional plausibility check for the data gathered through the survey and used for analysing the different impacts of the Policy Options was performed. This check was done especially to account for possible differences regarding response behaviour in the three different stakeholder groups (Public Administrations, Pharma Industry, and MedTech Industry).

Four different additional checks were performed:

a. A test for elimination of duplicated responses to account for prearranged answers.
b. A comparison of usage of mode (most frequently appearing value in a data set).
c. A comparison of standard deviation between stakeholder groups, impacts and Policy Options.
d. A calculation of intracorrelation coefficients, describing how strongly answers in the same stakeholder group resemble each other.

The results from these data checks are described in the following subsections.

7.3.7.1 Test for elimination of duplicated responses

A **plausibility test was performed to check for the similarity between responses to the survey by stakeholder group** (Table 66) because the similarity of assessment by MedTech raised the suspect of strongly coordinated responses.

Table 66: Percentage of duplications in data sets (exactly matching responses)

Pharma Industry	MedTech Industry	Public Administration	All
2 out of 16	12 out of 99	0 out of 23	14 out of 138
12.5%	12.1%	0.0%	10.1%

Source: GÖ FP / LSE survey 2017

For Public Administration, no duplications of answers were found, though for several sub questions, answers coincided.

For both, Pharma and MedTech, around 12% of answers were found to be complete matches, meaning that all answers for all sub questions included the same values.

For the whole survey, answers taken into account for analysis of the percentage of similarity amounted to **around 10 percent of all responses** (138 responses taken into account in total).

Table 67: Mean of all answers before and after elimination of duplicates

Means	Pharma Industry	MedTech Industry	Public Administration	All
Before elimination	3.46	3.63	NA	NA
After elimination	3.56	3.67	NA	NA

Source: GÖ FP / LSE survey 2017

Even though this might appear to be a non-negligible fact, the question is whether this was due to pre-agreed answers or simply because of similar assessments by stakeholders. To find out if duplicate answers had an impact on the result, those exactly matching responses were eliminated for testing. **A comparison between the means of all questions before and after elimination of duplicates showed that there is only a very low difference in the responses from the Pharma and MedTech industries, irrespective if duplicate answers were eliminated or not** (Table 67). For Public Administration, no duplicates were found at all. Subsequently also similar assessments were considered for our analysis.

7.3.7.2 Comparison of usage of mode

The mode is the most frequently appearing value in a data set (which could be every value on the scale of -100 to +100). The percentage of usage of mode can also be used to analyse how 'aligned' answers of the respondents to the questionnaire were. The overall percentage of usage of modes is 69% for Pharma Industry, 52% for the MedTech Industry and 32% for Public Administration (see Annex 22 for further details).

Answers from the Pharma Industry show comparatively high percentages of usage of mode (69%, expressing how often the mode was stated per impact). This shows that respondents of the Pharma Industry often assessed Policy Options in a similar way. Answers from the MedTech Industry show slightly lower percentages of usage of mode (52%). Respondents from Public Administration seemed to assess Policy Options the least alike. This is most probably also due to the fact that respondents from Public

Administration represented different countries and therefore different HTA process characteristics.

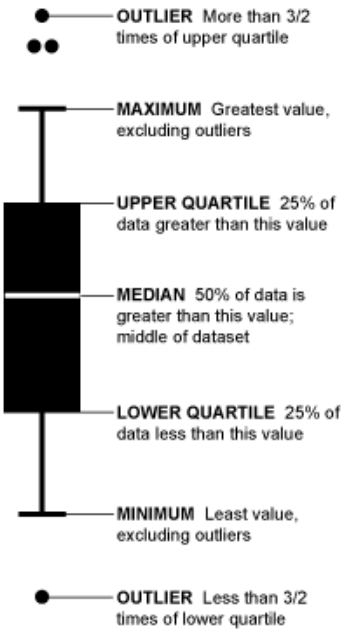
7.3.7.3 Comparison of standard deviation

Another supplementary data analysis is based on the comparison of standard deviation. These were sorted and compared by:

- Stakeholder group (Public Administration, Pharma Industry and MedTech Industry)
- Policy Options (PO1, PO2, PO3, PO4.1, PO4.2, PO5)
- Impacts (EC1-EC8, SH1-SH5)

As display format box-plots were chosen for the different elements, see Figure 57.

Figure 57: Box-plot elements

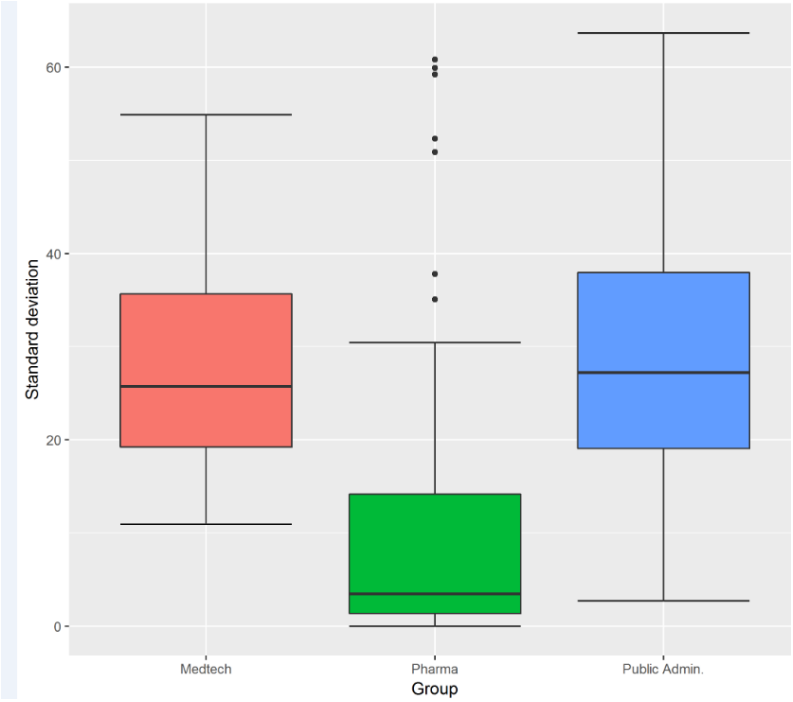


Source: Flowing Data

For the interpretation of the results following statements are relevant:

- The lower the LEVEL of the median, the lower the mean variance of answers from the different respondents in the stakeholder group.
- The lower the SPREAD of standard deviation, the lower the differences in variance between answers from different respondents in the stakeholder group.

Figure 58: Standard deviation by stakeholder group

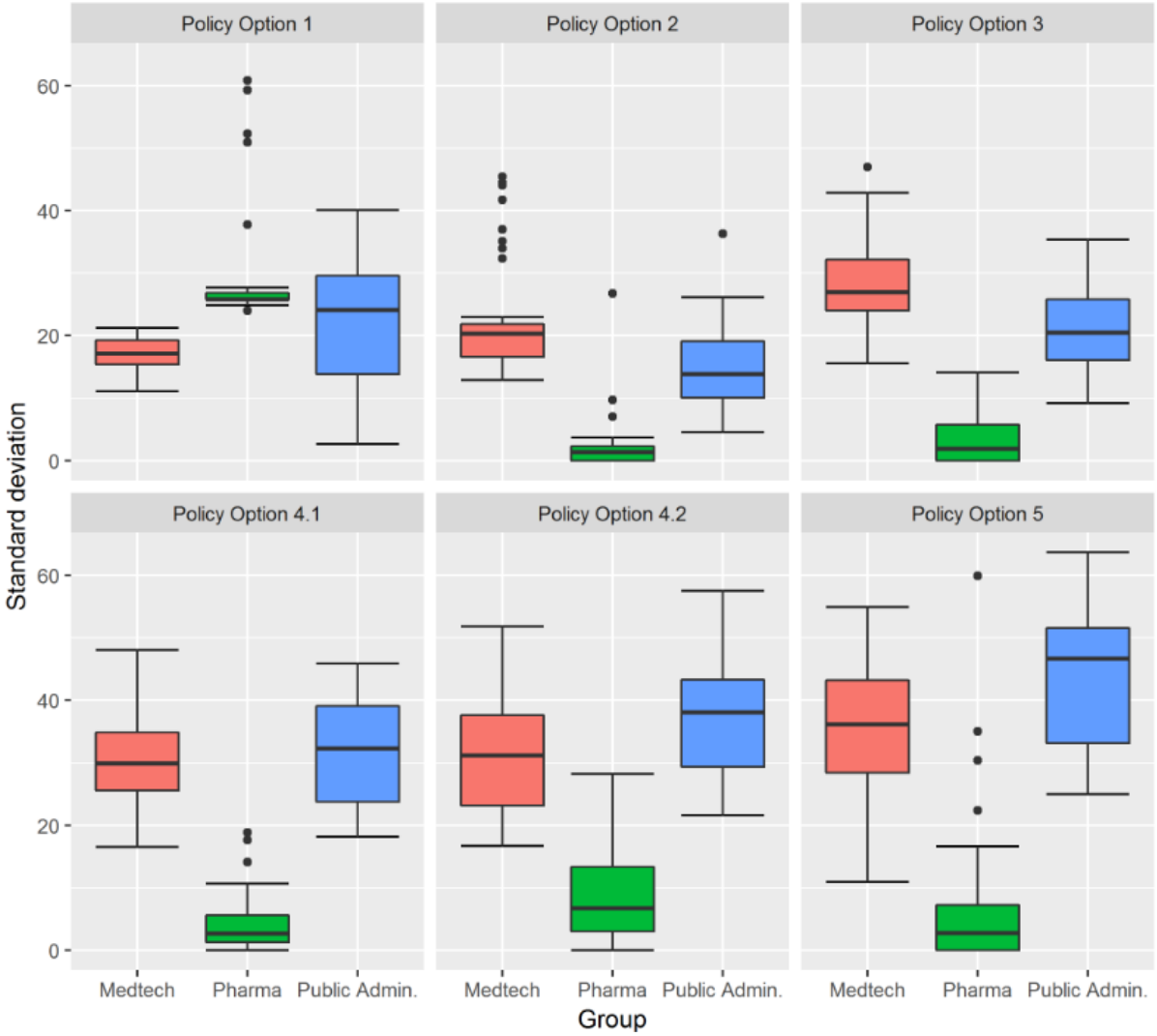


Source: GÖ FP / LSE survey 2017

There is comparatively low standard deviation in the Pharma Industry stakeholder group, suggesting a low variance in answers from different respondents. The medians for the standard deviation for MedTech Industry and for Public Administration are higher and close to each other. There is respectively more variance in answers from the different respondents in each stakeholder group. For Public Administration, variation in standard deviation is higher, meaning that standard deviation between single answers varies to a higher extent. Even if mean standard deviations from around 25 seem to be non-negligible, it is to be reminded that the scales provided within the questionnaire range from -100 to +100 and respondents within the Public Administration stakeholder group again represent different countries and therefore different HTA process characteristics.

Standard deviations were further compared not only by stakeholder group but also by Policy Option (see Figure 59). Lowest standard deviation was found again for the Pharma Industry for all Policy Options except Policy Option 1. Standard deviation for the MedTech Industry increases with ascending Policy Options. The same observation can be made for the Public Administration stakeholder group of (except Policy Option 1). This seems to represent the fact that assessments for Policy Options closer to the status quo are probably easier to picture (with the exception of Policy Option 1 for Public Administration, which could be argued with the different systems of HTA represented in the survey).

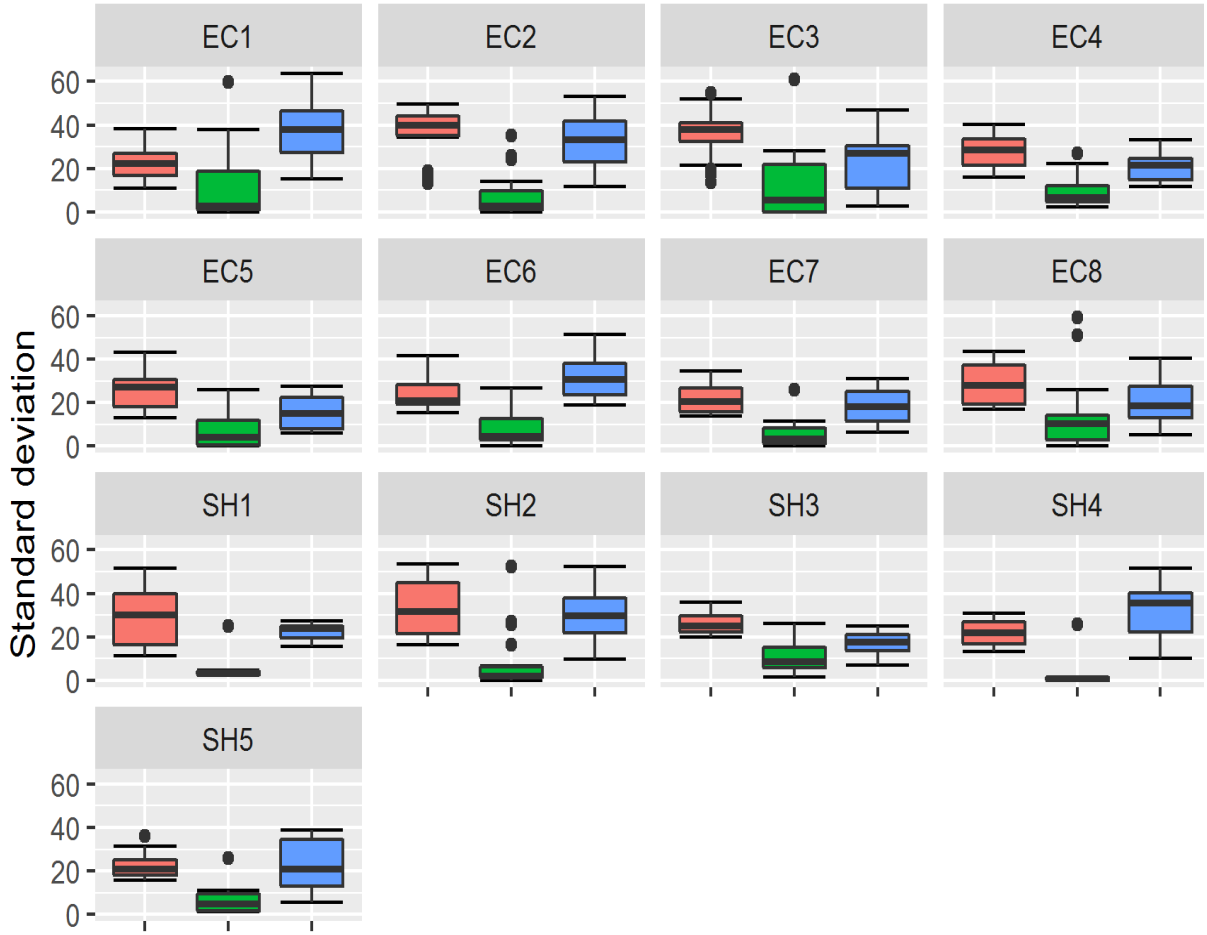
Figure 59: Standard deviation by stakeholder group and Policy Option



Source: GÖ FP / LSE survey 2017

Finally, standard deviation was compared by impact and stakeholder group (see Figure 60). Besides the comparatively lowest standard deviations for Pharma Industry for all impacts, no further pattern could be recognised through this additional itemization.

Figure 60: Standard deviation by stakeholder group and impact



Source: GÖ FP / LSE survey 2017

7.3.7.4 Calculation of intracorrelation coefficients

As a fourth and final test for plausibility of data, a calculation of **intracorrelation coefficients** (ICC) for each stakeholder group was performed. This coefficient describes **how strongly units in the same group resemble each other**. It is zero if no systematic resemblance between respondents and answers can be found and one if there is complete resemblance between respondents and answers. Figure 61 shows the calculated ICCs for the three stakeholder groups.

Figure 61: Intracorrelation coefficients (ICC) per stakeholder group

	Pharma	Medtech	Public Administration
ICC	0.18	0.02	0.04
Lower Confidence Interval	0.10	0.01	0.02
Upper Confidence Interval	0.35	0.03	0.08

Source: GÖ FP / LSE survey 2017

The 'highest' ICC was found for answers given by respondents of the Pharma Industry. This also corresponds well to the findings in the previous sections. Nonetheless, there are very low ICCs for all stakeholder groups, leading to the conclusion that no systematic resemblance between respondents and answers could be found. **This means that similar answers are rather built on common assessment than concordance of answers.**

7.3.7.5 Conclusions

The data checks for robustness and validity of results show that there is a common view on the different Policy Options, but no intra-sectorial coordinated assessments could be verified. Therefore, survey results are considered robust and reliable.

7.4 Summary conclusions for effects of Policy Options

HTA is considered a valuable tool that can contribute to the sustainability of national health systems. Still, the generation of HTA outputs (namely Early Dialogues, REA and finally Full HTA reports with economic evaluation) is quite diverse in Europe, because HTA systems are fragmented.

To support MS activities in the field, the EC has set a number of steps, including the co-funding of in the meantime three Joint Actions in the field and the establishment of the HTA-Network of MS' competent authorities.

In 2016, the EC developed a number of so-called 'Policy Options' with the objectives to: 1) Ensure a better functioning of the internal market of health technologies and to 2) Contribute to a high level of human health protection, as stated in Article 168 TFEU and Article 35 of the Charter of Fundamental Rights.

The potential Policy Options (PO) reach from PO1 (No EU action after 2020) to PO5 (Legislation covering Joint work on full HTA (including REA) plus common tools and Early Dialogues), see section 4.2 for a detailed explanation.

For each of these POs, different combinations of **voluntary or mandatory** participation and uptake per joint output are possible (leading e.g. to a further differentiation of PO 4.1. and PO 4.2 in the analysis, depending if the national uptake of joint REA is voluntary or mandatory, see Table 7).

For organizing the creation of these joint HTA outputs, a number of different **organisational mechanisms** (so-called Business models) are conceivable, ranging from **MS-only project-based cooperation to a permanent secretariat in a new EU agency** (6.2.2.5).

This study investigated, based on the Better Regulation Guidelines (5), a number of economic and social health impacts (e.g., costs, administrative burden, innovation, employment, public health, see 6.2.1) in order to establish a comprehensive picture of how the different POs and Business Models under consideration would affect different stakeholder groups.

The analysis of impacts focused on three main stakeholder groups, i.e. **Public Administration**, **Pharmaceutical Industry** and **MedTech Industry** (see section 5 for data collection and section 6 for methodology) due to data availability. Whenever information was available the potential impact on patient groups were analysed as well ([129]). Health professionals were covered mainly in their roles in the abovementioned sectors, but could not be captured as separate group. Moreover, a cost prognosis on the different Policy Options was performed (section 7.2).

Information collected indicates that, for **Public Administration,** there will **be no major effects with regard to HTA-related processes for PO1 and PO2**. However, with **Policy Options covering a legislative framework (PO3-PO5), positive effects on**

([129]) These both groups hardly contributed to the survey, so findings were derived from other sources a/o indirectly

national Public Administrations are likely, which are amplified with each output that is covered by the legislative framework. This increase in positive effects with stronger and central governance can be related to the expectation that the uptake of joint outputs will increase with each subsequent Policy Option.

Apparently, the **number of evidence-based assessments available for decision-making can be increased** with joint outputs since potentially more health technologies could be covered due to the fact that single HTA bodies might not have the capacities to assess the same numbers per year. **Countries with less established HTA processes might especially profit from joint output,** in particular from **joint REAs**.

None of the Policy Options is estimated to have a substantial effect on the administrative burden of Public Administrations across Europe and no or only little effect on costs for HTA-related outputs were indicated in the online survey. This might relate to the fact that national processes will still remain in some way. However, some HTA bodies voiced the expectation that indeed a closer collaboration would lead to potential cost decreases, which was confirmed by our cost calculations. These indicate **potential savings across MS especially from PO4.1 onwards**.

For **Pharmaceutical Industry,** gathered information indicates no changes for PO1 and PO2, while **positive effects of Policy Options including joint work on REA at European Union level, namely PO3 and PO4, are stated**. These POs seem likely to lessen inefficiencies, increase the functioning of the internal market and reduce workload for the Pharmaceutical sector. Furthermore, an increase in predictability of HTA processes and requirements is expected, which is a very important factor for companies and their research and investment decisions.

The Pharmaceutical Industry **expects negative effects for PO5,** which includes a strictly mandatory and binding HTA process also covering Full HTA in Europe. Underlying reasons are mandatory joint economic evaluations, as foreseen in Policy Option 5, were 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. Especially **joint work on REA was repeatedly indicated to have the potential to reduce inefficiencies and diminish workload for the Pharmaceutical sector**.

With regard to costs for HTA processes, the respondents of the Pharmaceutical sector expect no major changes with the exception of PO5, where a substantial cost increase is anticipated. This relates to the fact that possible increases and decreases of cost components would level each other out according to discussions in a focus group.

Still, the results of our cost prognosis for 2021+ indicate that actual savings due to a reduction in duplicated assessments can be achieved for the Pharmaceutical Industry across Europe for all Policy Options. Potential savings are considerable higher in Policy Options that comprise both a mandatory production and mandatory uptake of joint REAs (PO4.2 and PO5). Options comprising a permanent secretariat and higher joint output lead to substantially larger savings as compared to the project-based cooperation (EUR 3.7 million in PO2 versus more than EUR 60 million in PO 4.2).

For the MedTech sector, information gathered reveal a **different picture**: MedTech industry perceived negative effects of all Policy Options except for Policy Option 2. This assessment is in our opinion related to the peculiarity of the Medical devices market. Whereas Pharmaceutical products have a well-established pathway from Marketing Authorisation to HTA evaluation and an established HTA process in a large number of European countries, medical devices, IVD and other technologies follow heterogeneous rules or processes regarding their evaluation. This is also reflected in the sample selected for the case study. Indeed, Pharmaceuticals were selected only if they had undergone an evaluation for the exact same indication across settings. In the medical device sample, there would be the same generic type, but with a different branded name or/and a

different manufacturer. Additionally, medical devices should have undergone an evaluation for the same disease area and not the exact same indication. This is because the market for medical devices is intrinsically different from that of Pharmaceuticals with a higher level of competition from market entry onwards. While HTA has been largely developed for Pharmaceuticals, there appears to be a need for adaptation and development of established HTA processes to the medical devices sector as well.

The **negative assessment of Policy Options covering a legislative framework** can be related to the expectation that this will function as a driver for an upsurge of HTA activities in MS. This was perceived as a very important element of unpredictable change and additional burden for the MedTech industry. This uncertainty was seen to subsequently lessen the attractiveness of the European market and potential delays in first revenues are anticipated due to the expected longer processes. Another key impact is the expected decline in competitiveness and innovation. According to MedTech Industry, this is caused by unpredictable changes in the market access path (also attributed to the two new EU Regulations on Medical Devices ([132]) and potential new hurdles, which are typically the most burdensome for the first movers (innovators).

A further important aspect is the expected increase in costs, driven by additional evidence generation. However, the **cost calculations within our study did not confirm the expectation of cost increase** for the MedTech Industry. On the contrary, findings indicate that the MedTech industry might also benefit from the 'tighter' Policy Options under consideration when it comes to costs (aggregated across Europe). Potential savings are especially noticeable for POs with a legislative framework (PO 4.1, 4.2 and 5). It thus seems that this impact is overestimated by the Med Tech industry, one identified reason being that the actual level of experience with HTA for the respondents from this sector is considerably lower than for the respondents from the Pharmaceutical Industry.

Table 68 allows a concise overview of the potential effects of the Policy Options – aggregated across all investigated impacts – for each stakeholder group. Green colours indicate positive and red colours negative perceptions based on the judgment of the study team, considering all collected evidence and information.

Table 68: Conclusion – Effect of Policy Options

Stakeholder group	Baseline scenario (PO1)	Project-based co-operation (PO 2)	MS/EU secretariat (PO 3)	Existing EU agency (PO4.1)	Existing EU agency (PO 4.2)	New EU agency (PO 5)
Public Administration						
Pharma						
MedTech						

Source: The authors

Overall, the estimated effects of the Policy Options as well as the perceptions and expectations regarding the future cooperation on HTA in Europe differ between the stakeholder groups:

- **For Public Administration,** POs providing a legislative framework for HTA cooperation in Europe (PO3 onwards) will potentially have a positive effect.
- **For Pharmaceutical Industry** POs with mandatory uptake of joint REAs will have a positive effect, while PO5 is considered unrealistic by industry representatives. In the view of the authors, working with common tools and technologies is important in the future, and there is sound evidence that more **joint REA will be beneficial.**
- **MedTech Industry** is in favour of voluntary Project-based cooperation (PO2), as **any legislative framework is perceived as additional burden with negative effects**. This relates to the fact that HTA is not as common and related methods are not as developed for the medical devices sector as compared to the Pharmaceutical sector. Moreover, market access pathways for medical technologies are different, with less connection to HTA assessment. While these are issues that have to be taken into account when establishing a system for joint output production, ultimately positive effects regarding the safety of medical devices and increased transparency of processes are expected by authors. However, because of the peculiarities of the market and the yet unknown effects of the two new regulations in the field a **different timeline for implementing mandatory joint work, as compared to the Pharmaceutical sectors, is advisable.**

Future effects on the stakeholder groups depend on the final **structure and specificities of the joint cooperation.** Success factors identified for sustainable joint cooperation include:

- Use of common tools and templates
- Business models with stronger governance
- Cross-country expertise and inputs
- Mandatory uptake of joint outputs

Those success factors are closely interrelated. Sufficient institutional capacity and strong governance is helpful to provide timely assessment processes and to allow for faster market availability of health technologies, correspondingly, adequate expert input is needed to ensure the quality of assessments performed, thus increasing the efficiency of processes for all stakeholder groups involved (40).

These factors will be relevant for setting up future cooperation on HTA. A legislative cooperation can especially create institutional capacity for this cooperation and expertise can be bundled. Our analysis indicates that processes can be set up more efficiently when they are coordinated and facilitated by one institution, since all relevant information are in one hand, thus leading to savings for current stakeholders.

Potential savings are considerably higher in policy options that comprise both a mandatory production and mandatory uptake of joint REAs and Joint HTA (PO4.2 and PO5). Options comprising a permanent secretariat or a new Agency (which is linked to higher joint output) lead to substantially larger savings as compared to project-based cooperation for European industry (in total nearly EUR 4 million across all countries in PO2 versus around EUR 70 million with PO 4.2 and EUR 77 million in the case of PO 5). The results of the cost prognosis being impressive, we need to point out that there is still need for additional data and discussions to verify the informed assumptions that were made for the cost prognosis.

8 Key findings

- Overall, the vast majority of clinical evidence considered by HTA bodies in the case of Pharmaceuticals comes from phase III clinical trials and less so from phase II trials. The latter are increasingly used in those cases where the production of evidence from phase III trials is challenging, or in those circumstances where the likely clinical benefit is considered significant and the treatment would merit conditional marketing authorisation (CMA). Only a fraction of the clinical evidence is considered related to other types of clinical evidence (extension trials or observational studies). It is thus reasonable to suggest that there is a **fair amount of duplication taking place as the evidence considered across settings is by and large the same.**

- There is a clear difference in the preferences of HTA bodies for the type of evidence required for Pharmaceuticals compared with medical devices/technologies and 'other technologies'; this is partly driven by what is feasible in the context of either medical devices or 'other technologies' and is highlighted by the high proportion of retrospective studies and safety studies (in the medical devices sample) and literature reviews (in the 'other technologies' sample).

- In terms of economic evidence, although there are both similarities and differences across MS in terms of preferences in approach, modelling or models, one issue worth noting was that across MS, and for those MS pursuing economic evaluation, in **68% of all cases, the comparator was the same across HTA bodies.**

- From an industry perspective, harmonisation of evidence requirements, if accompanied by MS acceptability, would facilitate easier investment decisions. Additionally, an 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 beneficial, and could be facilitated by early advice and greater clarity on payer expectations. Finally, harmonisation of evidence requirements would give the EU a stronger influence on clinical trial development.

- **The Pharmaceutical Industry is in favour of options covering mandatory uptake of joint REAs.** Due to the currently fragmented HTA systems, they will benefit from a reduction in submissions and better predictability across the EU. It might be necessary to relocate staff to a central level, but the number of staff is expected to remain stable.

- **Both the MedTech and the Pharmaceutical Industry perceive Full HTA at EU level as not meaningful, despite cost estimates showing that industry in general could benefit from additional savings compared to REA only.** That, however, very much depends on the nature of topics that are chosen for coverage under Full HTA. Experience with Full HTA at EU level so far is limited. The additional domains of Full HTA (economic, organizational, legal, ethical and social aspects) tend to contain many 'non-transferable' issues; to that end, they need to be substantially adapted at national level. These points may explain in part the perceived scepticism on the industry side.

- **The MedTech industry sees the most challenges when introducing a legislative framework for future cooperation in HTA at EU level.** Currently, the MedTech industry faces lower regulations regarding market access for their products due to the significant heterogeneity of products, pointing out the great fragmentation within the sector. Two recently established regulations on medical devices at EU level aim to better govern the heterogeneous market. Because the MedTech industry has little experience with HTA processes, they expect a massive burden on procedures and processes and slower market access for their products.

- **Synergies for Public Administration can be expected since potentially more assessments will be available for decision-making.** One HTA body might not have the capacity to conduct all assessments decision-makers would need in their country. Additionally, with potential future growth in patient mobility in Europe, as addressed by the Cross-Border Healthcare Directive, it can be seen as advisable to base decision-making on the same evidence.

- **General success factors identified for sustainable joint cooperation include (1) the use of common tools and templates, (2) business models with stronger governance structures (3) timely assessment processes (4) cross-country expertise and inputs and (5) mandatory national uptake of joint outputs** ([130]), **all of which are inter-related**. The latter applies in the Pharmaceutical sector only. Using common tools and templates facilitates joint work while sufficient institutional capacity and strong governance form the basis to provide timely assessment processes. Timely assessment is important to ensure that uptake can occur at a time when the results are relevant in national settings. Adequate expert input is needed to ensure the quality of assessments performed, thus increasing efficiency of process for all stakeholder groups. Finally, mandatory uptake of results is important and ensures that the purpose of joint work is met. These factors will be relevant for setting up future cooperation on HTA, although the peculiarities of the MedTech sector may need to be taken into account and success factors may be more relevant for HTA in Pharmaceuticals.

- **Legislative cooperation can create institutional capacity for HTA cooperation and expertise can be better streamlined**. Our study findings suggest that processes can be set up more efficiently when they are coordinated and facilitated by one permanent institution, since all relevant information is centralised, expertise can be streamlined and overall savings can materialise.

- **Potential savings are considerably higher in POs that comprise both a mandatory production and mandatory uptake of joint REAs and Joint HTA (PO4.2 and PO5)**. Options comprising a permanent secretariat or a new Agency, which is linked to higher joint output, lead to substantially higher savings in the long run as compared to project-based cooperation (in total nearly EUR 4 million across all countries in PO2 versus around EUR 70 million with PO 4.2 and EUR 77 million with PO 5). Regarding the results of the cost prognosis, there are uncertainties in data collection, as is clearly outlined in the corresponding sectors of our study.

- **Improved 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 the evidence-base for decision-making across the EU, especially in MS where HTA is not well-developed, thus also contributing to a decrease in cross-country inequalities.

- From a **patient perspective,** future EU cooperation in HTA POs with mandatory participation and uptake **will increase availability of safe and effective Pharmaceuticals and medical technologies and ensure standardised monitoring of health technologies prior to market access**. Transparent and independent HTA processes require consideration of all relevant stakeholder perspectives to increase efficiency and prevent conflict of interest. Sufficient financial resources are vital to

([130]) Up-take concerns using or considering the results and findings of the HTA cooperation, reaching from jointly developed submission templates to outcomes in full HTA. The subsequent pricing and reimbursement decision remains purely on national level.

establish a respective mechanism. Besides required investments, stakeholders should draw their attention to the potential return on investment different mechanisms offer.

- Previous patient involvement in HTA processes is characterised by good intentions on the part of involved stakeholder groups, but successful implementation was limited so far by either the extent or the role of involvement. There are clear signals both from Public Administration and the Pharmaceutical Industry **to improve and standardise patient involvement in HTA processes. Stronger governance regarding HTA assessment might positively influence patient involvement**. Overall, sustainable and transparent long-term cooperation in the field of HTA offers the potential to prevent selective assessment of Pharmaceuticals, reduce availability of health technologies with little or no added value and improve the accessibility of publicly available information.

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