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Clara Monleón Bonet

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**THESE de DOCTORAT DE
L'UNIVERSITE CLAUDE BERNARD LYON 1**

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**HTA DELIBERATIVE PROCESSES IN
WESTERN EUROPE : ANALYSIS OF THE
INFLUENCE OF IMPLICIT FACTORS AND
DEVELOPMENT OF A CHECKLIST TO
REVEAL THEM**

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« Pas de patience, pas de science », JP. Jarroux

INDEX

INDEX	4
LIST OF TABLES	8
LIST OF FIGURES	9
LIST OF PUBLICATIONS	10
LIST OF ABBREVIATIONS	11
ABSTRACT	14
RÉSUMÉ.....	15
INTRODUCTION.....	16
CHAPTER 1: INTRODUCTION TO HEALTH TECHNOLOGY ASSESSMENT: CONTEXT, ORIGINS AND PROCESSES	20
1. Context of Health Technology Assessment	20
1.1. Origins, purpose, and evolution of HTA.....	20
1.2. Phases of the HTA within the healthcare decision-making process	23
1.3. Technologies subject to assessment	25
2. Health Technology Assessment process in the countries of scope	27
2.1. Geographical scope of this PhD thesis	27
2.2. France	27
2.2.1. General concepts of the healthcare system.....	27
2.2.2. Health Technology Assessment bodies.....	27
2.2.3. Health Technology Assessment process	30
2.3. United Kingdom.....	32
2.3.1. General concepts of the healthcare system.....	32
2.3.1.1. Health Technology Assessment bodies.....	32
2.3.1.2. Health Technology Assessment process	33
2.3.2. Scotland.....	36
2.3.2.1. Health Technology Assessment bodies.....	36
2.3.2.2. Health Technology Assessment process	36
2.4. Germany.....	37
2.4.1. General concepts of the healthcare system.....	37
2.4.2. Health Technology Assessment bodies.....	38
2.4.3. Health Technology Assessment process	38
2.5. Italy.....	39
2.5.1. General concepts of the healthcare system.....	39
2.5.2. Health Technology Assessment bodies.....	40

2.5.3.	Health Technology Assessment process	40
2.6.	Spain.....	42
2.6.1.	General concepts of the healthcare system.....	42
2.6.2.	Health Technology Assessment bodies.....	42
2.6.3.	Health Technology Assessment process	44
2.7.	Comparison between countries	45
3.	Deliberation in Health Technology Assessment	48
4.	CONCLUSIONS OF CHAPTER 1.....	49
CHAPTER 2: IMPLICIT FACTORS AND THEIR INFLUENCE IN THE HEALTH TECHNOLOGY ASSESSMENT DELIBERATIVE PROCESS.....		51
1.	Biases in human decision-making.....	52
2.	Biases in Health Technology Assessment.....	54
3.	Diverging Health Technology Assessment recommendations.....	56
3.1.	Overview	56
3.2.	Examples illustrating the presence of other factors influencing the HTA recommendations	57
3.2.1.	Heterogeneity in the decision-making factors and in the tools to address uncertainty.....	57
3.2.2.	Country-specific examples.....	58
3.2.3.	Contextual factors	60
4.	Definition of “implicit factors”	64
5.	Systematic literature review on the implicit factors influencing Health Technology Assessment deliberative processes in Europe	66
5.1.	Introduction	66
5.2.	Materials and methods	68
5.2.1.	Eligibility criteria	68
5.2.2.	Information sources and search strategy	68
5.2.3.	Study selection	69
5.2.4.	Citations’ and full-text screening by eligibility criteria	69
5.2.5.	Data Extraction and Analysis.....	70
5.3.	Results	70
5.3.1.	Articles description	70
5.3.2.	Articles description	71
5.3.3.	Articles suggesting a framework to address implicit factors	75
5.3.4.	Categories of implicit factors	78
5.4.	Discussion	85
5.5.	Strengths and limitations.....	87

6. Implicit factors influencing the Health Technology Assessment deliberative process in Europe: decision makers' perspectives.	88
6.1. Introduction	88
6.2. Methods	89
6.2.1. Study participants and geographic scope	89
6.2.2. Data collection.....	92
6.2.3. Data analysis	93
6.3. Results	93
6.3.1. Perceptions on the HTA deliberative processes: analysis across countries	94
6.3.1.1. Main explicit and implicit factors influencing the HTA deliberative process	94
6.3.1.2. Degree of influence of the implicit factors on the Health Technology Assessment deliberative process	97
6.3.1.3. Attributes of the Health Technology Assessment deliberative process	100
6.3.2. Recommendations on how to improve the Health Technology Assessment deliberative process.....	101
6.4. Discussion	106
6.5. Strengths and limitations.....	113
6.6. Conclusions	114
7. CONCLUSIONS FROM CHAPTER 2	115
8. ANNEXES FROM CHAPTER 2.....	117
CHAPTER 3: A SOLUTION THAT ACCOUNTS FOR IMPLICIT FACTORS IN THE HTA DECISION-MAKING	138
1. Introduction.....	138
2. Targeted literature review	140
2.1. Methods.....	140
2.1.1. Eligibility criteria	140
2.1.2. Article selection.....	141
2.2. Results	141
3. Appraisal of the checklist from the joint HTAi/ISPOR Taskforce	142
3.1. Methods.....	142
3.2. Results	142
3.3. Discussion	146
4. Development of the RELIANT checklist: a tool to address implicit factors in the HTA deliberative process.....	147
4.1. Methods.....	147
4.1.1. Development of the first version of the checklist	147
4.1.2. Content validity phase.....	148
4.2. Results	150

4.2.1.	Characteristics of the checklist.....	150
4.2.2.	Feedback from the group of experts.....	155
5.	Discussion	164
6.	Conclusions from Chapter 3.....	169
GENERAL CONCLUSIONS		171
BIBLIOGRAPHY		176

LIST OF TABLES

Table I. Comparison of the different HTA agencies in the countries of scope.....	47
Table II. Cognitive biases.....	53
Table III. Overview of contextual factors used in HTA decision for nivolumab, benzodiazepines and smoking cessation therapies (110).....	60
Table IV. Articles proposing a concept as a way to address the research question.	74
Table V. Articles proposing a framework as a way to address the research question.	77
Table VI. Implicit factors identified in the literature: frequency of mention and impact in the HTA deliberative process.....	79
Table VII. Profile characteristics of the study participants.....	91
Table VIII. Profile characteristics of the experts who were contacted but did not participate in the interviews.	92
Table IX. Main explicit and implicit factors influencing the HTA deliberative process.....	95
Table X. Degree of influence of the implicit factors on the HTA deliberative process across countries (median and interquartile range).....	99
Table XI. Quantification of a set of attributes in the HTA deliberative process across countries (median and interquartile range)	101
Table XII. Recommendations to improve the HTA deliberative process.	102
Table XIII. Assessment of the different phases of the HTAi/ISPOR checklist	143
Table XIV. Profile characteristics of the eight study participants	149
Table XV. The RELIANT checklist version prior to the experts' review.	152
Table XVII. Final version of the RELIANT checklist following the experts' review.....	160

LIST OF FIGURES

Figure 1: Phases of the HTA process	24
Figure 2: Overview of the bodies involved in the pricing and reimbursement process in France.	29
Figure 3. PRISMA Flow diagram	71
Figure 4. Scores (median and IQR) given by experts to the degree of influence of implicit factors in the HTA deliberative process.....	97
Figure 5. Scores (median and IQR of medians) given by experts to a set of attributes pertaining to the HTA deliberative process.....	100

LIST OF PUBLICATIONS

Articles

Clara Monleón, Hans-Martin Späth, Carlos Crespo, Claude Dussart & Mondher Toumi (2022) Systematic literature review on implicit factors influencing the HTA deliberative processes in Europe, *Journal of Market Access & Health Policy*, 10:1, 2094047.

Clara Monleón, Hans-Martin Späth, Carlos Crespo, Claude Dussart & Mondher Toumi. Implicit factors influencing the HTA deliberative processes in 5 European countries: results from a mixed-methods research. *Health Policy Open* 5 (2023) 100109.

Communications at International conferences

Systematic Literature Review on the Implicit Factors Influencing the HTA Decision-Making Process in Europe, *ISPOR Europe 2020*. Milan, 16 November - 19 November 2020.

Analysis of the influence of implicit factors on the HTA deliberative process: results from a survey in 5 European countries, *Virtual ISPOR Europe 2021*, 30 November - 3 December 2021.

Analysis of the influence of implicit factors on HTA deliberative process: results of a survey in 5 European countries. *EUHEA 2022*, Oslo July 5-8, 2022. Accepted as oral presentation.

Analysis of the influence of implicit factors on HTA deliberative process: results of a survey in 5 European countries", *HTAi 2022 Annual Meeting*, Utrecht, June 28th, 2022.

Development of the Reliant Checklist to Support the HTA Deliberation. Presented as a poster in *ISPOR Europe 2023*, 12-15 November 2023.

LIST OF ABBREVIATIONS

Abbreviation	Full Name
ACD	Appraisal Consultation Document
AEMPS	<i>Agencia Española de Medicamentos y Productos Sanitarios</i> / Spanish Agency for Medicines and Healthcare Products
AETSA	<i>Evaluación de Tecnología Sanitarias de Andalucía</i> / Andalusian Health Technology Assessment Department
AGENAS	<i>Agencia Nazionale per i servizi sanitari Regionali</i> / Italian National Agency for Regional Health Services
AIFA	<i>Agencia Italiana del Farmaco</i> / Italian Medicines Agency
AMNOG	<i>Arzneimittelmarkt-Neuordnungsgesetz</i> -/Pharmaceuticals Market Reorganisation Act
ANSM	<i>Agence nationale de sécurité du médicament et des produits de santé</i> / French National Agency for Medicines and Health Products Safety
ASMR	<i>Amélioration du service médical rendu</i> /Improvement in actual benefit
ATMP	Advanced Therapy Medicinal Products
AQUAS	<i>Agència de Qualitat i Avaluació Sanitàries de Catalunya</i> / Agency of Health Quality and Assessment of Catalonia
AVALIA-T	<i>Agencia Gallega de Conocimiento de la Salud</i> / Galician Agency for Health Technology Assessment
AWMSG	All-Wales Medicines Strategy Group
BFARM	Bundesinstitut für Arzneimittel und Medizinprodukte/Federal Institute for Drugs and Medical Devices
CatSalut	Catalan Health Service
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CE	Cost-Effectiveness
CEA	Cost-Effectiveness Analyses
CEESP	<i>Commission Evaluation Economique et de Santé Publique</i> / <i>Economic and Public Health Assessment Committee</i>
CEPS	<i>Comité Economique des Produits de Santé- Healthcare Products Pricing Committee</i>
CHMP	Committee for Medicinal Products for Human Use
CIPM	<i>Comité Interministerial de Precios de Medicamentos y Productos Sanitarios-Interministerial/ Committee on Pricing and Healthcare Products</i>
CNEDIMTS	<i>Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé</i> / <i>Medical Device and Health Technology Evaluation Committee</i>
CPR	<i>Comitato Prezzi e Rimborso</i> / Pricing and Reimbursement Committee
CRD	Center for Reviews and Dissemination
CSC	<i>Consorci de Salut i Social de Catalunya</i> / Catalan Health and Social Care Consortium
CTS	<i>Commissione Tecnico-Scientifica</i> / Technical scientific committee
CUA	Cost-Utility Analysis
DAHTA	<i>Deutsche Agentur für HTA</i> / German Health Technology Assessment
EASP	<i>Escuela Andaluza de Salud Pública</i> / Andalusian School of Public Health in Spain

Abbreviation	Full Name
EC	European Commission
ECEA	Extended Cost-Effectiveness Analysis
ECHTA	European Collaboration on Health Technology Assessment
EDP	Evidence-informed Deliberative Process
EMA	European Medicines Agency
ERG	Evidence Review Group
EU	European Union
EUHTAR	EU Health Technology Assessment Regulation
EUNETHTA	European Network for Health Technology Assessment
EVIDEM	Evidence and Value: Impact on DEcision-Making
FAD	Final Appraisal Determination
GENESIS	<i>Grupo de Evaluación de Novedades, EStandarización e Investigación en Selección de Medicamentos/</i> Group for the Evaluation of Innovations, Standardisation and Research in Drug Selection
G-BA	<i>Gemeinsamer Bundesausschuss/</i> Federal Joint Committee
GKV-SV	<i>Gesetzlichen Krankenversicherung Spitzenverband/</i> National Association of Statutory Health Insurance Funds
HRQOL	Health Related Quality of Life
HT	Health Technology
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
HTAR	Health Technology Assessment Regulation
HAS	<i>Haute Autorité de Santé/</i> French National Authority for Health
HST	Highly Specialized Technologies
IACS	<i>Instituto Aragonés de Ciencias de la Salud/</i> Health Sciences Insitute in Aragon
ICER	Incremental Cost-Effectiveness Ratio
INAHTA	The International Network for Agencies for Health Technology Assessment
IPT	<i>Informe de Posicionamiento Terapéutico/</i> Therapeutic Positioning Report
IQR	Interquartile Range
IQWIG	<i>Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen/</i> Institute for Quality and Efficiency in Health Care
ISCIH	<i>Instituto de Salud Carlos III/</i> Institute of Health Carlos III
ISPOR	The Professional Society for Health Economics and Outcomes Research
JCA	Joint Clinical Assessment
JCVI	Joint Committee on Vaccination and Immunization
MECIR	Methodological Expectations of Cochrane Intervention Reviews
MESH	Medical Subject Headings
MCDA	Multi-criteria Decision Analysis
MHRA	Medicines and Healthcare products Regulatory Agency
MOH	Ministry Of Health
MTA	Multiple Technology Appraisal
NDC	New Drugs Committee (UK)

Abbreviation	Full Name
NHS	National Health System
NICE	National Institute for Healthcare and Care Excellence (UK)
OSTEBA	<i>Servicio de Evaluación de Tecnologías Sanitarias/</i> Basque Office for Health Technology Assessment
OTA	Office of Technology Assessment
PAS	Patient Access Schemes
PICO	Population, Intervention, Comparator, Outcomes
PKV	<i>Verband der Privaten Krankenversicherung /</i> Joint Federal Association of Private Health Insurance
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality Adjusted Life Years
REDETS	<i>Red Española de Agencias de Evaluación de Tecnologías Sanitarias/</i> The Spanish Network of HTA agencies
SAS	<i>Servicio Andaluz de Salud/</i> Andalusian Health Service
SD	Standard Deviation
SESCS	<i>Servicio de Evaluación del servicio Canario de Salud/</i> Evaluation Unit of the Canary Islands Health Service
SHI	Statutory Health Insurance
SHITA	<i>Società Italiana di Health Technology Assessment/</i> Italian Society of HTA
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SMR	<i>Service Médical Rendu/</i> Actual medical benefit
SSN	<i>Servizio Sanitario Nazionale/</i> Italian National Health Service
STA	Single Technology Appraisal
TC	<i>Commission de la Transparence/</i> Transparency Committee
TLR	Targeted Literature Review
UETS	<i>Unidad de Evaluación de Tecnologías Sanitarias/</i> Health Technology Unit in Madrid
UK	United Kingdom
UNCAM	<i>Union Nationale des Caisses d'Assurance Maladie/</i> French National Union of Health Insurance Funds
US	United States
UVEF	<i>Unità di Valutazione dell'Efficacia del Farmaco /</i> Drug Efficacy Assessment Unity
ZIN	<i>Zorginstituut Nederland/</i> Dutch National Health Care Institute

ABSTRACT

In an era in which global healthcare expenditure is rising considerably within a context of dwindling budgets, demand for evidence and justification of value have become paramount to support funding and reimbursement decisions. Because of this, HTA agencies play a major role in deliberative decision-making processes as enablers by determining the value of health technologies and subsequently by informing pricing and reimbursement decisions across countries.

Across most HTA bodies there are two distinct phases: assessment and appraisal. The same medicine assessed by different HTA agencies may result in different HTA recommendations and, consequently, in divergency in patient access to this medicine.

The HTA deliberative process may not be strictly evidence-based but may also be influenced by other key considerations in the decision-making such as political, social, or ethical considerations. Few studies have been performed on this topic.

In this context, the objective of our PhD thesis is twofold. Firstly, to identify and understand the implicit factors influencing the HTA deliberative process in France, Germany, Italy, United Kingdom (UK) and Spain. Secondly, to develop a checklist as a solution to address these factors.

In the first chapter we assessed the HTA processes in the countries in scope focusing on the explicit factors. In the second chapter, we described two different research projects. First, we developed a systematic literature review (SLR) to identify the implicit factors involved in the HTA appraisal in the five European countries to categorize these factors and identify approaches to deal with them. Secondly, we performed interviews with HTA experts to better understand their perceptions on the implicit factors influencing the HTA deliberative process in their countries.

The last chapter of this PhD thesis focuses on the **RELIANT (REvealing Implicit factors in HTA)** checklist, a tool that we developed with the goal to reveal the influence of the implicit factors in the HTA process. This novel checklist has the potential to support the HTA deliberative processes at a national, regional, or local level prior to the HTA recommendations. The checklist can serve as a vehicle to bring these implicit factors into consciousness and contribute ultimately to the transparency and legitimacy of the process.

RÉSUMÉ

Ces dernières années les dépenses de santé ont considérablement augmenté et les budgets parfois diminué. La justification de la valeur des technologies de santé est donc primordiale afin de soutenir les décisions concernant leur financement et leur remboursement. Pour cette raison, les agences HTA (“Health Technology Assessment”) jouent un rôle majeur dans les processus délibératifs en déterminant la valeur des technologies de santé et, par la suite, en éclairant les décisions concernant leur prix et leur remboursement dans les différents pays.

Dans la plupart des organismes HTA, il existe deux phases: l'évaluation et “l'appraisal”. Le même médicament évalué par différentes agences HTA peut donner lieu à des recommandations différentes et, par conséquent, à une divergence concernant l'accès des patients à ce médicament.

Il se peut que le processus délibératif HTA ne soit pas uniquement basé sur l'évidence, mais qu'il peut également être influencé par d'autres considérations lors de la prise de décision. A ce jour, peu d'études ont été réalisées sur ce sujet.

Dans ce contexte, les objectifs de notre thèse de doctorat sont tout d'abord d'identifier et de comprendre les facteurs implicites influençant le processus délibératif HTA dans cinq pays européens (France, Allemagne, Italie, Royaume-Uni et Espagne), puis de développer une checklist permettant de tenir compte de ces facteurs.

Dans le premier chapitre nous avons analysé les processus HTA dans les cinq pays européens en nous focalisant sur les facteurs de décision explicites. Dans le deuxième chapitre nous avons décrit deux projets de recherche différents. Tout d'abord, nous avons présenté une revue systématique de la littérature permettant d'identifier les facteurs implicites impliqués dans l'évaluation HTA dans les cinq pays européens afin de catégoriser ces facteurs et d'identifier des approches permettant d'en tenir compte. Deuxièmement, nous avons réalisé des entretiens avec des experts HTA pour mieux comprendre leurs perceptions concernant les facteurs implicites influençant le processus délibératif HTA dans leurs pays.

Le dernier chapitre de cette thèse porte sur l'élaboration de la checklist RELIANT (**RE**vea**L**ing **I**mplicit **f**actors **i**n HTA), un outil que nous avons développé afin de révéler l'influence des facteurs implicites dans le processus délibératif HTA. Cette nouvelle checklist pourra être utilisée lors des processus délibératifs de HTA au niveau national, régional ou local avant l'élaboration des recommandations des agences HTA. La checklist pourra permettre de faire prendre conscience des facteurs de décision implicites et contribuer finalement à la transparence et à la légitimité du processus délibératif des agences HTA.

INTRODUCTION

Over the past decades, healthcare systems have evolved at a different pace and with different degrees of complexity, reflecting the different circumstances in each country. Despite differences, healthcare systems share a common objective, which is improving the health of the population. This goal may be achieved most notably through funding and delivery of health services (1).

In an era of healthcare budget constraints and fast growth innovation, there has been an increasing demand for evidence and a justification of the value delivered by health technologies, to support funding and reimbursement decisions (2).

HTA is defined as a multidisciplinary process using explicit methods to determine the value of a health technology at different points of its lifecycle. The objective of HTA is to inform decision-making to promote an efficient, equitable, and high-quality health system (3) (4).

HTA is used to determine the value of new health technologies. Countries differ in terms of the assessment and appraisal of the evidence and most concretely on the criteria that are considered in the appraisal step (5). Assessment requires the evaluation of relevant aspects of the technology to form a basis for decision, while appraisal implies some sort of recommendation about the implementation of the technology, based on this assessment (6).

According to Health Technology Assessment International (HTAi) (7), the deliberation is the critical assessment and discussion of an issue involving the weighting of reasons for and against a measure. Deliberation enables exchange between those assessing and discussing through participatory processes. In HTA, the deliberation takes place from the horizon scanning to the monitoring, assessment, appraisal, and evaluation of the recommendation that has been issued (8). For the purpose of this PhD, we will focus on the appraisal step.

There are some common factors that have been the focus of the HTA. Those usually are safety, efficacy, and cost-effectiveness (CE) of the intervention (9) and these criteria are described in Chapter 1 by country.

In the appraisal step, an advisory committee interprets the results of the assessment from a broader perspective and formulates a recommendation to inform decision-makers. This is intrinsically complex and requires a careful judgement process for two reasons.

First, appraisal involves social judgements on the importance of decision criteria. Second, the assessment step typically considers different types of evidence involving varying degrees of uncertainty, and an advisory committee needs to judge the relevance of this evidence for the decision under scrutiny (10) (11).

The HTA deliberative process may not be strictly evidence-based but may also be influenced by other key considerations in the decision-making such as political, social, or ethical considerations (12). Evidence shows that even in similar health systems assessing the same health technologies, different HTA recommendations have been issued. In most of the key European countries with established HTA agencies there is clarity on the explicit factors that are used to perform HTA and that subsequently influence the deliberative process. General factors such as safety, efficacy and CE of the intervention are shared in the HTA (9) (13) with nuances among them. For instance, HTA agencies in France and Germany focus on clinical added value, the ones in the UK focus on the CE of the intervention, while HTA agencies in Italy and Spain base their assessments mainly on a budget impact analysis (14).

At the same time, there are some implicit factors such as social values, ethics, value judgments, biases, affordability among others, that may influence the deliberative process and that are not always explicitly stated (15–18). This notion will be extensively covered in Chapter 2 through the mixed-methods research performed.

The non-acknowledgment of the implicit factors leads to a lack of transparency and understanding of all reasons behind HTA recommendations, delegitimizing the decision-making process by challenging its fairness and explicitness.

As an example, Solvadi[®] (Sofosbuvir), despite a sustained virologic response greater than 95% and the therapy being considered cost-effective, it was not affordable and as a result, several countries decided to control budget impact by delaying reimbursement or limiting the target population.

In Europe, politicians reacted to its high price through a media campaign. Fourteen member states were against this price. In France, the health minister and members of the parliament started a controversial media and political campaign advocating for a lower price (19).

Because of this, most EU countries issued a regulation to cap budget expenditure for drugs for Hepatitis C (20).

Despite affordability being a key issue for the reimbursement of this therapy, it was not an explicit criterion in most of the HTA guidelines (e.g., Germany, Spain, Italy) (17,21).

Similarly, in the highly specialised technologies (HST), the reasons for NICE's prioritisation are not explicit compared to other technologies that it appraises. NICE claimed that in recommending these technologies it cannot apply the "rule of rescue". Even if NICE approach to evaluate HST is not motivated by this rule, the reasons for prioritising these technologies (22).

This example suggests that recommendations are not always grounded solely on the criteria described in the HTA guidelines and that there are implicit criteria influencing the recommendations. Criteria for decision-making are not always explicit and this highlights the importance of revealing them (23).

However, while deliberative processes are not new to HTA and their importance is acknowledged, little research has been done on understanding the implicit factors contributing to the final decisions that determine the reimbursement of medicines (24).

The implication of diverging HTA recommendations is that a particular treatment may be funded in one region but not in another, creating a disparity in access to medicines (25) .

This disparity in criteria often results in heterogeneity of coverage decisions across settings even for the same treatment or indication. Inconsistencies in HTA recommendations and medicines' eligibility for reimbursement across countries even in the same geographical region can have important implications for equity and fairness, especially when differences remain unexplained. It has been acknowledged the need for well-defined decision-making processes that are fairer and more explicit. By providing a better understanding of the rationale behind decision-making, decisions will also have enhanced legitimacy and acceptability (26) (27).

A better understanding of these factors that influence and drive decisions is critical to determine whether and how HTA processes across countries can be homogenized, propose solutions to reveal these implicit factors and subsequently the disparities.

For these reasons, the main objectives of this thesis are divided as follows:

- The first one is the identification and comprehension of the implicit factors influencing the HTA deliberative process in France, Germany, Italy, UK, and Spain.
- The second objective is the development of a checklist as a solution to address these factors.

The following questions aim to respond to the objectives of this thesis:

- Are the HTA deliberative processes influenced by implicit factors?
- What are the implicit factors that influence the deliberative processes in the countries in scope?
- How can we address them in a standardized way to mitigate their impact on the HTA recommendations that ultimately determine the reimbursement of health technologies?

To address these questions, we first assessed the HTA processes in the countries in scope focusing on the explicit factors (Chapter 1). We then developed a systematic literature review (SLR) to identify the implicit factors involved in the HTA appraisal in five European countries, specifically in the deliberative decision-making process, to categorize these factors and identify approaches to deal with them (Chapter 2).

In order to address the gaps that were found in this SLR, in a third phase we performed interviews with HTA experts to better understand their perceptions on the implicit factors influencing the HTA deliberative process in their countries (Chapter 2).

The outcome of this research is a novel checklist aiming to overcome the lack of awareness on the implicit factors in the HTA deliberative process. In Chapter 3, we present the tool that we developed to reflect on these implicit factors, so they can be acknowledged prior the final recommendation.

CHAPTER 1: INTRODUCTION TO HEALTH TECHNOLOGY ASSESSMENT: CONTEXT, ORIGINS AND PROCESSES

Understanding both the general and the specific details of the HTA process is a sine qua non requisite to further understand the research question of this thesis. Consequently, this first chapter aims to describe the foundations of HTA starting with the background, then describing the different phases of the process and the technologies subject to be assessed.

In the second section it is described the different HTA bodies and processes in the countries in scope with the purpose of analyzing the information that is officially described.

1. Context of Health Technology Assessment

1.1. Origins, purpose, and evolution of HTA

Technology assessment (TA) was first introduced in the mid-1960s as a result of an appreciation of the critical role of technology and its unintended, and sometimes harmful, consequences (side effects). Early assessments included pesticides, nuclear power plants, automobile pollution, weather modification, and the artificial heart. TA was intended to identify the desirable effects of technology as well as its unintended environmental, social, and economic effects (25).

HTA was started in 1976, in United States (US), when the first report of the Office of Technology Assessment (OTA) was published. Thereafter, in the late 1980s, HTA spread to the rest of the world (28). HTA was born as a result of three main factors: soaring costs in healthcare between the period of 1980's and 1990's, an emerging interest in the efficacy of health technologies and a variation in access across countries in Europe (5).

An important contribution toward the advancement of HTA in the individual countries of Europe was the establishment of agencies in the field. The first national agency, The Swedish Council on Technology Assessment in Healthcare was established in 1987. Then, other formal HTA agencies were established in Europe, notably in France and in Catalonia in Spain. In the 1990's additional agencies were established in Denmark, Finland, Norway, Scotland, Germany, Switzerland, Austria, and Hungary. In 1999, the UK government established the National

Institute for Health and Care Excellence (NICE). Then in 2000's other countries like Ireland, Belgium, Latvia, Poland, and Italy followed.

Several reviews of the development and institutionalization of HTA in Europe have been conducted, each with different focuses and levels of comprehensiveness. The result is a picture showing the heterogeneity of HTA institutions in Europe and the variety of socioeconomic contexts of health care systems. There are HTA agencies with national competencies and those with regional ones. HTA might be directly committed and funded by governments (national or regional) or by non-governmental organizations spending publicly collected money. The bodies performing HTAs are mainly funded by the health care system or from the research and development budget (1).

The International Network for Agencies for Health Technology Assessment (INAHTA) was founded in 1993 by several of the early European agencies (29). The main objective of INAHTA is to connect HTA agencies and to support the exchange of information and knowledge (30).

The European Commission (EC) became a key actor in promoting HTA at the European level, along with INAHTA. It supported several studies related to the HTAs when HTA was perceived as a form of health services research. By mid-1980's, the Health Service Research Committee of the EC started to support HTA with contracts on economic appraisal and mechanisms for regulating specific technologies representing a high budget impact (28,29).

From 1994 to 1997, the EC funded the EUR-ASSESS project composed of several member states of European Union (EU) with the purpose of exploring ways to improve the coordination of HTA in Europe. To further explore how to improve the coordination of HTA in Europe, from 2000 to 2002, the EC funded the European Collaboration on Health Technology Assessment (ECHTA). Finally in 2005, the EC funded a project called EUnetHTA (European Network for Health Technology Assessment) to continue developing HTA initiatives among the 27 member states in Europe (28). EUnetHTA was created in response to a need for a sustainable European Network for HTA. The main objectives of this project were to reduce duplication of effort and promote effective use of resources for HTA, increase the influence of HTA in decision-making and strengthen the link between HTA and healthcare policy. In total, 33 countries (25 members of the EU, Iceland, Norway, Switzerland, Serbia, and four countries outside Europe: Australia, Canada, Israel, and US) participated in the project (28).

The current gold standard constituting the basis of the procedural and methodological understanding of conducting HTA in Europe is called “HTA Core Model®” (31), assessing different dimensions of value with the main aim to facilitate production and sharing of HTA evidence (32).

The domains of the HTA Core Model include:

1. Health problem and current use of the technology
2. Description and technical characteristics
3. Safety
4. Clinical effectiveness
5. Costs and economic evaluation
6. Ethical analysis
7. Organisational aspects
8. Legal aspects (33).

Only three of the domains mentioned above: safety, clinical effectiveness, costs, and economic evaluation are considered by all HTA agencies. However, important limitation of the HTA Core Model is the lack of consideration of non-explicit factors, that influence the decision-making process (11,34,35).

While member states have carried out some joint assessments within the framework of EUnetHTA, the voluntary cooperation has been inefficient with considerable duplication of assessments on the same health technology by HTA authorities and bodies in different member states (29).

There is a plan to implement, from 2025, a regulation on HTA (HTAR) that aims to harmonize methodological standards for HTA and foster collaboration among the European HTA bodies. This regulation replaces the current system based on the voluntary network of national authorities (HTA Network) and the EU-funded project-based cooperation (Joint Actions EUnetHTA) with a permanent framework for joint work. The new framework covers joint clinical assessments (JCA), joint scientific consultations, the identification of emerging health technologies, and voluntary cooperation. The general objectives of the initiative are to ensure a better functioning of the internal market of health technologies and to contribute to a high level of human health protection. With regards to the specific objectives of the initiative these are to

promote convergence in HTA tools, procedures, and methodologies, to ensure efficient use of resources and strengthen the quality of HTA across the EU and to improve business predictability (36).

The EU HTAR will be adopted in a stepwise approach. From January 2025 onwards all new oncology medicines and advanced therapy medicinal products (ATMPs) will be jointly assessed. From January 2028 joint clinical assessments will also apply to orphan drugs. All other medicines approved under the EU centralized procedure will be subject to JCAs from January 2030 (36,37).

1.2. Phases of the HTA within the healthcare decision-making process

HTA is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making to promote an equitable, efficient, and a high-quality health system (3).

The overall HTA process starts with the priority setting in which HTA agencies decide which technologies are most suitable for assessment. This is mainly given by characteristics such as societal values, uncertainty on effectiveness and safety, budget impact and the unmet need. This phase is followed by the scoping, in which the research questions are defined based on the population, comparator etc., and the type of evidence needed is determined.

The HTA has traditionally been based on a distinction between facts and values which is reflected in two separate processes constituting HTA (Figure 1) (38,39).

Following the scoping, there is the assessment focused on the analysis, interpretation, and synthesis of the evidence. During the assessment, the scientific evidence is gathered and synthesised. The starting point of the assessment process is the formulation of a defined research question. A standard format for a research question may be provided by the PICO framework (Population, Intervention, Comparator, Outcomes) (34).

The appraisal (or “contextualization”) is defined as the review of the assessment previously done with the consideration of additional factors (e.g., social, political, cultural, economic, and ethical) by a committee to issue a recommendation. These factors can be both explicit, for example severity of the disease in France, the end-of-life criteria in England or implicit like the

possible impact on family and carers. Comprehensive approaches to appraisals involve multiple perspectives and therefore should not be undertaken by a single individual (16,39,40).

Usually, assessment and appraisal are assigned to different expert groups. For example, in Germany the evaluation of the drug is carried out by IQWiG, while the appraisal and decision-making are responsibilities of the G-BA (39,41).

Similarly in the UK, ERG reviews evidence received by the company and produces an ERG report, while the Appraisal Committee is responsible for the technology appraisal (42).

The assessment can be relatively easily put in a HTA framework, like for example IQWiG guidelines, therefore the impact of deliberation on this phase is limited. By contrast, in the appraisal phase, deliberation plays a much more important role (43).

Finally, there is the implementation and monitoring phase in which the output of the HTA process (i.e., recommendation) is communicated and the impact of HTA is evaluated to ensure that the information is correctly disseminated (44) (18).

Health Technology Assessment process: Three-phase model

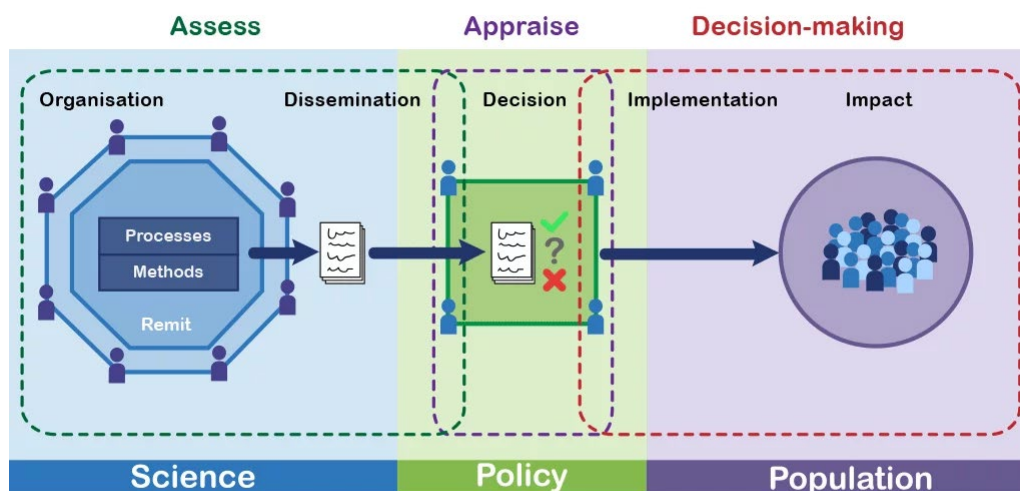


Figure 1: Phases of the HTA process

(Extracted from <https://toolbox.eupati.eu/resources/health-technology-assessment-process-fundamentals/>)(45)

1.3. Technologies subject to assessment

The scope of HTA includes interventions, which may be provided within the healthcare system, as well as those applying to the policies regarding the organisation and funding of the healthcare system. It includes drugs, medical and surgical procedures used in healthcare as well as the organizational and supportive systems within such care is provided (1). It can be used in various ways to advise or inform:

- Payers (on pricing and reimbursement);
- Clinicians and patients (on appropriate use of healthcare interventions);
- Health professional associations (on the role of a technology in clinical protocols or practice guidelines);
- Hospitals (on decisions regarding technology acquisition and management);
- Healthcare and standard-setting organizations (on different aspects of healthcare technologies);
- Government officials and lawmakers (on undertaking public health programs and policies);
- Companies and investors (on product development and marketing decisions);
- Research institutions/bodies, for example universities (on evidence gaps and unmet need) (1).

Many of the institutions listed above, (e.g., payers or hospital networks) have their own HTA units and functions (46).

For the sake of this thesis, we will focus on the HTA related to medicines, fundamentally for two main reasons. The first one is because pharmaceuticals are the most frequently, comprehensively, and extensively evaluated than any other health intervention, both from a clinical trial design as well as from a HTA perspective. There is an increasing global HTA production on pharmaceuticals (47).

The second reason that may be a consequence of the first one is that the expenditure of the other health technologies such as medical devices may not be so visible and the procedure to approve the inclusion of these technologies is not so formal like in the case of medicines (48).

These reasons allowed to deduce that more information was going to be able to collect by focusing on medicines.

After having explained the generalities of the HTA process, we will focus on the main HTA features of the countries in scope.

2. Health Technology Assessment process in the countries of scope

2.1. Geographical scope of this PhD thesis

The geographical scope of this PhD thesis is focused on France, Germany, Italy, Spain, and the UK. These countries represent 73% of the EU population and have established formal HTA agencies and recognized HTA processes (49). Additionally, the healthcare expenditure of all providers in these countries represented 72% of the EU-28 in 2019 (50).

Additionally, these countries have a solid and long history of HTA. By the end of the 1980's, the health technology assessment agencies were established in France and Spain. In the 1990's, additional agencies or formal programs were established in Germany and Italy. In 1999, the UK established NICE, which has a strong mandate to provide guidance for best practice.

Compared to these countries from western Europe, the central eastern European countries are in general less advanced in the implementation of HTA despite showing need and interest in evidence-based resource allocation decisions (51). The western countries have HTA processes that serve as a model for other countries such as some eastern European countries. Countries such as Hungary and Poland have a longer history of HTA compared with other countries such as Romania and Bulgaria. Still, all these countries have generally followed the standards of mature HTA organizations such in the case of Romania and Bulgaria where it is officially accepted to use the appraisal decision of European countries (France, Germany and the UK) for their own decision (29,52).

2.2. France

2.2.1. General concepts of the healthcare system

The French healthcare system is based on Bismarckian approach and characterized by universality and solidarity. Statutory Health Insurance (SHI) covers almost 100% of the resident population, while the delivery of health care is shared between private physicians, public and private hospitals. Jurisdiction over policies and regulations of the healthcare system is divided between the parliament and the government (particularly the Ministry of Health, MOH), SHI and the local communities at the regional level (53).

2.2.2. Health Technology Assessment bodies

The French National Authority for Health (*Haute Autorité de Santé*, HAS) is the HTA agency responsible for evaluation of drugs, procedures, medical devices, and other health technologies from a medical and economic perspective. It has two separate committees (54) (Figure 2):

- Independent scientific committee called Transparency Committee (*Commission de la Transparence*, TC) responsible for the scientific and medical assessment (analysis of clinical evidence) of health technologies for reimbursement purposes (55).
- An affiliate body named the Economic and Public Health Assessment Committee (*Commission Evaluation Economique et de Santé Publique*, CEESP). The Social Security Funding Law of 2012 included the CEESP in the Social Security Code as a specialised committee in charge of providing health economics recommendations on medical procedures, products, or health services (56). CEESP is commissioned to provide advice on health economics, determining the CE of the health technologies (57). An economic opinion issued by CEESP is sent to the Healthcare Products Pricing Committee under the MOH (*Comité Economique des Produits de Santé*, CEPS) to guide price negotiations for assessed products. It is delivered independently from the opinion issued by TC or Medical Device and Health Technology Evaluation Committee (*Commission Nationale d'Évaluation des Dispositifs Médicaux et des Technologies de Santé*, CNEDIMTS) (58).

All drugs seeking reimbursement in France must be evaluated by TC, which means that marketing authorisation holders' submission is required. Submission of cost-effectiveness analysis (CEA) to CEESP is required for the products with new indication that claim moderate (III) to major (I) improvement in actual benefit (*Amélioration du Service Médical Rendu*, ASMR) and that are considered to have a substantial financial impact on healthcare expenditure (more than €20 million per year). Additionally, budget-impact analysis is compulsory if sales after 2 years are anticipated to exceed €50 million (59).

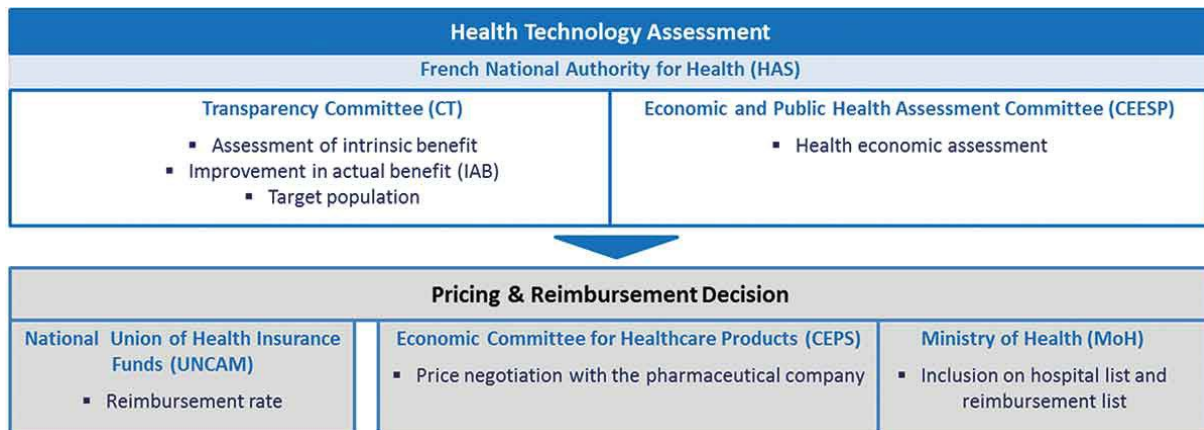


Figure 2: Overview of the bodies involved in the pricing and reimbursement process in France.

Extracted from Toumi et al. Analysis of health economics assessment reports for pharmaceuticals in France- understanding the underlying philosophy of CEESP assessment & Health Policy. 2015 (54).

2.2.3. Health Technology Assessment process

The TC is composed by 22 full members, seven alternate members and six consultative members. One or two members from the Committee can be assigned as rapporteurs of the dossier. The rapporteur is responsible for presentation of the disease, treatment strategy and therapeutic alternatives to the Committee. The deliberations are valid only if 12 members with deliberative voice are present. Once the dossier from the marketing authorisation holder is submitted to the TC, a synopsis is prepared by a designated project manager with the relevant information and is presented to the members of the Committee. Following this presentation, the deliberation between the Committee members takes place and then the President of the Committee asks the different members to vote, concretely to qualify on the medical benefit (*Service Médical Rendu*, SMR) and ASMR (60). These two elements determine a new drug's reimbursement and pricing respectively (27) .

SMR is the drug's perceived medical benefit (actual benefit) and is the primary factor influencing reimbursement rate.

ASMR reflects drug's improvement in actual benefit and is a primary factor influencing price negotiation.

The SMR considers the severity of the disease, the product's efficacy and safety, position of the treatment in the therapeutic pathway, the impact on public health and the type of treatment (preventive, curative or symptomatic) (61–63).

There are four levels of SMR set by the French National Union of Health Insurance Funds (*Union National des Caisses d'Assurance Maladie*, UNCAM) that drive different reimbursement rates for outpatient medicines:

- Important (reimbursement rate: 65%);
- Moderate (reimbursement rate: 30%);
- Weak (reimbursement rate: 15%);
- Insufficient (reimbursement rate: 0%, not eligible for reimbursement).

For inpatient medicines, the MOH decides if the medicine will be reimbursed or not based on the SMR. If it is included in the positive list, it will be reimbursed at 100%. The decision about the utilization of the drug will be made locally by the different hospital pharmacy committees (64).

The ASMR is granted based on the benefit improvement (given by the effect size of the incremental clinical efficacy benefit). Safety and quality of life are also considered, especially when the clinical burden of disease is important.

There are five ASMR levels driving price negotiations with the CEPS:

- I: Major improvement;
- II: Substantial improvement;
- III: Moderate improvement;
- IV: Minor improvement;
- V: No improvement (61–63).

Following the vote from the Committee, the recommendation is written by the project manager to be adopted and is shared with the marketing authorisation holder. After this phase, the marketing authorisation holders have ten days from the moment they receive the notification, to make comments or ask the TC for an oral hearing. In case of absence of comments or oral hearing request, the TC's opinion becomes conclusive (60).

The reports from HAS assessments are publicly available (40).

The CEESP is composed of 33 members appointed for a three-year term. Assessments of the drug CE are considered by the CEPS at the stage of pricing. Apart from CEA, the responsibility of CEESP is also to evaluate the dossier for methodological limitations, errors, and deviations from the HAS methodological guidelines, and assess their impact on the reliability of the health economics analysis results.

The methodological concerns issued by CEESP are scored on a three-level scale:

- Minor methodological concern: limited or negligible impact on the conclusion.
- Important methodological concern: important impact on the conclusion, especially regarding uncertainty.
- Major methodological concern: partial (partial major methodological concern) or complete (global major methodological concern) invalidation of the health economics study (54,65).

2.3. United Kingdom

2.3.1. General concepts of the healthcare system

The healthcare system of the UK is mainly funded by taxes, based on a Beveridge system. Residents may use the services of National Health Service (NHS) or purchase private health insurance. The UK government allocates health funds in England and gives block grants to Northern Ireland, Wales, and Scotland to allocate separately, as they each have a separate framework for the healthcare system and make their own decisions about organisation of health services (66).

2.3.1.1. Health Technology Assessment bodies

The UK has three HTA bodies assessing medicines for its constituent countries: the Scottish Medicines Consortium (SMC), NICE and the All-Wales Medicines Strategy Group (AWMSG) (67–69).

NICE is responsible for conducting HTA in England on behalf of the NHS. NICE's HTA guidance applies in England and Wales. This means that patients in NHS England and NHS Wales will be able to access a new medicine if its use is recommended by NICE (67,70).

AWMSG advises Welsh Government about the use and management of medicines and takes NICE's guidance into account when considering whether to assess a medicine. AWMSG use the same criteria as NICE to assess clinical effectiveness and CE and they do not usually assess a medicine if NICE will publish its final appraisal of the same medicine within 12 months of the medicine's marketing authorization date (71).

The Appraisal Committee is a standing advisory committee of NICE. Its members include people who work in the NHS, academia, the pharmaceutical industry, and lay members (committee members with a patient, service user, carer, or community background). The Appraisal Committee makes recommendation regarding the clinical value and CE of treatments with the support of the consultee organisations. Consultee organisations may comment on the appraisal documents during the consultation process and nominate clinical, commissioning, or patient experts to present their personal views to the Appraisal Committee (65,72–75).

2.3.1.2. Health Technology Assessment process

In the UK, the organization of the HTA process to inform decision-making on reimbursement reflects the fact that the decision-making is performed at the level of the administrations of the devolved countries: England, Scotland, and Wales that inform decision-making process in each of the countries. For the purposes of this PhD thesis, UK will be identified as one country with a national HTA system with one national HTA organization (NICE) (76).

NICE selects medicines and other HT for HTA where national guidance is expected to add value (clinical impact, variation in practice, need for information or resource impact). These evaluations can be initiated when NICE receives notification that the company is applying for regulatory approval (horizon scanning), but if NICE is not tracking a regulatory submission, the process may be initiated after launch. The process and timelines depend on whether the appraisal is single technology (STA) or multiple technologies (MTA). An STA will take at least 32 weeks to complete from initiation to publication of guidance. An MTA can take at least twice as long (64).

The STA process consists of three phases: initiation of the process and submission of the evidence, evidence review and appraisal.

The first phase begins after receiving a formal referral from the Secretary of State for Health by NICE. Then the pharmaceutical company can discuss the decision problem with the NICE team and representatives from the Evidence Review Group (ERG). ERG reviews evidence received by the company and produces an ERG report. Additional evidence from consultees including information on the potential clinical and cost effectiveness of the treatment is provided to ERG by NICE. The ERG report is presented to the company which has five working days to review it, before the appraisal committee meeting takes place.

In the next step, NICE invites consultee and commentator to take part in the appraisal and invites the company to provide an evidence submission.

Members of the public and press are most often able to attend the first part (public session) of the appraisal committee meetings. During the meeting either the Final Appraisal Determination (FAD) or Appraisal Consultation Document (ACD) are delivered. Usually, if an ACD is produced, the appraisal committee meets again to reconsider the preliminary recommendations.

After FAD is finalized and approved by NICE Guidance Executive, it is published as technology appraisal guidance on NICE website (42).

During the NICE's technology appraisal the medico-economic value of a health intervention is determined. There are five categories of NICE recommendation: recommended, optimised (recommended with restrictions), only in research (recommended for use only in the context of a research study), not recommended, recommended for use in the Cancer Drug Fund (CDF) (for cancer drug appraisal) (77).

The CDF was established by the UK Government in 2011 as a temporary solution to support patients get access to cancer drugs not available on the NHS. The fund was originally due to end in 2014, however it was extended further. It has benefited over 95,000 patients since its inception but the lack of clear criteria for how long it should fund drugs, has placed it under financial pressure as it is argued that the fund is not sustainable in its current form.

CDF provides earlier access for patients to innovative treatments or to other promising treatments while further evidence is collected to address clinical uncertainty. In those cases, pharmaceutical companies have the option of accessing interim funding from the time of the marketing authorisation. Reimbursement during this interim period will be 100% of the price. Interim funding by CDF ends 90 days after positive final guidance is published or 30 days in the case of drugs with an Early Access Scheme. Whilst the drug is in the CDF, data will be collected to ensure uncertainties are addressed (78).

In England, NICE considers different factors in the evaluation process: the broad balance between benefits and costs (i.e., CE), the clinical need, the clinical priorities for the NHS and the effective use of resources and the encouragement of innovation (27).

NICE focused during his negotiations and decisions on cost-utility analysis, where the main criterium is the incremental cost-effectiveness ratio (ICER) defined as an incremental cost per quality adjusted life-year (QALY) with consideration to the thresholds set at £20,000 and £30,000/QALYs. Generally, it is rare to receive a positive recommendation for a technology whose ICER exceeds £30,000. However, if the drug is considered as “life extending” in end-of-life scenarios (for example many oncology drugs) it may be recommended with an ICER of up to £50,000. The end-of-life criteria include:

- Indication for patients with a short life expectancy (usually less than 24 months);

- Sufficient evidence indicating that the treatment offers an extension of life (usually at least an additional three months versus current treatment);
- Indication for small patient populations (73,79).

The “Budget Impact Test” introduced in 2017, is an additional step for NICE assessments. Any product that was assessed to be CE but is likely to cost the NHS more than £20 million in any of the first three years of its use is subject to further negotiations between the manufacturer and the NHS to lower the price.

There is a specific pathway for “Highly Specialised Technologies” (HST) in which recommendations on the clinical and CE of new and existing ultra-rare conditions are made. These conditions are often associated with likely higher cost and limited clinical data. Under this pathway, NICE will usually recommend drugs that have an ICER of lower than £100,000 or, in special circumstances, £300,000.

This group of technologies is systematically prioritised through NICE’s HST programme. One of the NICE’s principles is that whenever possible, the agency considers value for money by calculating the ICER. They explain that one of the implications of this consideration is that they cannot apply the ‘rule of rescue’, which refers to the “desire to help an identifiable person whose life is in danger no matter how much it costs”(80).

Nevertheless, Charlton V. argues several facts that demonstrate that NICE follows this rule for this kind of technologies. The author examines three criteria that constitute the rule of rescue and through facts she demonstrates that NICE follows this rule. The first one states that the intervention must offer significant benefits to those patients in severe conditions. The second criterion is about the identifiability of the rescue and the third one specifies that a significant opportunity cost must be considered to carry out the rescue.

In most of the HST appraisals from NICE, the treatment condition had a significant decrease of life expectancy. Additionally, patients whose needs are addressed via HST programme are identifiable in sense much more likely to elicit the identifiable victim effect. Lastly, HST programme methods allow NICE to commit the NHS to a significant opportunity cost in order to provide access to these drugs.

All these arguments point towards a disparity between NICE's rejection of the rule of rescue and its apparent accordance with the rule in its treatment of HSTs. The fact that the reasons for NICE's prioritisation of HSTs compared to the many other technologies appraised are not explicitly explained, undermines the fairness and transparency of NICE's approach (22).

Following an unfavourable decision by NICE, payers are not obliged to fund the medicine. The manufacturers in some cases enter negotiations with the MOH over "patient access schemes" to try to improve its CE (64).

Lastly, NICE evaluations are publicly available (40).

2.3.2. Scotland

2.3.2.1. Health Technology Assessment bodies

The Scottish Medicines Consortium (SMC) is a committee of clinicians, pharmacists, board representatives of NHS, public and pharmaceutical industry providing the advice to NHS Scotland about the value for patients of every new licensed medicine. Diverse backgrounds of members ensure a broad perspective of decision-making process. The committee meets once a month and is supported by a team including pharmacists, public involvement professionals, health economists, and administration support. When appraising the evidence, the main criteria used are clinical effectiveness and CE. In some cases, other factors may also be taken into consideration when voting for a decision in specific cases, for example, high level of uncertainty may be accepted in the case of orphan drugs (10,81,82).

2.3.2.2. Health Technology Assessment process

Once HTA dossier submission is performed, it is evaluated by an assessment team completing both clinical and economic checklists. It is then forwarded to the New Drugs Committee (NDC), which is a committee of 20 members composed of clinicians, pharmacists, and pharmaceutical industry members responsible for completing the technical assessment of a company's submission and making a preliminary recommendation to the SMC committee. The meetings of NDC are not held in public.

The SMC further reviews the evidence considering additional information. There are three categories of recommendations for SMC: accepted, accepted with restrictions, and not recommended.

The SMC does not have a formal ICER threshold. As a rule of thumb, drugs with an ICER < £20,000 are likely to receive a positive recommendation, whereas for the drugs with an ICER > £30,000 recommendation is likely to be negative. Manufacturers may suggest a Patient Access Scheme (PAS) to reduce the costs and secure a positive recommendation. Medicines which treat rare and end-of-life conditions (condition leading to death within three years), orphan medicines and ultra-orphan medicines are eligible for a more flexible decision-making process where greater level of uncertainty in the economic case is accepted (83).

Appraisal meetings can be open to public but occasionally, parts of the discussion may legally require confidentiality. During these meetings, all eligible members vote based on the recommendation.

SMC evaluations are publicly available (40).

2.4. Germany

2.4.1. General concepts of the healthcare system

Germany was the first country worldwide that introduced a system of social health insurance in 1883.

The governance of health system represents the Bismarck system is divided between the federal level (setting the overall legal framework) and state level (responsible for hospital planning and public health services) (84). The healthcare system is based on several principles. For example, everyone must have a statutory health insurance or a private insurance. Another principle is that everyone covered by statutory insurance has an equal right to medical care. While the state sets the conditions for medical care, self-governing bodies are responsible for organisation and financing of individual medical services (85). All prescription drugs are reimbursed by health insurance unless included in a negative list maintained by the Federal Joint Committee (*Gemeinsamer Bundesausschuss*, G-BA) (86).

2.4.2. Health Technology Assessment bodies

The most important bodies involved in HTA in Germany are the G-BA and the Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*, IQWiG)

- The G-BA is the supreme decision-making body of the self-governing system in Germany. This body entails physicians, dentists, hospitals, sickness funds and patients (13 members with voting rights). As a rule, resolutions are passed in public sessions. Closed sessions or voting is possible only in specific cases.
- IQWiG is an independent institution providing preliminary benefit assessment. On behalf of the G-BA and MOH, IQWiG assesses effectiveness, quality, and efficiency of the health technologies. IQWiG's assessments are used to inform the G-BA for its decision-making (10,87).

2.4.3. Health Technology Assessment process

The G-BA commissions IQWiG to do a preliminary benefit assessment. Outcomes considered by IQWiG during their assessment are mortality, morbidity, health-related quality of life (HRQoL) and adverse events.

Early benefit assessment performed by IQWiG includes the “quality of available evidence” (or certainty of conclusions) graded from one to three, and the “extent of the effect size” (or additional benefit) graded from one to six, relative to an appropriate comparator. Quality of clinical evidence can be graded as high (proof of benefit), moderate (indication of benefit) and low (hint of benefit). The additional benefit compared to the appropriate comparator may be major, considerable, minor, non-quantifiable, no additional benefit proven, and lower benefit versus the comparator (64) (88).

If the G-BA ranks the added benefit in any of the categories related to major added benefit, considerable or minor, then the manufacturer can negotiate the price with the public health insurance providers. If a medicine offers no additional benefit over the comparator (the other

three categories), then payers will reimburse only at the price set for the comparator. Pharmaceutical companies can choose to price their medicines higher, but patients will have to pay the difference out of their own pockets.

A manufacturer can opt for their medicine to not be assessed, in which case a medicine's price is set based on the price of others in the same therapeutic class, including generics (64).

Thereafter, an oral hearing involving physicians, experts and manufacturers' representatives takes place to facilitate further discussion. The final decision is made by G-BA considering the outcomes of IQWiG evaluation, the results of public hearing and the evidence provided by the pharmaceutical company (no economic analysis is required). As the final assessment made by G-BA includes additional features, the decision may differ from the IQWiG recommendation. The result of this benefit assessment is called Pharmaceuticals Market Reorganisation Act (*Arzneimittelmarkt-Neuordnungsgesetz*, AMNOG) procedure. This is the starting point for the price negotiations between the National Association of Statutory Health Insurance Funds and the pharmaceutical company and no economic analysis is needed (64) (88).

G-BA and IQWiG evaluations are publicly available (40).

2.5. Italy

2.5.1. General concepts of the healthcare system

The Italian National Health Service (*Servizio Sanitario Nazionale*, SSN) is tax-funded and provides universal coverage to its residents. It has adopted since 1978 a "Beveridge" or "National Healthcare Service" model, where the State is the most important financer and provider of health care services. There are three levels in the organization of the healthcare system in Italy:

1. National (the MOH);
2. Regional (the regional government);
3. Local (public and private hospitals).

The national level ensures the general objectives and fundamental principles of the healthcare system, while regional governments are responsible for delivering the package of benefits through local health authorities and hospitals (89).

Regions have played a key role since the beginning of the SSN. Although price and reimbursement are decided at the national level, the regions have the competencies to introduce market access barriers to access to medicines (90,91).

2.5.2. Health Technology Assessment bodies

In Italy, the price setting of new drugs reimbursed by the SSN is regulated at the central level by the Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA). AIFA provides the clinical, scientific, and economic evaluation on medicines through two main Committees: the technical scientific committee (*Commissione Tecnico-Scientifica*, CTS) and the reimbursement committee (*Comitato Prezzi e Rimborso*, CPR) (92). AIFA has a dual function since it is also the organism in charge of the regulatory approval of medicines in Italy (93).

The CTS is responsible for the activities related to marketing authorisation applications of the medicines, such as analysing the drug, determining the CE ratio, and providing an opinion on the classification of the drugs for reimbursement purposes.

On the other hand, the CPR focuses on negotiations on reimbursement of the medicines. Its resolutions are submitted to the assessment of CTS to issue the final opinion (94).

The CTS and CPR are appointed by decree of the MOH and each of them is made up of ten members: one member acts as president, three members are designated by the MOH, one member is appointed by the Minister of Economy and Finance and four members are appointed by the Permanent Conference for relations between the State, the Regions and the Autonomous Provinces of Trento and Bolzano (94).

2.5.3. Health Technology Assessment process

In Italy both the HTA process and decision-making on reimbursement (and pricing) of pharmaceuticals takes place at AIFA, a governmental body that is also responsible for marketing authorization of medicines. MOH oversees the decision-making on reimbursement (76).

To start the pricing and reimbursement procedure, the marketing authorisation holder must submit the dossier for AIFA (CTS and CPR) evaluation. This may happen after the publication

of the Commission Decision in the Official Journal of the EU or after positive opinion of the Committee for Medicinal Products for Human Use (CHMP) for non-orphan and orphan drugs, respectively. The reimbursement of pharmaceuticals at the central level is evaluated by AIFA's Pricing and Reimbursement Committee, which sets prices and reimbursement conditions for drugs with a based on the following factors: the product's therapeutic value and safety, the degree of therapeutic innovation, internal market forecasts, the price of similar products within the same or similar therapeutic category and product prices in other EU Member States (27).

The product can be assigned one of the following categories:

- Class A: essential products and products for chronic diseases, fully reimbursed by the SSN (retail);
- Class H: products fully reimbursed only in the hospital;
- Class C: not reimbursed.

As a particularity, regions may decide to reimburse drugs classified as Class C if they demonstrate having enough regional funds and if they have already reimbursed drugs in Classes A and H (90).

Once the reimbursement is granted, a monitoring system may be considered as necessary to check for economic parameters and appropriateness of use. After completion of the national phase, the decision is published in the official journal, *Gazzetta Ufficiale*, and there are further steps at the regional level that are requested to grant access regionally to the medicine at issue. At regional and hospital levels, therapeutic formularies determine which drug can be used, in which circumstances and the length of the treatment. Also, at local level, additional formularies can be put in place. The administrative decisions to include or exclude a drug into the formulary at regional and local levels, are defined by different technical and scientific committees (95).

Once the pricing and reimbursement process is concluded at the national level, the regions which are accountable of the health care budget, decide upon the access of the medicine.

Despite regions do not have competencies on list prices setting, many pharmaceutical policies are managed on a regional level, including binding regional formularies, guidelines on drug procurement by hospitals, direct distribution of drugs by hospitals, and regulations of information and advice provided by the pharmaceutical companies' representatives and prescription targets for general practitioners. Any decision made at the national level may be legitimately challenged at the regional level (90).

In 2017, a standardised process to appraise innovativeness of medicines was introduced to ease the market access of innovative drugs. Innovative status can be given only to the drugs indicated for serious diseases that fulfil the following criteria: high unmet therapeutic need, added therapeutic value, and high quality of the evidence. Both unmet medical need and added therapeutic value may be rated as: maximum, important, moderate, poor, or absent (96).

AIFA evaluations are not publicly available, in contrast to regional evaluations (40).

2.6. Spain

2.6.1. General concepts of the healthcare system

The Spanish NHS is based on several principles: universality, equity, free access, and fairness of financing. It is mainly funded by taxes (Beveridge system) and the competencies for provision of healthcare are for the most part decentralised to the 17 regions since 2004. However, healthcare decision-making is split between different levels:

1. Central: The MOH is responsible for issuing health proposals, planning and implementing government guidelines;
2. Regional: 17 Autonomous Communities responsible for offering integrated health services to the regional population;
3. Local/Hospital: *Areas de Salud* responsible for the management of the health services offered at the level of the Autonomous Community (97,98).

2.6.2. Health Technology Assessment bodies

The HTA system in Spain involves multiple organizations and potentially multiple assessments for the same medicine at three different levels.

At the national level, there is the Spanish Agency for Medicines and Healthcare Products (*Agencia Española de Medicamentos y Productos Sanitarios*, AEMPS), assessing the therapeutic positioning of new medicines.

Before any medicine is marketed, the decisions on price and reimbursement are made by the Interministerial Committee on Pricing and Healthcare Products (*Comité Interministerial de Precios de Medicamentos y Productos Sanitarios*, CIPM). This body includes nominees from the Ministries of Health, Industry, Economics and Finance, plus members of three of the regions on a rotating basis (64).

At the regional level, there are several bodies assessing pharmaceuticals both in primary and secondary care. The Andalusian and Catalan regions have shown greater commitment in the harmonization of processes for the assessment of new drugs. In 2002, the Andalusian HTA agency published a guide to the introduction of new medicines to facilitate the decisions on the inclusion of new medicines on hospital formularies. In 2008, the Andalusian Health Service (“Servicio Andaluz de Salud”, SAS), established an advisory commission to harmonize the utilization criteria for hospital medicines.

Similarly, in 2008, the Catalan Health Service (CatSalut) established a harmonisation programme for medicines to guarantee equity in access to medicines and to improve efficiency (99).

The Spanish Network of HTA agencies (“Red Española de Agencias de Evaluación de Tecnologías Sanitarias” RedETS) was created in 2012 to promote the development and dissemination of HTA reports to promote the national health care system sustainability. It is formed by eight regional HTA bodies (100,101):

1. UETS-Madrid (“Unidad de Evaluación de Tecnologías Sanitarias”, The Madrid Health Technology Unit)
2. AETSA (“Evaluación de Tecnología Sanitarias de Andalucía”, Andalusian Health Technology Assessment Department)
3. Aquas (“Agència de Qualitat i Avaluació Sanitàries de Catalunya”, Agency of Health Quality and Assessment of Catalonia)
4. Avalia-t (“Agencia Gallega de Conocimiento de la Salud”, Galician Agency for Health Technology Assessment)
5. IACS (“Instituto Aragonés de Ciencias de la Salud”, Health Sciences Institute in Aragon)
6. ISCIII (“Instituto de Salud Carlos III”, Institute of Health Carlos III)
7. SESCS (“Servicio de Evaluación del servicio Canario de Salud”, Evaluation Unit of the Canary Islands Health Service)
8. Osteba (“Servicio de Evaluación de Tecnologías Sanitarias”, Basque Office for Health Technology Assessment)

The corresponding regional governments fund each of the HTA agencies.

Since 2004 there are hospital pharmacy units that have been coordinated through Group for the Evaluation of Innovations, Standardisation and Research in Drug Selection (*Grupo de Evaluación de Novedades, EStandardización e Investigación en Selección de Medicamentos, GENESIS*), a group sharing assessments taking into consideration effectiveness and CE evidence (99).

2.6.3. Health Technology Assessment process

In Spain, the HTA process is differentiated from reimbursement process, but they are closely related. AEMPS, the 17 regional authorities and the MOH are involved in the HTA of pharmaceuticals (76).

After positive recommendation of a new medicine by European Medicines Agency (EMA), CIPM starts the HTA process at a national level. To inform pricing and reimbursement decision, AEMPS creates the Therapeutic Position Report (*Informe de Posicionamiento Terapéutico, IPT*). This report is focused on the relative efficacy, safety, the nature of the disease, therapeutic options and other social or medical aspects. However, it does not cover extensively the economic aspects. The marketing authorisation holder submits a dossier with information about the drug, proposed price, expected sales, the market price in other European countries, CE and budget impact analysis and information about manufacturer's investment in research. The price is negotiated between the MOH and the marketing authorisation holder. Following this negotiation, the CIPM makes the final decision on pricing and reimbursement. The decision should consider certain criteria including severity of the disease, the therapeutic and social value of the medicine, CE, special needs of some groups of people, budget impact, therapeutic alternatives, and the degree of innovation of the medicine.

After the national approval of the drug, the regions and hospitals may add some additional restrictions affecting for example the therapeutic positioning or in the utilization protocols. Autonomous regions are not only competent to establish access criteria for reimbursed drugs, but they are also able to participate in CIPM meetings either as members (on a rotating basis) or as observers. The degree of implementation of prescribing control systems varies among

regions. While in some of them they have an impact on prescribing choices, in the others they remain in the form of recommendation (64) (102,103).

Regional HTA evaluations are publicly available.

2.7. Comparison between countries

A summary table comparing the different HTA agencies of the countries in scope has been developed to show their main similarities and differences.

All the agencies have a national scope and additionally Italy and Spain have also other agencies who act at the regional level. For example, UVEF (*Unità di Valutazione dell'Efficacia del Farmaco*, Drug Efficacy Assessment Unity) is responsible for HTAs in the Veneto region and in Spain most economic evaluations for drugs are conducted at the regional level.

Across the study countries, HTA agencies exist mainly in the form of autonomous governmental bodies except Spain in which the institution depends on the MOH. Regulatory authorities in Italy and Spain in charge of the marketing authorization also perform HTA. The institution conducting the HTA, and the regulatory approval coincides in these countries (AIFA and AEMPS respectively).

All agencies follow a clinical assessment approach for their assessment and all countries except France and Germany follow some type of economic evaluation as the main analytical method to determine the value of new technologies. In France, economic evaluations are assessed by CEESP and might be used for pricing decisions. Both France and Germany used to apply a comparative assessment of clinical benefit as the sole methodology.

Additionally, NICE focuses on CEA, seeking to establish whether differences in expected costs between treatments can be justified in terms of changes in expected health benefit outcomes. Currently, the QALY is considered to be the most appropriate generic measure of health benefit that reflects both mortality and health-related quality of life effects. NICE is the only agency from the agencies in scope that uses an explicit CE threshold range.

When it comes to Spain and Italy, their HTA bodies focus mostly on budget impact.

There are currently no formal criteria for linking price to therapeutic value in Italy and Spain. France and Germany use a similar added therapeutic benefit classification scale where a drug is considered to have “less benefit,” “no evidence of benefit,” “minor benefit,” “considerable benefit,” and “major benefit” compared with the existing drugs. This scale is important because

the lack of benefit generally results in the price of the drug not being higher than that of the comparator and in a low rate of reimbursement for the general population.

France, Germany, and England use formal scales for defining health gain relative to a comparator (ASMR in France, Added Benefit in Germany, QALY gain in and England), and to an extent, the price of the drug is related to this measure of health gain (27,104,105).

Finally, as per the price negotiation, just AIFA and NICE integrate this part in the HTA decision-making process. In Germany it is managed by the sickness funds and in the case of France and Spain the price is decided by the MOH. In France, the price is negotiated by the CEPS with the concerned manufacturer.

Table I. Comparison of the different HTA agencies in the countries of scope

	FRANCE (HAS/CEESP)	GERMANY (IQWiG commissioned by G-BA)	ITALY (AIFA)	SPAIN (AEMPS)	ENGLAND (NICE)
Scope of the HTA process	National	National	National and regional	National and regional	National
Organization and governance of the healthcare system	Centralized	Centralized	Decentralized	Decentralized	Centralized
Institution conducting the HTA	HAS	IQWiG conducts clinical HTA on all new drugs. GB-A decides level of added benefit.	AIFA	AEMPS conducts clinical HTA on some new drugs (IPT). The regions and hospital pharmacies may conduct further HTA	NICE
Institution responsible of pricing and reimbursement	CEPS (MOH) decides price. UNCAM decides level of reimbursement	GKV-SV	CPR (AIFA)	CIPM (MOH)	NICE
Price negotiation as part of the HTA decision-making process	No	No	Yes	No	Yes
Type of HTA criteria	Clinical	Clinical	Clinical, budget impact	Clinical, budget impact	Clinical, cost-effectiveness
Criteria used for decision making	Inpatient drugs included in the positive list are reimbursed at 100%. For outpatient drugs, the reimbursement rate (between 15% and 65%) depends on whether the actual benefit level is judged mild, moderate or important. The price depends on the improvement in	Price and reimbursement depend on whether the added benefit level is judged major, considerable, or mild, and the strength of evidence.	Additional therapeutic value, budget impact.	Therapeutic usefulness, budget impact, and cost-effectiveness	Incremental cost per QALY

	actual benefit offered by the drug.				
Regulatory agency	ANSM	BFARM	AIFA	AEMPS	MHRA

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios- Spanish Agency for Medicines and Healthcare Products
AIFA: Agenzia Italiana del Farmaco- Italian Medicines Agency, ANSM: *Agence nationale de sécurité du Médicament et des produits de santé*, French National Agency for Medicines and Health Products Safety
BFARM: Federal Institute for Drugs and Medical Devices, CEESP: *Commission Evaluation Economique et de Santé Publique- Economic and Public Health Assessment Committee*, CIPM: *Comité Interministerial de Precios de Medicamentos y Productos Sanitarios- Interministerial- Committee on Pricing and Healthcare Products*
CPR: *Comitato Prezzi e Rimborsio- Pricing and Reimbursement Committee*, GKV-SV: *Gesetzlichen Krankenversicherung Spitzenverband*, National Association of Statutory Health Insurance Funds, HAS: Haute Autorité de Santé, French National Authority for Health, IPT: *Informe de Posicionamiento Terapéutico- Therapeutic Positioning Report*, IQWiG: *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen- Institute for Quality and Efficiency in Health Care*, MHRA: Medicines and Healthcare products Regulatory Agency, NICE: National Institute for Healthcare and Care Excellence, MOH: Ministry of Health, UNCAM: *Union National des Caisses d'Assurance Maladie- French National Union of Health Insurance Funds*, QALY: Quality adjusted life-year

3. Deliberation in Health Technology Assessment

Deliberation is the critical examination of a problem, which involves the weighing of reasons for and against specific action (7). While deliberative process involves a group of people, it can be further defined as process enabling receiving and exchanging of the information between the group of actors, in order to critically review an issue, and to achieve agreement and subsequently inform decision making (106).

Within the HTA arena, the definition of deliberation implies a series of coordinated activities allowing a group of people to gather information to critically examine an issue and come up with a recommendation (7).

While deliberation can take place in several stages of HTA process, including horizon scanning, monitoring, assessment, appraisal and evaluation of the recommendation, the impact of deliberation is the highest in appraisal phase. Therefore, for the purpose of this PhD thesis we will focus on the appraisal (43,107).

Proper conduction of high quality, reliable and reproducible deliberative process is not easy, therefore people responsible for designing the HTA deliberative processes should consider an appropriate selection of desired outcomes and examination of general factors, such as key decision criteria, identity of participants and their roles, the measurement of benefits and costs, as well as the significance to be attached to factors like equity and public acceptability. It is important to note, that the HTA deliberative process may be also influenced by other, often

subjective, and not clearly defined, considerations such as political, social, behavioural, or ethical aspects that affect the final decision (12,107,108). Previous HTA have perceived the difficulty of integrating subjective factors, for example, difficulty in developing CEA considering equity principles such as disease severity (108).

In Chapter 2 we will focus on the implicit factors that are present in the HTA deliberative process and that may influence the recommendations. We will identify them, and we will explore the degree of influence these factors have on the deliberative process.

4. CONCLUSIONS OF CHAPTER 1

HTA is well-established in Europe, notably in the western European countries and has a solid history since the late 1980's. The heterogeneity of the different healthcare systems and HTA institutions in the continent has been addressed throughout different initiatives promoted by the EC since the early 1990's. First, with the foundation of INAHTA, and EUR-ASSESS with the goal to improve the coordination and support best practices through the continuous exchange of information. Then, with the foundation of EUNETHTA in 2005 to improve efficiencies and avoid duplication of efforts by creating a sustainable European network for HTA. However, this initiative did not achieve a complete harmonisation in terms of HTA on the same HT given an inefficient voluntary cooperation.

There are similarities and differences between the five countries in scope of this thesis (France, Germany, Italy, Spain, and UK). As previously described in 2.4., each country has different ways to conduct its HTA process.

All the agencies have a national scope except of Italy and Spain who have also regional agencies. The five agencies focus on a clinical assessment approach for their assessment and all countries except for France and Germany follow some type of economic evaluation as the main method to assess the value of new technologies. France and Germany use a similar added therapeutic benefit classification.

There are currently no formal criteria for linking price to therapeutic value in Italy and Spain. Finally, the price negotiations with manufacturers happen as part of the HTA process just in Italy and England.

The heterogeneity in the assessments across these countries, which also may result in differences in reimbursement recommendations has led to the proposal of the regulation from the EC to support Member States cooperation for a joint clinical assessment of HT, expected to come into force from 2025 to specific medicinal products and planning to apply for all medicines from 2030.

In the appraisal phase there are factors other than the classical ones that are considered in the deliberation that are not explicitly acknowledged. For these reasons, in the next chapter we will study additional factors that can influence the HTA deliberative process and that are not explicitly considered in the decision-making process to better understand the weight they have in the process and in the subsequent recommendations. A SLR and a mixed-methods research will be presented as part of the research projects that contributed to elevate our understanding around the degree of influence of these implicit factors in the HTA deliberative process.

CHAPTER 2: IMPLICIT FACTORS AND THEIR INFLUENCE IN THE HEALTH TECHNOLOGY ASSESSMENT DELIBERATIVE PROCESS

Chapter 1 described the different HTA bodies and processes from the countries in scope. Despite having a number of criteria consistent across the five countries in scope, it has been found heterogeneity in the HTA and pricing and reimbursement recommendations in these countries. Although some of these discrepancies could be explained by the specific particularities of the country and of the HTA processes themselves, there may be additional criteria remaining implicit in the deliberative decision-making process, resulting in some form of bias.

This chapter will focus on different biases that are intrinsic to the decision-making and therefore difficult to clearly identify them. We will go through country specific examples showing the heterogeneity in HTA recommendations when assessing the same medicines.

Then we will present the definition of implicit factors that we have developed and that we believe is a key contribution in this PhD thesis.

We will then present the two articles that constitute the core of this chapter and that address the implicit factors in the HTA process. The first one is an SLR that will be presented in a subsequent section in this chapter. The objective of this SLR was to identify the implicit factors influencing the HTA deliberative process in Europe. This research was published in the Journal of Market Access and Health Policy.

The last part of the chapter will deal with a mixed-methods research that was performed to contrast and expand the findings from the SLR. This article has been published in Health Policy OPEN. This piece of research will lead us to our final chapter and project of this PhD thesis.

1. Biases in human decision-making

Human decision-making is a fundamental process for problem-solving, and therefore has influence on many aspects of our lives. The key attributes of decision making that are closely linked with each other are the reasoning and recognition. Reasoning has a logical basis as it relates to weighing alternatives and choosing decisions based on criteria. However, recognition may result in a decision or action without a logical basis. Therefore, human decision-making is characterised by simplifications and deviations from rationality (“heuristics”) (109).

There are several types of factors that can impact decision-making. As of now we can list:

- Contextual factors, or “situation specific considerations” such as equity, severity of the disease and affordability and any type of external influence coming from politics, society, media, or industry for example (110) ;
- Cognitive biases that may be defined as a systematic deviation from rationality in decision-making or judgment (111).

Cognitive biases seem the most complex as they cannot be clearly defined and captured, therefore they are extremely difficult to eliminate. There are certain situations, in which cognitive bias may be positive by allowing people to make quicker and more optimal decisions when little information is available, or a fast decision is needed. Nonetheless, in many situations cognitive bias may lead to inaccurate conclusions, misjudgement, and misinterpretation of information (112). There are many types of cognitive biases that can be classified in different categories in Table II. The definitions of each of the biases can be found in Annex 1.

Table II. Cognitive biases

Biases at the individual or group level	Biases generally at a group/organizational level	Conflict of interest	Fallacies	Ethical violations
<ul style="list-style-type: none"> • Self-serving bias • Anchoring • Confirmation bias • In group conformity • Authority bias • Affect heuristic • Framing effects • Search satisfying • Consistency tendency • Reductionism bias • Overconfidence bias • Automation bias • Novelty • Optimism bias • Intellectual bias 	<ul style="list-style-type: none"> • Group thinking • Halo effect • Thinking inside the box • Herd effect • Specialty bias • Scientific inbreeding 	<ul style="list-style-type: none"> • Financial • Non-financial 	<ul style="list-style-type: none"> • Planning fallacy • Sunk-cost fallacy • Fallacy of silence 	<ul style="list-style-type: none"> • Dishonesty • Cheating • Misinterpretation of data • Fraud

Adapted from Seshia S. et al. Evidence-informed person-centered healthcare (part I): Do ‘cognitive biases plus’ at organizational levels influence quality of evidence? *Journal of Evaluation in Clinical Practice* 20 (2014) 734–747 (112)

2. Biases in Health Technology Assessment

The term 'bias' is typically used to refer to both prejudices and implicit stereotypes and raises serious concerns in healthcare. Implicit biases have been identified as one potential factor of healthcare disparities.

According to Seshia et al. "cognitive biases are inherent to all humans and no organization or member of organization can claim immunity" (112). Cognitive biases are also an unavoidable part of healthcare decision-making and can compromise the quality of healthcare evidence. Implicit associations may influence our judgments resulting in biases (113).

As all decisions made by humans, decisions in healthcare are also associated with some subjective factors like experience, opinion, preference, value judgements and trade-off tolerance (114,115).

Value judgments are present in the HTA decision-making, mostly in those countries that have less formalized explicit processes in place. In the appraisal, judgments are made on the importance of different factors such as burden of disease, effectiveness, that are valued differently by different stakeholders. This in turn influences the resource allocation. Many value judgments are implicit, and it is recommended to make them explicit to make the HTA process more transparent and clearer (16,116,117).

The occurrence of biases has been perceived as one of the main barriers to ensuring quality in the HTA decision making. Subjective influences and biases need to be acknowledged and considered when making decisions and minimized where possible (15).

There are biases that may have particular relevance to healthcare. Those are self-serving bias, specialty bias, automation bias, novelty bias, group thinking and thinking inside the box, herd effect and political influences (112).

Self-serving bias "is associated with rationalization of one's actions and impairment of self-view of morality".

Specialty bias in healthcare can lead to compromise care given the own perspective acquired through the discipline.

Automation bias relates to the “biases that can occur with the use of automated and decision support systems”.

Novelty bias is the tendency to believe that a new treatment is better than the old one.

Group thinking is associated with confirmation and in group conformity. In this case, opposing views to the group are discouraged.

Thinking inside the box is the tendency towards inflexibility of thinking.

Herd effect refers to the alignment of thoughts in a group often led by an individual or organization (112).

However, to our knowledge there is no extensive literature on the specific biases found in the HTA process. Bujar et al. refer to the importance for the HTA agencies to assess the impact of the so-called “intellectual biases” on decision-making during meetings, which may lead the committee members believing information which appears more convenient (118). Hofmann et al. stress out the value judgments as an important element constitutive of the HTA process (16).

We believe additional biases found in HTA can be authority bias, affect heuristic, halo effect and conflict of interests.

Authority bias is present when an individual feels confident in a decision validated by an authority figure.

Affect heuristic is the tendency for subjective feelings to influence decisions. People let their likes and dislikes determine their beliefs and their emotional attitudes.

Halo effect refers to the significant weight that beliefs of individuals within a group have in decision-making (119).

Lastly, conflict of interest is associated with incentive bias and other biases and can apply to individuals or organizations (112).

The presence of these factors may be one of the important reasons for differences between recommendations by HTA advisors and related reimbursement decisions reducing the transparency and fairness of healthcare resource allocation (44) (38,39).

3. Diverging Health Technology Assessment recommendations

3.1. Overview

Health systems in Europe share common values and principles, including universality (e.g., equal access to health care), access to high quality of care, equity, and solidarity. The key question is how such broad criteria are explicitly defined and applied by HTA agencies and ultimately interpreted by decision makers who use HTA to support coverage decision making (120).

It is known that divergences in HTA recommendations exist. The implication of diverging HTA recommendations is that a particular treatment may be funded in one region but not in another, creating a disparity in access to medicines (26). Divergences in HTA recommendations between countries may be partially explained by differences in HTA frameworks. For example, decisions made with the use of the clinically driven German HTA framework may be different from decisions made with the use of the CE driven English HTA framework. However, as previously noted in the introduction of this PhD thesis, there are situations where differences in coverage decisions cannot be explained by differences in HTA frameworks (21–23). A better understanding of factors which are beyond the HTA frameworks and influence and drive decisions, is critical in attempts to determine whether and how HTA processes across countries can be approached. This will enable to propose solutions to mitigate these not well-defined factors and subsequently the disparities derived from them.

Legitimacy of the decision-making processes informed by HTA can be strengthened by linking health system values and the criteria used, that is, by making them explicit and transparent. For that reason, HTA agencies and health authorities need guidance on how to explicitly address health system values and how to involve all relevant stakeholders (114,121).

In the last years, significant efforts have been made to improve decision-making and promote fair, efficient, and high-quality healthcare. In connection with these efforts, HTA process should use clear methods and criteria to determine the real value of a drug to inform decision-making (3). However, evidence from the literature shows that a formalized set of criteria may not always capture all factors impacting the decision. Some of the examples illustrating this statement are presented below in paragraph 3.2.

3.2. Examples illustrating the presence of other factors influencing the HTA recommendations

In this section we provide some examples of cases that were identified in the literature and in which the influence of other factors beyond the classical and conventional factors in the HTA recommendations are presented.

3.2.1. Heterogeneity in the decision-making factors and in the tools to address uncertainty

Despite similar HTA decision frameworks, unexplained heterogeneity of decisions for the same drug and indication may be observed (27) (110). This was illustrated by the study of Nicod et al. (26) evaluating similarities and differences in the HTA decisions when assessing social and value judgments across five countries with CE driven HTA frameworks (England, Scotland, Sweden, Australia, and Canada). The study demonstrated that 46% of recommendations diverged and showed mainly poor to moderate level of agreement across the five evaluated countries. Such a significant difference may be the evidence that HTA recommendations are influenced by different perceptions of benefit and value, different priorities in individual settings, and use of different tools for addressing uncertainty of the evidence (26).

Another study performed by the previous author explored how broader aspects of treatments value and the impact on patients not captured by HTA may influence HTA processes in England, Scotland, Sweden, and France (122). One hundred and twenty-five factors were identified as “other considerations” which included unmet need, innovativeness, severity of the disease, the impact on families’ and friends’ life, the nature of the disease and the need for treatment alternatives. Some of them, such as unmet need and disease severity are difficult to define since they include several determinants. Depending on the country, 18% to 100% of these factors were the main reasons for the final decision with the lowest percentage for England and the highest for France. Some of them were non-quantified or non-elicited and related to the assessor’s judgement, for instance, assumptions based on economic modelling and considerations around treatment and disease based on previous experience.

The study identified differences in the acceptance of ICER values between some drugs in both NICE and SMC assessments, agencies sharing the same HTA philosophy. In France, there is no ICER threshold, so informal methods are used to integrate social and political values into

assessments. It is not clear whether these determinants of value are consistently accounted for in all evaluated cases.

In another study by Jommi et al. conducted in Italy, authors indicated that empirical evidence related to variables influencing orphan drug prices in Italy is quite scarce (123). They concluded that both prevalence and therapeutic value are somehow correlated with the pricing decisions, however the role played by the quality of the evidence is more controversial. As the people responsible for the drug assessment and appraisal are aware of the difficulty of providing robust evidence for orphan drugs, the quality of the evidence has a lower influence on the reimbursement decision. It was also stated that more transparency in the orphan drug decision-making is needed, highlighting the presence of some non-explicit drivers in pricing and reimbursement process.

3.2.2. Country-specific examples

Another study showing the influence of non-explicit factors and impact of different perspectives across stakeholders on decisions in healthcare, was a survey conducted by Wahlster et al (124). The first part of the survey captured individual perspectives of German stakeholders on the most important criteria for the value of healthcare interventions. Participants representing different types of stakeholders were asked to provide relative weights for each criterion derived from the multi-criteria decision analysis (MCDA) core model. Stakeholders indicated that the most important criteria for the reimbursement were “improvement of efficacy/effectiveness”, “improvements in patient reported outcomes”, “disease severity”, “improvement in safety”, and “quality of evidence”. Even though severity of the disease was assessed as one of the most important factors for the healthcare decision making, current policies in Germany do not actively take it into account. The process of incremental benefit assessment mentions consideration of the disease severity, but it is not clear how it is evaluated.

Although comparative analysis was not possible due to the small group size, “disease severity” appeared to be less important for the group of policymakers compared to all participants, which may indicate a discrepancy between policies and ethical considerations.

On the other hand, “quality of the evidence” was more important for policymakers than for other stakeholders. The “budget impact of the intervention” had the lowest weight for all stakeholders. However, the highest standard deviation across all criteria implied a poor agreement on the relevance of economic issues, where the lowest importance of economic

criteria was observed among health professionals. Moreover, most of stakeholders reported that criteria such as “goal of healthcare” or “fairness and priorities” should be considered and more formally integrated into reimbursement processes (124).

Although some factors are directly included in the HTA framework, they may be complex to address, and their weighting may not be explicit.

In the study by Bryan et al. (108) examining the factors impacting the use of CEA in the NICE decision-making process, the difficulty of reconciling CEA with equity considerations, such as disease severity, was raised. Diverging views were expressed from NICE committee members with different backgrounds and expertise. Some criticized CEA, pointing out that currently, no methodological approach was available to take equity into consideration within this kind of analysis. Equity is an important element of NICE assessment framework; however, it is not part of the CEA methodology. Therefore, it would be beneficial to be considered in the HTA deliberative process. While equity is an explicit factor present in the NICE deliberative process, the weight attributed to it by different stakeholders is different and is implicit.

3.2.3. Contextual factors

The study by Kleinhout-Vliek et al. shows that contextual factors, which are not described in HTA frameworks play a significant role in decision-making in different countries (110).

This study evaluated the use of contextual factors in HTA in England, Germany, the Netherlands, and Belgium. Four interventions were analysed (nivolumab, benzodiazepines, smoking cessation therapies - both psychotherapeutic and pharmaceutical, and walking aids with wheels). For the sake of this thesis, we will focus just on the pharmacological therapies.

The number of contextual factors considered in decision-making varied across the countries from six factors in Germany, seven factors in England and Belgium up to 16 types of contextual factors in the Netherlands. Some of them were made explicit and were stated in decision documents, while others were used implicitly in the deliberation and not clearly communicated (Table III).

Table III. Overview of contextual factors used in HTA decision for nivolumab, benzodiazepines and smoking cessation therapies (110).

Contextual factor	Nivolumab	Benzodiazepines	Smoking cessation therapies
Definition of illness	NL		NL, BE, EN, DE
Equity/Fairness/Justice			NL, EN
Individual cost	NL	NL	NL
Individual responsibility			NL
Medical necessity		NL	
Morbidity/Severity	NL, BE, EN, DE	NL, EN	NL, BE, EN
Need	NL, BE, EN, DE		
(No) Alternative	NL, BE, EN	NL, EN	
Patient-diagnosis		EL, EN	
Range of normality			
Similar treatments			NL, DE
Social impact			NL, BE
Societal Functioning	BE, EN	EN	NL, DE
Vulnerability/Compassion			NL, BE
Substitution		NL	

Under-consumption			NL
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Legend: BE – Belgium; DE – Germany; EN – England; NL – The Netherlands

Adapted from Kleinhout-Vliek T. et al. Around the Tables – Contextual Factors in Healthcare Coverage Decisions Across Western Europe. *Int J Health Policy Manag* [Internet]. 2020 (110).

The specific cases of the study are described below. The following cases were assessed across the four countries based on the contextual factors shown in the above table.

3.2.3.1.1. Case of nivolumab

This case suggests that contextual factors such as disease severity and high unmet need were considered, even though they are not present in some HTA frameworks. The authors of the study identified some similarities between argumentations in HTA decisions for nivolumab in both Belgium and Germany, which issued positive reimbursement decisions. In both countries, price and reimbursement recommendations relied strongly on the quality of life, severity of the disease and low survival rate. Even though disease severity is not part of the HTA decision framework in Germany, it was an important factor influencing the decision. Initially, NICE recognised nivolumab as not cost-effective and noted great uncertainty of the evidence. However, as the committee determined a high medical need, high morbidity, symptoms that are difficult to manage and lack of alternatives (the factor that is not usually considered in NICE appraisal process), additional social value judgments were included. This additional argumentation finally resulted in positive reimbursement decision, but only through the CDF after renegotiation of the price. Similarly in the Netherlands, the initial recommendation was negative due on CE grounds. However, as high effectiveness was noted, additional factors such as high burden of the disease and limited life expectancy were considered. After negotiations with MOH, the drug was finally included into the benefit package (110).

3.2.3.1.2. Case of benzodiazepines

In this case, as the result of the deliberative process, two different decisions addressing the same issue (misuse of benzodiazepines) were made. More restrictive approach was shown by the Dutch agency, while NICE acknowledged the unmet need in the population and issued a less restrictive recommendation.

In the Netherlands, the HTA agency called Dutch National Health Care Institute (*Zorginstituut Nederland*, ZIN) advised against continued coverage of benzodiazepines. It was caused by the

fact that although the indication was for short-term use, there was a large number of chronic users. A negative decision was made, despite the high burden of the disease and medically justified short-term use of benzodiazepines. Mitigation of misuse and possibility of potential switch of benzodiazepine users to other covered medicines outweighed other criteria and were the key decision drivers. The exception was made for anxiety disorders, epilepsy, and multiple psychiatric disorders.

On the other hand, in England short-term use of benzodiazepines was recommended for more medical indications compared with the Netherlands (each with separate appraisal document), even though benzodiazepines over-use was also noted as a problem. The decision was driven by high humanistic burden and the risk of misuse was mitigated by recommendation of second-line use of benzodiazepines – only in case of non-response to other drugs (110).

3.2.3.1.3. Case of smoking cessation therapies

The case of smoking cessation therapies suggests that contextual factors, such as political impact and different perception of severity may have a major impact on the reimbursement decision.

In the Netherlands, there were several changes in the coverage decision for smoking cessation therapies. One of the reasons for the changes, was that smoking cessation became a political issue and changes in the government affected the reimbursement status. The final decision was to fund a limited number of interventions, such as nortriptyline. In this complex decision-making process, several contextual factors were considered, for example individual's personal responsibility for his own health, increasing the number of people who would attempt to quit smoking and the fact that smoking was defined as an addiction leading to reduction in quality of life and causing damage to others.

In England smoking cessation therapies are covered broadly for all residents over 12 years of age. The guidelines from NICE highlighted that smoking is the main cause of premature death and preventable illness.

In Belgium, smoking-cessation has never been formally discussed. However, €20 of the first eight sessions of smoking cessation therapies is covered by Belgian National Cancer Initiative and smoking cessation aid prescribed by a tobaccologist is reimbursed in Flanders. In the past, the compulsory health insurance covered smoking cessation therapies only for pregnant women, revealing a potential societal impact argumentation.

Lastly, in Germany smoking cessation therapies were excluded from the benefits package as they were considered “lifestyle medicines” (110).

Ultimately, contextual factors are an important element of decision making related to orphan drugs. Due to the small population as well as heterogeneity of the diseases, generating robust evidence for these drugs is especially challenging. Because of this, scientific and social value judgments are an inseparable part of the decision processes for these drugs (122).

4. Definition of “implicit factors”

HTA is a very complex matter that spans beyond written HTA frameworks. The examples provided above prove the existence of factors that influence the HTA deliberative process and that are not explicitly disclosed in the HTA guidelines. From now, we will refer to these factors as “implicit factors”. Since there is no formal definition of implicit factors related to the HTA deliberative processes in the public domain, we propose a definition that will be elaborated in the text further below.

As we saw in the Section 2 of Chapter 1, the explicit criteria more frequently identified across the HTA agencies in scope of this PhD thesis are efficacy, safety, severity of disease, therapeutic added benefit, CE, and quality of life.

In healthcare, explicit criteria are associated with scrutiny and scientific validity, whereas implicit criteria are linked to judgments and subject to empirical verification. While an explicit factor involves well-defined criteria, objectivity and insensitiveness, an implicit factor is referred as a global impression, that can be biased by the experience and judgment (124).

The implicit biases in healthcare, described as “implicit and unconscious associations that may influence our judgments resulting in biases” may operate to the disadvantage of vulnerable populations such as minority ethnic populations, populations with low resources, the elderly, etc. Fitzgerald C. and Hurst S. found evidence for biases amongst physicians and nurses, affecting their interactions with patients and diagnosis. The authors of the study highlighted the need for the healthcare profession to address the role of implicit biases in disparities in healthcare (113).

The **implicit factors** accommodate considerations that are not represented in any particular set of explicit criteria. The ‘explicit’ is related to the objectivity and defined criteria while the ‘implicit’ is related to subjectivity, biases, and non-defined criteria (125).

We chose the term “implicit” because we wanted to stress the differences between both kind of factors and since “explicit” clearly conveys the well-defined idea of factors, we considered the best way to call them out was by using its antonym.

We identified different terms in the literature that refer in some way to the implicit factors. These terms can be classified in the following categories: ethics, psychology, qualification and experience, politics and society, culture, functional role, and disease perception (11,15,16,18,115,116,121,126).

Translating this into the HTA space, we understand explicit factors as all the factors that are well described in the HTA frameworks/guidelines and are used as a reference to guide the HTA recommendations. To ensure we have the same understanding when we allude to implicit factors in HTA, we developed the following definition: **Implicit factors in HTA refer to all non-defined factors that are not explicitly collected or described in the HTA guidelines and that may influence the HTA deliberative process and the subsequent HTA recommendations.**

While deliberative processes are not new to HTA and their importance is acknowledged, little research has been done in understanding the implicit factors contributing to the final decisions that determine the recommendations (24).

There is also scarce research to inform the design and development of effective and efficient deliberative processes (18,127). For these reasons, we developed an SLR and a mixed-methods research that will be presented in the subsequent sections of this chapter.

5. Systematic literature review on the implicit factors influencing Health Technology Assessment deliberative processes in Europe

The research presented in this section has been published as an article in the Journal of Market Access & Health Policy.

Clara Monleón, Hans-Martin Späth, Carlos Crespo, Claude Dussart & Mondher Toumi (2022) Systematic literature review on implicit factors influencing the HTA deliberative processes in Europe, Journal of Market Access & Health Policy, 10:1, 2094047

5.1. Introduction

In the last decades, substantial efforts have been made to improve decision-making and promote equitable, efficient, and high-quality healthcare systems. As part of such efforts, the process of HTA has arisen as one that uses explicit methods and criteria to determine the value of a health technology at different points in its lifecycle to inform decision-making and promote an equitable and high-quality system (Chapter 1, Section 1) (3).

With global healthcare expenditure rising significantly in the first quarter of the 2000's (from 478.81 US\$ per capita in 2000 to 1,015.87 US\$ per capita in 2016 (128)), the HTA process is becoming increasingly relevant as a tool for assessing the value of new drug therapies in the healthcare system and subsequent decisions on price and reimbursement (Chapter 1, Section 1) (129).

In an era where healthcare systems strive to deliver innovation and healthcare coverage, the HTA process has come to play a critical role in deliberative decision-making processes, as a means of demonstrating added value of new health interventions (i.e., drugs, medical devices, surgical procedures (4)) beyond efficacy and safety (9) to inform reimbursement decisions (18).

One of the key strategic objectives of the EUnetHTA has been to promote more effective use of resources and increase HTA input into decision-making processes in Europe (32). As previously mentioned, the EUnetHTA Core model comprises nine dimensions of value, with safety, efficacy and CE being the most assessed factors in Europe and country-specific guidelines have been described elsewhere (64) (87,130–133) (Chapter 1, Section 1).

Beyond the evidence supporting the technology under review, HTA recommendations may be influenced by implicit factors inherent in the decision-making itself. As a result, decisions based

on such factors may question the quality of decision-making (16). Additionally, depending on the country, HTA systems vary in their role and in the way decisions are made (40).

There is evidence showing that discrepancies may occur between recommendations by HTA advisory bodies and their related reimbursement decisions, which could potentially compromise the transparency and fairness of healthcare resource allocation (117). Such discrepancies may to some extent be explained by variations in decision criteria, and result from contextual or implicit factors such as implicit preferences (38,39).

The definition of implicit factors was already presented (see Chapter 2, Section 4).

However, there has been limited systematic research on how features of the deliberative processes themselves influence the outcomes. Both producers and users of HTA, as well as other stakeholders, are interested in better understanding the reasons and the way HTA decisions are made (117).

The geographic scope of this research covers France, Germany, Italy, Spain and the UK. As previously mentioned in Chapter 1 Section 2.1., these five countries represent 73% of the EU population in 2020 and according to Eurostat the health care expenditure of all providers in these countries represented 72% of the EU-28 in 2019 (50); they all have established HTA agencies and recognized HTA processes (27) (49).

This group of countries also represent the Bismarck and Beveridge systems. In the first group, there are countries like Germany, France and Italy in which healthcare is financed by third party payers, based on employers 'mandatory contributions. In the second group, there are countries like UK and Spain in which health systems are funded by the state through taxation. Beveridge systems are more likely to establish HTA agencies, whereas Bismarckian systems are likely to resist. This could also explain why the HTA agencies in Spain and the UK were in late 1990s whereas Germany and Italy saw their HTA bodies set in 2000s (134).

The term deliberation refers to critical assessment and discussion of an issue and involves the weighing of arguments for and against a measure (117).

Deliberation can take place in several stages of HTA process, including horizon scanning, monitoring, assessment, appraisal, and evaluation of the recommendation (135).

Following the assessment phase, the information is synthesized and integrated through an appraisal process, after which recommendations are made (38) (117).

The objective of this SLR was to identify and categorize implicit factors involved in the HTA

deliberative process of medicines in Germany, France, Italy, UK, and Spain.

5.2. Materials and methods

5.2.1. Eligibility criteria

A systematic review was conducted using the reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (136). Two reviewers (CM, CC) screened the citations (titles, abstracts, and full text from eligible articles), and performed data extraction and analysis. CM is a specialist in Market Access. CC is an expert in statistics. Each methodological step was performed independently by both reviewers. Each reviewer's results were compared and discussed, and in case of divergence, a consensus was reached. The reviewers agreed on all but one article, however this was resolved on discussion by revisiting the eligibility criteria. Additionally, a third reviewer (JM) helped to resolve these disagreements to reach a final decision. JM is an expert in Health Economics.

5.2.2. Information sources and search strategy

The literature review was performed in the following databases: Pubmed, Google Scholar, The Cochrane Database of Systematic Reviews (CDSR), and Centre for Reviews and Dissemination (CRD). ISPOR (The Professional Society for Health Economics and Outcomes Research) presentations database was searched manually. The reference sections of all identified articles were screened for additional articles that may be relevant for this SLR.

Searches were limited to the period 2009-2019, and to English, French, German, Italian and Spanish languages. We aimed to identify a time window for the SLR reflective of the period with most of the scientific production in the HTA field. We used the search strategy "HTA [tiab]" on Pubmed with no filters, to retrieve all the publications with the acronym HTA in the title or in the abstract. Almost 80% of all publications retrieved with this search strategy (1972-2019) were published between 2009-2019, which served as the criterion for the final time window for our SLR.

In accordance with the Methodological Expectations of Cochrane Intervention Reviews (MECIR) (version February 2022), for developing search strategies for bibliographic databases, appropriate controlled vocabulary (Medical Subject Headings MeSH) and free-text terms were

defined (137).

Results were imported into an Excel file and duplicated articles were removed.

In addition, grey literature searches were conducted using Google to identify documents not indexed in scientific journals, for instance, reports or textbooks, which were added to the bank of references as applicable.

5.2.3. Study selection

Data selection was performed based on the Cochrane Handbook for Systematic Reviews of Interventions (138). Citations were screened following a stepwise approach. First, all titles and abstracts identified in the search strategy were independently reviewed by two reviewers based on pre-defined eligibility criteria from the study protocol. Studies were categorised as “included”, “unsure” or “excluded”. The second step included a full-text review of all studies categorised as “included” or “unsure” during the first phase. The full-text review was continued until all articles were categorised as either “included” or “excluded”. Following this step, data collection was conducted.

5.2.4. Citations’ and full-text screening by eligibility criteria

The inclusion criteria in this SLR were the following:

- Articles containing information regarding implicit factors influencing HTA deliberative processes on medicines.
- Articles containing information about any of the five target countries together with information about other countries, were eligible for inclusion. However, only information pertaining to the target countries was synthesised.

Regarding the exclusion criteria, we focused on the following:

- Languages other than English, French, German, Italian and Spanish
- Year of publication: articles published before 2009 and after 2019
- Articles describing HTA decision-making processes related to medical devices,

diagnostic tests or medical procedures, specific therapeutic areas, and regional or local HTA decision-making processes.

- Articles describing shared decision making between patients and healthcare providers.

5.2.5. Data Extraction and Analysis

Data extraction from eligible articles was performed in two steps. The first step was to perform an extraction of implicit factors affecting HTA from each eligible article. This was followed by analysis of the data collected from the first extraction, and a second extraction was performed using a method known as the general inductive method (126). This method allows the development of general conclusions based on particular facts. Thus, the collected information was classified into categories of implicit factors.

5.3. Results

5.3.1. Articles description

A total of 1,021 references were obtained from the literature search strategy (Pubmed: 961; Google Scholar: 45; Cochrane: 5 and CRD: 10) and from the ISPOR Presentations database manual search (13). Removal of 459 duplicates resulted in 575 references, 100 of which were selected for full text assessment (Pubmed: 98; CRD: 2). From this selection, 92 articles were excluded for the following reasons: lack of relevant information on the decision-making process (n=76); methodology design for HTA (n=12); HTA decision-making in excluded countries (n=4). Thus, eight articles were selected for data extraction and analysis (Figure 3). The detailed search strategy is presented in Annex 2.

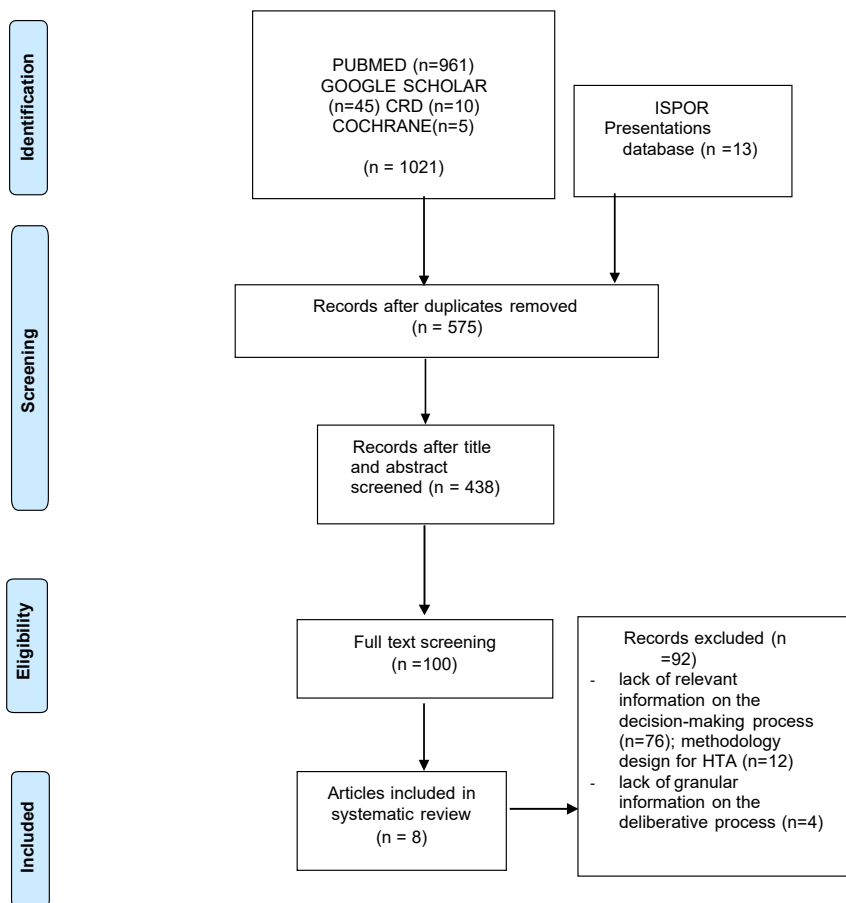


Figure 3. PRISMA Flow diagram

5.3.2. Articles description

Among the eight articles found in the literature, there were five that recognise and explain the occurrence of implicit factors in the HTA deliberative process, highlighting the need to further improve the deliberative process, and outlining a conceptual approach to address the problem (11,15,16,18,139). On the other hand, there are three articles that recognise the implicit factors and suggest a framework to address them and improve the transparency of the HTA decision-making (81,115,116).

When it comes to the first group of articles, the focus of their recommendations is on assessing and understanding the process and quality of HTA decision-making, as a mean to provide insights into the factors that influence the recommendations and decisions derived from it.

Interventions like increasing the degree of participation from stakeholders or getting formal feedback from internal and external stakeholders regarding the decision making could help to improve the quality of the decision-making process itself, and ultimately transparency and consistency in key decisions (11,16,115). Another approach to formalising the HTA decision-making process and making it more transparent is the use of the MCDA method. This method expands upon implicit factors not captured in the CEA such as fairness, equity, or disparities (116). Making explicit the implicit factors in the HTA process could contribute to improve transparency and legitimacy of the decision-making process (139).

In the study by Bujar et al. the quality of the decision-making processes of pharmaceutical companies was evaluated by the development of two questionnaires that were sent to 24 pharmaceutical companies and 16 HTA agencies. Responses from 11 companies and 11 HTA agencies were obtained. The authors identified some similarities between the decision-making processes of companies and agencies, for example, a primarily mixed internal decision-making system, the lack of systematic assessments of quality decision making, the use of committees and the rare use of formal frameworks.

However, there were some differences including using diverse processes to get the final decision. Most of the companies and agencies believed that there is a need to measure quality of decision. Moreover, the occurrence of biases was considered as relevant within the organization and almost all the participants thought that there was room for improvement in term of quality of decision making.

The findings of the study supported the need for more predictable and consistent processes of decision-making. This could be achieved by a systematic evaluation of the quality of decision making and using formal decision-making frameworks (15).

The aim of the study by Fisher et al. was to analyse influences of decision-making characteristics on the outcomes of reimbursement decisions. The authors assessed the likelihood of positive and negative coverage decisions with the use of non-parametric univariate tests, as well as binomial logistic regression. A negative correlation was found between a positive decision and whether the assessed technology is a medicine available on prescription. Other factors with the significant influence on a positive decision were CE, single disease area and higher number of stakeholders involved in voting.

The study suggested that despite claims for participative and transparent process, evidence generation seemed the most critical phase of decision-making, while differences in process

components had very limited influence on decision outcomes. Decisions followed the lines of evidence-based decision making and the assessment recommendations were usually adopted by decision makers (11).

The fifth section of Special Task Force report by Phelps et al. identified and discussed aggregation of information for benefit plan decision making and combining multiple components of value. The authors claimed that although additional factors could be added to the measures of value, they were not included in the measures of QALYs, several important approaches were discussed including the extended CE analysis, the approach-augmented CEA, MCDA, budget-setting and prioritization, deliberative processes, and the use of stated preference methods for "hedonic" value frameworks development (139).

The study by Kristensen et al. summarises the ISPOR HTA Council Working Group Report on good practices in HTA process. The purpose of this report was to create a basis for improved consistency in HTA decision-making approaches. The authors stated that despite development of many good practices in areas of assessment, there are many areas where they are lacking, like in measuring the impact of HTA and the use of deliberative processes (18).

Hofmann et al. aimed to show how numerous value judgments play a role in the HTA process and how important it is to acknowledge and address them. A panel of experts involved in HTA analysed whether value judgments have an impact on HTA results.

The findings showed the presence of value judgements during the selection of health technologies, as well as during the assessment and appraisal. The authors claim that they are basic elements of the HTA process, rather than a source of bias (16).

The summary of these articles is presented in Table IV.

Table IV. Articles proposing a concept as a way to address the research question.

Authors	Objective	Issues found in the HTA process	Recommendations
<i>Bujar et al. 2019 (15)</i>	<ul style="list-style-type: none"> - To identify and investigate decision- making framework utilisation within 24 pharmaceutical companies and 16 HTA agencies and assess the use of different methodologies for the quality of decision- making process. - To investigate the different cognitive biases in decision- making 	<ul style="list-style-type: none"> - Unstructured process - Presence of biases - Decision- making influenced by biases and emotional judgements. - Need to improve the quality of the decision- making process by making it more formal and predictable. - Divergence in HTA and reimbursement decision- making. - Most organisations do not measure the decision- making even if there is the belief that this assessment is key 	<p>Need for having more consistent, structured and predictable decision- making processes during the life cycle of medicines. This could be achieved through systematically evaluating the quality of decision making and encouraging utilisation of an international formal decision-making framework within companies and agencies.</p>
<i>Fischer et al. 2013 (11)</i>	<p>To analyse influences of transparency, stakeholder participation and the scientific assessment on decision outcomes in the deliberative process.</p>	<p>Impact of transparency on the reasonableness of decisions is contested.</p>	<p>Decision outcomes of coverage decisions appeared to be influenced mostly using evidence rather than the degree of transparency or participation. The inclusiveness of the HTA process increases the likelihood of a positive reimbursement decision</p>
<i>Phelps et al. 2018 (139)</i>	<p>Identify and analyse the value judgements present in the HTA process</p>	<p>Deliberative processes today are often informal and unstructured and often lack transparency.</p> <p>It is unclear what factors have been</p>	<p>MCDA models may provide the best opportunity for improvement, but they must be refined.</p> <p>Greater testing and use of MCDA models are</p>

		considered and how the decisions have been reached.	recommended.
<i>Kristensen et al. 2019.</i> (18)	To synthesize HTA good practices to support decision-making to create a basis for education and improved consistency in approaches to HTA informed decision making.	Lack of research on structured approach	Need to focus on developing good practices in using evidence to support decision-making through monitoring of HTA implementation and its inputs to various types of decision-making
<i>Hofmann et al. 2014</i> (16)	Review of existing methods solving aggregation issues through a health economics approach.	Value judgments are not explicit in the HTA appraisals and decision-making processes. Acknowledging and explicitly addressing value judgments may improve the accountability of HTA.	Making explicit the value judgments implicit in HTA as well as in the appraisal phase can promote the robustness of the decision-making. This can be supported by guidelines on the HTA appraisal and decision-making process. More research on how to highlight and integrate value judgments in HTA is needed.

5.3.3. Articles suggesting a framework to address implicit factors

The articles proposing a framework and guidelines on how to formalize the decision-making process call for a more integrative perspective on HTA, aligning it with evidence-informed deliberative and legitimate processes. Frameworks for improved HTA conduct and processes have been developed aiming for an explicit, transparent, and inclusive process (81,115,116).

The aim of the study by Donelan et al. was to investigate issues influencing the quality of decision-making. For this purpose, 29 semi-structured interviews were carried out with senior decision-makers. The analyses resulted in the identification of more than 30 major and almost 100 sub-themes that were subsequently consolidated into 19 themes. All of them were integrated into a

framework for quality decision-making. It was found that there is evidence of biases, organizational culture, and behavior of the organizations and other factors impacting the decision-making. A structured approach and a systematic framework addressing bias is proposed as a way to improve the quality of the decision-making (115).

Oortwijn et al. aimed to assess the comprehensiveness of HTA practices around the world and to provide recommendations for the improvement of legitimacy and fairness of decision-making processes. The authors developed an evaluation framework including thirteen criteria based on the INTEGRATE-HTA model and the Accountability for Reasonableness framework. Desk research and structured interviews were conducted to analyse HTA systems in selected middle-income and high-income countries. Both desk research and interviews showed that scoping is often not part of the HTA process and that both monitoring and evaluation of the HTA process are not well established across the countries. It was also stated that creating transparent and robust processes is time consuming. Based on the framework, the study provided recommendations on moving toward a more integrated decision-making process such as increasing stakeholder participation, improving transparency, and putting in place standardized methods to identify evidence (81).

Lastly, Baltussen et al. introduced "evidence-informed deliberative processes" as an alternative framework with an objective to enhance the legitimacy of the process. The proposed framework integrated both multicriteria decision analysis and accountability for reasonableness and aims to support the HTA agencies in their efforts to organize their processes, leveraging the key elements of the framework which are stakeholder involvement and implications for the HTA process.

In authors' opinion the responsibility of organizing stakeholder involvement should be taken by the agencies. They should also integrate their assessment and appraisal phases, subject their decision-making criteria to public scrutiny, use a checklist of potentially relevant criteria and publish their argumentation. Additionally, to make the process more democratic, the importance of HTA agencies having permanent lay members on their appraisal committees, as representatives of the public interest (116).

A summary of these three articles is presented in Table V.

Table V. Articles proposing a framework as a way to address the research question.

Authors	Objective	Issues found in the HTA process	Framework	Recommendations
<i>Donelan et al. 2015</i> (115)	To investigate and identify the issues that influence quality decision-making through semi-structured interviews to decision-makers.	Clear evidence of the presence of personal biases of decision-makers, other factors impacting the subjective decision-making approach of individuals, the culture and behaviour of the organisations in decision-making.	Integrated approach to quality decision-making capturing four stepwise domains: the structure, bias, impact and culture. The next phase following the design of a ‘framework for decision-making’ would be the development of a quantitative tool its psychometric robustness.	Quality decision-making needs a “structured approach”, education and training in decision-making techniques, evaluating the importance of the options an appreciation of the impact of the decision made.
<i>Oortwijn et al. 2017</i> (81)	To assess the level of comprehensiveness of HTA practices around the globe and formulate recommendations to enhance legitimacy and fairness of the decision-making Process.	Assessment and appraisal processes does not seem aligned in some systems. Regarding the appraisal phase, the monitoring and assessment of the process is not well established across HTA systems.	INTEGRATE-HTA model and the Accountability for Reasonableness framework	-Broad and multidisciplinary stakeholder involvement -Standardised methods to identify and appraise evidence for clinically important moderators or predictors of treatment effects. -Monitor and review the processes and results to assess their efficiency, consistency, and sustainability over time. - Transparency and robustness of the process will increase accountability and predictability

<p><i>Baltussen R. et al 2017 (116)</i></p>	<p>Describe the key elements of the framework Presents the implications for the conduct of HTA.</p>	<p>Presence of “vested interests” in the formal HTA processes.</p>	<p>Adopting evidence-informed deliberative processes as a value assessment framework could be an important step forward for HTA agencies in optimising the legitimacy of their priority-setting decisions.</p>	<p>-HTA agencies should take responsibility of organising stakeholder involvement. -Agencies are advised to integrate their assessment and appraisal phases -HTA agencies should subject their decision-making criteria to public scrutiny. -HTA agencies are advised to use a checklist of potentially relevant criteria and to provide argumentation for how each criterion affected the recommendation. -HTA agencies must publish their argumentation and establish options for appeal.</p>
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5.3.4. Categories of implicit factors

The HTA deliberative process is influenced by a number of implicit factors related to the behaviour and personal values of the individuals involved as well as to the context in which this process is performed. These factors have been grouped under categories based on the frequency they have been mentioned in the literature. The categories are ethics, psychology, qualification and experience, politics and society, culture, functional role, and disease perception (Table VI).

Table VI. Implicit factors identified in the literature: frequency of mention and impact in the HTA deliberative process.

Category	Implicit factors	Frequency of mention	Impact on the HTA decision making
Ethics	Value judgments (16,18)	76	Fairness of resources allocation to health technologies may be compromised. May capture particular interests to the detriment of public interests, compromising equal access to good quality healthcare.
	Bias (15)	34	
	Equity (16)	12	
	Equality (16)	4	
	Intrinsic values (16)	2	
	Moral values (16)	2	
	Interests (11)	2	
	Implicit assumed desire (16)	2	
	Vested interests (116)	2	
	Values of knowledge (16)	1	
	Ethical issues (18)	1	
	Ethical implications (18)	1	
	Fairness (16)	1	
Psychology	Preferences (16)	16	Not mentioned
	Subjective (115)	13	

	Training (115)	9	
	Gut feeling (115)	6	
	Opinion (115)	4	
	Personal considerations (115)	2	
	Personal values (139)	1	
	Personality (139)	1	
	Overconfidence in own judgement (115)	1	
Qualification and experience	Qualification (115)	5	Not mentioned
	Precedents for similar previous decisions (115)	1	
	Previous decision-making mistakes (115)	1	
	Experience in previous decision-making (115)	1	
	Experience (16)	1	
	Precedents for similar previous decisions (115)	1	
Politics and society	Social values (116,139)	4	Not mentioned
	Political processes of the country (121)	1	
	Political influences (115)	1	
	Political pressures (15)	1	
	Societal perceptions (116)	1	

Culture	Cultural values (139)	1	Not mentioned
	Organizational culture (15)	1	
Functional role	Individual responsibility (16)	1	May impact the healthcare resource allocation.
	Power of status (139)	1	
Disease perception	Disease severity (139)	1	
	Burden of disease (16)	1	

The implicit factors under “Ethics” are the most frequently mentioned (143 times), across the identified articles (11,15,16,18,81,116,139) and this category includes:

- “Value judgments “, defined as judgments about what is good (16);
- “Biases “, defined as subjective and personal considerations (115);
- “Intrinsic values “, defined as value judgments that are good by themselves (16);
- “Values of knowledge “, defined as epistemological values in HTA, for example, goodness of study design hierarchy, inquiry, study quality, endpoints and comparator selection (16);
- “Ethical issues “, stemming from the different types of information patients and other participants bring to an HTA collaboration and the resulting influence that information has within the assessment and decision-making process (140);
- “Ethical implications “, which can be equivalent to “ethical issues” (141)
- “Moral values “, for example to help someone who requires assistance (16);
- “Equity “, defined as the value of promoting more fair distribution of access to health care (139);
- “Equality “, defined as lack of discrimination by age, sex, income, or ethnicity in the provision of healthcare (16);
- “Fairness “, that may be claimed if the four conditions are fulfilled: publicity condition, relevance condition, appeals condition, and enforcement condition) (142);
- “Vested interests “, defined as situation when stakeholders vote according to their own interests (116);

- “Interests “, includes tangible interests, such as financial interests and intangible interests such as relationships and associations (143);
- “Implicit assumed desire” defined as preferences (16).

Value judgments are the most referenced under the category “Ethics” and are constitutive of HTA decision-making. However, they may differ from appraisal to appraisal, and they may be considered differently by the stakeholders involved in the appraisal committees since values, principles and considerations differ from person to person. Many of these value judgments are implicit and the objectivity is compromised making the HTA decision-making process biased (16).

Psychology may entail all factors related to the personality and subjective factors such as:

- “Preferences “, defined as criteria weights (124);
- “Personal values”, for example equity and fairness (139);
- “Personal considerations “, defined as personal preferences related to the subjective interpretation (81);
- “Personality “, associated with human performance. Traits, and particularly conscientiousness and emotional stability, are associated with performance at many different types of work. Personality also appears to influence various aspects of decision-making (144);
- “Opinion “, divided on the effectiveness of the technology and the cost of the technology (145);
- “Subjective”, defined as perception emerging from a subject’s point of view (146);
- “Training” defined as systematic acquisition and development of the knowledge, skills, and attitudes required by employees to adequately perform a task or job or to improve performance in the job environment (147);
- “Gut feeling “, defined as overconfidence in own judgment or intuition (115);
- “Overconfidence on own judgment “defined as gut feeling or intuition (115,139).

Qualification and experience refer to the qualification and previous experience in similar situations of the members providing the recommendations (16,115). This category includes:

- “Qualification”, which refers to the learning outcomes, express what people know, understand, and can do. They can take different forms such as a (university) diploma or (skills crafts) certificate (148);
- “Precedents for similar previous decisions”, defined as earlier decision being followed in a later case because both cases are the same (149);
- “Previous decision-making mistakes”;
- “Experience in previous decision-making”;
- “Experience”, defined as a complex interaction between body, sensory input, and neurological processing a relationship with the world as humans encounter, interpret, and shape messages. Experience is a multilayered phenomenon; individuals make sense of experience through cultural, cognitive, subconscious, and personal interpretive layers, by negotiating norms and dominant values, attending to immediate human relationships, and through an individual’s context within larger societal and historical positioning (150).

Political influences and societal values or perceptions may also impact the HTA process. This category can include:

- “Political processes“, defined as influence of the health system on the role of HTA in a particular country (84);
- “Political influences“, defined as political values or ideologies influencing health policies (151);
- “Political pressures“, in some cases assessment recommendations can be reversed in appraisal process, possibly due to political pressure (152);
- “Social values“, defined as the values related to the well-being of patients and the communal welfare” (16);
- “Social perceptions“, defined as a result from social values and interests on what makes health interventions valuable (116).

The cultural values of individual HTA members or the organisational culture, are also factors that may impact the recommendations. They are referred in the literature as “cultural values” (what is cultural determined or believed (153)).and “organizational culture” (the story in which people in the organization are embedded, and the values and rituals that reinforce that narrative. It is shaped by and overlaps with other cultures especially the broader culture of the societies

in which it operates (15,139). As per the functional role, this is related to the roles and responsibilities of the HTA members on the committee such as “individual responsibility” (when the persons have the responsibility to act ethically, both on practical and ethical grounds. (154)) and “power of status” (prestige, honor, esteem, power derived from the social standing in managerial and organizational work. (155)) (16,139).

Finally, the disease perception such as the “burden of disease“ (comprehensive demographic and epidemiological framework to estimate health gaps for an extensive set of disease and injury causes, and for major risk factors, using all available mortality and health data and methods to ensure internal consistency and comparability of estimates (156)) and “unmet need“ (availability of adequate alternative treatments (157)) may differ from person to person and may thus interfere with the recommendations on the technology (16,139).

Regarding the impact these implicit factors may have on the HTA deliberative process, it is argued that factors that fall into the categories of ethics (value judgments, bias, and fairness) functional role (individual responsibility), and disease perception (disease severity) may have consequences for resource allocation. To illustrate, personal biases of HTA members may result in individual interests being favoured over public interests, which has consequences for resource allocation compromising the fairness and legitimacy of these decisions (116).

If deliberative processes are informal, unstructured, and unstandardized, these key issues may be overlooked, making it difficult to address the personal preferences or subjectivity of decision-makers (15,18,139).

5.4. Discussion

Like other deliberative decision-making processes, HTA deliberative process is a complex process that is affected by factors that are generally recognised and agreed upon (such as safety and CE), as well as other factors that are not explicitly stated and vary between countries, systems, and individuals. The last factors account for variability in the decision-making criteria (32,116).

This SLR found that implicit factors, being constitutive of the HTA deliberative process, may interfere with the HTA recommendations. It also found a lack of a standardized framework for addressing these factors across the studied countries. For this reason, there is a need to unmask and clarify these factors to increase the transparency, fairness, impartiality, and formality of the process (11,81,158,159).

Some HTA agencies have used frameworks for specific deliberative processes. However, these frameworks do not account for subjective elements such as behavioural and cognitive aspects that may influence the final decisions (160).

Inconsistencies, variability, and lack of predictability have been reported in current HTA value frameworks; to address these challenges, methodologies such as MCDA for healthcare decision making have been frequently debated over the last years (161). This method seems appropriate for integrating diverse attributes as part of an explicit approach (158). However, due to practical limitations with respect to its implementation, it is mainly used for experimental or academic purposes (118).

EUnetHA's Core Model is an example of an HTA framework that is used to assess and appraise new technologies. EUnetHTA proposed its HTA Core Model to harmonize the HTA process across countries (34,162,163). However, the HTA core model does not address the implicit factors, except for marginally alluding to them in a section called "value judgements". Nor does this framework assign a dimension to these value judgments and their influence, to allow their impact on the deliberative and HTA processes to be monitored and quantified (163).

Other initiatives that have been developed to guide the HTA deliberative process were highlighted in the Background Paper from the HTAi Global Policy Forum 2020, which

proposed a range of questions, principles and actions that could be used to guide the development of deliberative processes within HTA. This includes guidance on the selection of committee members and allocation of roles, as well as recommendations regarding stakeholder involvement and the cognitive aspects present in the deliberation process such as the management of biases. The HTAi Global Policy Forum also recommends using decision-making frameworks to make the process more structured, explicit, and formal and minimize the influence of individual stakeholder interests on the decision-making process to safeguard its fairness (117).

Other elements that could be integrated into formal HTA or frameworks include broader dimensions of value, such as cultural and social values that are not commonly addressed in HTA (11,117,118).

Additionally, the patient perspective is an important feature to be considered in these formal assessments (38,45). In some areas with high unmet medical needs, such as rare diseases, the role of patients is being increasingly recognized at all stages of evidence development, resulting in active patient involvement in the HTA process. Also, in cases where the evidence is uncertain, increased participation of patient organizations may increase the likelihood of a positive reimbursement decision (27) . From a societal standpoint, decision criteria need to be informed by society's values and preferences, which involves seeking to incorporate the priorities and perspectives of citizens into the decision-making process (162).

The results of this SLR highlight the need for a standardised framework that addresses implicit factors in the HTA deliberative process. Further research is advised to better understand the impact that the identified implicit factors may have on the deliberative process in each country and explore potential ways to mitigate the influence of these factors on the HTA deliberative process.

5.5. Strengths and limitations

To the best of our knowledge, this is the first SLR focused on the implicit factors in the HTA deliberative process, which is the main strength of this study. To facilitate the analysis, the identified implicit factors were categorized by type. Acknowledging the scarcity of information on this matter, the research group aimed to have a broad linguistic scope and for this reason, the SLR included publications in English, Spanish, French, Italian and German languages.

As for the limitations of this study, there is scarce literature published on the research question with limited authors and HTA agencies involved.

This SLR comprehends articles published in the period 2009-2019 in a limited number of countries in Europe.

Lastly, as any SLR, in the identified literature it is not always evident to find the information needed to answer all the relevant questions to perform the required analysis. In our case, there was scarcity of information regarding the description of many implicit factors and their impact on the HTA decision-making from a general and country level perspective.

Given the scarcity of information in the literature, our SLR was not able to totally address our research question. Because of this, we performed a mixed-methods research to analyze the impact of the implicit factors in the HTA deliberative process.

6. Implicit factors influencing the Health Technology Assessment deliberative process in Europe: decision makers' perspectives.

The research presented in this section has been published as an article in Health Policy Open.

Monleón C. et al. Implicit factors influencing the HTA deliberative processes in 5 European countries: results from a mixed-methods research. Health Policy Open. Volume 5, 2023, 100109

6.1. Introduction

HTA relies on evidence-based medicine which can be defined as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients (11,164) (Chapter 1, Section 1). When applying evidence-based medicine to HTA, it considers facts or explicit criteria related to the use of health technologies like clinical effectiveness, safety, and CE.

HTA is used to inform the appraisal on the value of new HT and its guidelines are described elsewhere (130–133,165). There is clarity on the explicit factors that are used to apply the evidence-based medicine to HTA and that subsequently influence the deliberative process. Factors such as safety, efficacy and CE of the intervention are shared in the assessments of the countries in scope (13,166) with nuances among them. For example, France and Germany focus on clinical added value while the UK focuses on the CE of the intervention, while Italy and Spain base their assessment mainly on a budget impact analysis (Chapter 1, Section 2) (27).

However, there is a lack of understanding of other factors that may influence the deliberative process and that are not explicitly stated, creating a lack of transparency, and understanding of all reasons behind HTA recommendations.

For example, in HTA agencies in which there is an explicit CE guidance (e.g., ICER threshold in the UK), in some cases drugs with base case ICER above the threshold were recommended. This suggests that for some medicines, a higher weight is allocated in other factors that may not be necessarily explicit (167). These factors will be hereafter referred as “implicit factors”.

Implicit factors can be understood as any criteria playing a role in the deliberation but not being part of the HTA framework and that have an impact on the output of the HTA process (decision or recommendation) from a deliberative committee (Chapter 2, Section 4) (15,168). HTA of medicines may also be influenced by subjective and implicit elements such as behavioral aspects that affect the deliberative process and the final decision. Because of this, there is a

need to get a better understanding of the implicit factors that affect the HTA (15). Understanding these factors can help the different stakeholders to have a broader picture of the HTA deliberative process and describe key aspects often overlooked that are involved in the recommendation and reimbursement of health technologies.

The authors of this article performed a SLR on the influence of implicit factors in the HTA deliberative process, and the results suggested that there is paucity of data and research about the influence of implicit factors in the HTA decision-making process (168).

We then performed a mixed-methods research (169) to identify the implicit factors influencing the HTA deliberative process of medicines and to analyze their impact on the decision-making process in five European countries based on HTA experts' perspectives.

6.2. Methods

6.2.1. Study participants and geographic scope

Interviewees were HTA experts from France, Germany, Italy, Spain, and UK with a minimum of three years of experience in the HTA process, with direct or indirect interactions in the deliberative process over the last ten years. Direct interactions refer to HTA committee members who had voting rights in the deliberation. Indirect interactions refer to experts that could be subject matter experts present in the deliberation but without voting rights.

The five countries in scope represent 73% of the EU population and have established HTA agencies and recognized HTA processes (27) (49). Additionally, the health care expenditure of all healthcare providers in these countries represented 72% of the EU-28 total in 2019 (Chapter 1, section 2) (50).

Given the highly specialized area of research and the characteristics of the professional profile sought, the interviewees were recruited through snowballing method (170).

Twenty-five experts were contacted via email and from those, 20 participated in the interviews. From the five experts who did not participate, three experts refused to participate, and two experts did not respond, resulting in an overall response rate of 80%.

Most of the experts contacted had direct or indirect experience in decision-making bodies: G-BA, NICE, SMC, HAS, MOH, Social Services and Equality in Spain (MSSSI), AIFA, Catalan Health Service (CatSalut) or advisors like the Andalusian School of Public Health in Spain (EASP). Experts from the UK represented the perspectives from NICE and SMC.

The characteristics of all the experts contacted are presented in Table VII and Table VIII. Detailed information of the academic and professional background can be found in Annex 4.

Table VII. Profile characteristics of the study participants

Country	Organization from which experience was gained	Type of engagement when working for the HTA agency	Years of experience (until the moment the interviews were performed)
Spain	CSC ¹	Chair	17
	EASP ²	Committee member	10
	Malvarrosa Clinical Department, “Conselleria de Sanidad”, Valencia	Committee member	14
	ISCI ³	Chair	25
France	HAS ⁴	Chair	9
	HAS	Committee member	17
	HAS	Committee member	31
	HAS	Committee member	9
Italy	HTA National Center (“Centro nazionale per l'Health Technology Assessment”)	Advisor	15
	HTA National Center (“Centro Nazionale per l'Health Technology Assessment”)	Advisor	4
	SIHTA ⁵	Advisor	5
	AGENAS ⁶	Advisor	4
UK	NHS ⁷	Committee member	9
	NICE ⁸	Committee member	8
	NICE	Advisor	17
	JCVI ⁹	Committee member	5
Germany	G-BA ¹⁰	Committee member	20
	Arbitration board on drug prices	Committee member	10
	Professor at the University Duisburg-Essen	Advisor	10
	Consultant at PKV ¹¹ DAHTA ¹²	Advisor Chair	25

¹ Catalan Health and Social Care Consortium (“Consorci de Salut i Social de Catalunya”), ²Andalusian Public Health School (“Escuela Andaluza de Salud Pública”) ³Carlos III Health Institute (“Instituto de Salud Carlos III), ⁴French National Authority (“Haute Autorité de Santé”), ⁵ Italian Society of HTA (“Società Italiana di Health Technology Assessment”), ⁶ National Agency for the Regional healthcare services, HTA department (“Agenzia Nazionale per i Servizi Sanitari Regionali”), ⁷ United Kingdom National Health Service, ⁸ National Institute for Health and Care Excellence, ⁹ Joint Committee on Vaccination and Immunization, ¹⁰ Federal Joint Committee, ¹¹ Joint Federal Association of Private Health Insurance (“Verband der Privaten Krankenversicherung), ¹² German Health Technology Assessment (“Deutsche Agentur für HTA”)

Table VIII. Profile characteristics of the experts who were contacted but did not participate in the interviews.

Country	Organization in which they were HTA experts	Type of engagement when working for the HTA agency	Years of experience in HTA
France	HAS	Chair	12
	HAS	Committee member	7
	HAS	Committee member	5
UK	NHS	Chair	9
	NICE	Committee member	16

6.2.2. Data collection

Interviews were conducted and recorded between February and May 2021 using Webex (version 41.5.0.18911) and lasted 60 minutes.

Semi-structured interviews were selected to encourage the interviewees to discuss openly their individual approaches to decision-making when assessing medicines. A discussion guide and an interview checklist (Annex 3) were developed by the authors following a standard methodology (171).

The interview guide was divided into two main sections: perceptions on the HTA deliberative process based on the experts' experience (12 questions) and their recommendations on how to improve the deliberative process (five open questions). In the first section, 10 open questions were followed by two questions in which respondents were asked to score in a Likert scale the degree of influence that 10 factors may play in the HTA deliberative process, as well seven attributes related to the HTA deliberative process.

Two out of these 10 questions focused on the explicit factors and their importance in the HTA recommendations (Table IX). We asked these questions to highlight the differences between explicit and implicit factors, but the outcomes of these questions were not analyzed nor reported.

The implicit factors assessed were related to contextual factors (functional role, qualification, professional experience, culture of the committee, sense of equity, conflict of interest, political and social influences, and appreciation of the burden of disease), and to behavioral factors (value judgments and psychology) (Table X).

On the other hand, the attributes of the HTA deliberative process assessed were transparency, objectivity, standardization, predictability, fairness, reproducibility, and inclusiveness (Table XI). The definition of these implicit factors has been described elsewhere (168) and in this PhD thesis in section 4 of Chapter 2.

The scores ranged from 0 (lowest score) to 10 (highest score). Each implicit factor and attribute were described in the discussion guide.

Interviewees were briefed about the objectives of the research; all gave their consent to participate and for the interviews to be recorded.

6.2.3. Data analysis

All interviews were digitally recorded and transcribed into a Microsoft Word document. Two researchers independently coded the interviews. The researchers compared the code list and unified the codes. The unified code list was applied to all interviews, following the grounded theory approach (172,173). Any coding divergence was resolved by discussion between the 2 researchers. The quotations were then extracted into a Microsoft Excel file.

For the questions focused on the experts' recommendations, categories were created based on the frequency of topics that emerged from the answers. The final set of categories was illustrated with experts' quotations (Table XII).

For the questions involving scoring a descriptive quantitative analysis was performed (mean, median, interquartile range (IQR), and standard deviation (SD)). Country level median and IQR were calculated.

6.3. Results

A group of 20 experts (four per country) composed by HTA experts from different organizations across Europe were interviewed (Annex 4). The saturation point was reached after three interviews per country.

6.3.1. Perceptions on the HTA deliberative processes: analysis across countries

6.3.1.1. Main explicit and implicit factors influencing the HTA deliberative process

The perceptions on the main explicit and implicit factors influencing the HTA deliberative process are detailed in Table IX.

Experts from all countries stated that clinical efficacy and safety were explicit factors influencing the deliberative process (Table IX). The experts in Germany specifically mentioned that mortality, morbidity, safety, tolerability, and quality of life were the outcomes assessed, and that clinical trial design and comparator were also relevant to decision making. Burden of disease was stated to be an explicit factor in both France and Germany. In terms of the economic case, budget impact was considered in Italy and Spain, while the ICER was the key determination of economic value in the UK. Finally, the experts from France mentioned that public health interest was also a key factor. Most of the experts (18/20) concurred that, despite the process in each country being well defined with the key criteria published and available in the public domain, there are implicit factors that have not been integrated in the HTA frameworks or guidelines. They stated that it would be beneficial to acknowledge these factors. Concerning implicit criteria that could influence decision making, experts identified unmet need (UK, France, and Germany), burden of disease (UK and Spain), patient perspective (UK), social pressure (UK and France), and epidemiology, (France) (Table IX). The interviewees from Spain also mentioned confidential discounts as having an influence. One expert from the UK highlighted the importance of QALY weighting as a factor that may have been considered in the deliberative process in an unofficial way. In the case of Italy, one expert stated that the budget cap on the pharmaceutical expenditure was a factor that may influence the deliberative process.

Table IX. Main explicit and implicit factors influencing the HTA deliberative process.

Countries	What are the most relevant explicit factors in the HTA deliberative process?	Illustrative comment	Are there other criteria that could influence the decision-making and are not explicitly stated?	Illustrative comment
UK	ICER	“All the conversations should be around ICER. Clinical need and clinical efficacy are part of the conversation”. “80% of the decisions in a single technology appraisal is around the strength of that relative clinical and CE and if we focus even more is about CE, and the cost/QALY”.	Unmet need, duration of therapy, comparators, standard of care, QALY weighting, level of uncertainty of evidence, patients ages, duration of the treatment.	“Because HTA is a comparative discipline, what the comparators are matter and the robustness of evidence to facilitate this comparison. “Uncertainty is everywhere but sometimes we must make decisions despite the uncertainty.”
France	Burden of disease, efficacy, safety, public health interest	“In the assessment phase, just the clinical criteria are considered”	Treatment cost, disease prevalence, unmet need, mediatic diseases	“The goal of the TC is to assess the health technology intervention in an objective and rigorous way but there is the personal sensitivity that cannot be excluded. That’s why there are methodologists”
Germany	Clinical trial design, comparators, mortality, morbidity,	“We would expect the head-to-head study design. We must see	No implicit factors Unmet need	“I don’t think there are other criteria that are not official. Of course, there might be informal

Countries	What are the most relevant explicit factors in the HTA deliberative process?	Illustrative comment	Are there other criteria that could influence the decision-making and are not explicitly stated?	Illustrative comment
	safety, tolerability, and Health Related Quality of Life	whether the new product is able to reduce mortality. And then we must see whether the patient's condition improves. “		considerations, pre-conceptions but this is something you can amend prior to the procedure.” “The procedure is as described in the action paper of the G-BA. There is no secret paper”. “There might be informal considerations, pre-conceptions”
Italy	Efficacy, safety, unmet need, budget impact	“There is also the innovation request, that is assessed in the CTS and covers the unmet need, the therapeutic benefit and the quality of the evidence”	Budget cap on pharmaceutical expenditure	“Given the lack of fully objective criteria, subjectivity cannot be avoided. It is not a conscious process.” “Given that in Italy there is a budget cap on pharmaceutical expenditure, the committee considers this before, and this is one of the problems during the negotiations. We focus exclusively on the pharma expenditure and not in the overall healthcare expenditure”
Spain	Efficacy, safety, budget impact, cost-containment measures.	“In the last years, cost-containment has been increasingly	Uncertainty, burden of disease, confidential discounts, media pressure.	“The reimbursement of new hepatitis C treatments was highly influence by media pressure and

Countries	What are the most relevant explicit factors in the HTA deliberative process?	Illustrative comment	Are there other criteria that could influence the decision-making and are not explicitly stated?	Illustrative comment
		gaining traction.”		patients’ representatives.”

6.3.1.2. Degree of influence of the implicit factors on the Health Technology Assessment deliberative process

The overall perceptions across countries of the influence of implicit factors on the HTA deliberative process are shown in Figure 4. The appreciation of burden of disease was the highest scoring factor (median score 6.8 [IQR 0.5]) whilst conflict of interest was rated as having the lowest influence from the HTA experts’ perspective (median score 2.3 [IQR 1]).



Figure 4. Scores (median and IQR) given by experts to the degree of influence of implicit factors in the HTA deliberative process.

The degree of influence of implicit factors (positive or negative) on the HTA deliberative process and outcome in each country are shown in Table X.

Overall, the experts from Germany gave least weight to implicit factors (scoring the lowest in seven factors out of 10) whereas the experts from Italy gave most weigh overall (scoring the highest in seven factors out of 10).

To facilitate the interpretation and analysis of the results, the authors categorized the scores. Country aggregated median scores ≥ 6 , were classified as “high influence factors”, between ≤ 4 and >6 there classified as “medium influence factors”, and between 0 and >4 was classified as “low influence factors”.

Experts from Spain scored high burden of disease, professional experience, functional role, and qualification.

In France, burden of disease, professional experience, qualification, and equity had high scores.

The experts from Italy scored high the dimensions of burden of disease, professional experience, functional role, equity, value judgments and influence of politics and society.

In the case of the UK and Germany, burden of disease appeared to have a high influence in the HTA deliberation.

In terms of degree of implicit factors, Italy presented the highest number of median of scores ≥ 6 , with 6 scores above or equal to 6. Spain and France presented 4 and the UK and Germany one.

Individual responses within country are described in Annexes 5-9.

Table X. Degree of influence of the implicit factors on the HTA deliberative process across countries (median and interquartile range)

Dimensions	Spain	France	Italy	Germany	UK	Median	Interquartile range
Burden of disease	7,0	6,5	8,0	6,8	6,0	6,8	0,5
Professional experience	6,5	7,0	8,0	3,0	5,0	6,5	2
Functional role	6,0	5,0	6,8	1,0	5,5	5,5	1
Qualification	6,0	6,5	5,5	1,5	5,5	5,5	0,5
Equity	5,5	7,0	8,0	1,0	5,0	5,5	2
Committee's culture	4,5	5,8	5,5	1,0	5,3	5,3	1
Value judgments	3,0	4,5	8,8	5,0	5,0	5,0	0,5
Psychology	3,0	4,0	5,0	4,3	4,5	4,3	0,5
Politics and society	2,5	2,5	6,8	1,8	4,0	2,5	1,5
Conflict of interest	2,5	2,3	5,0	0,5	1,5	2,3	1

6.3.1.3. Attributes of the Health Technology Assessment deliberative process

The definitions of the different attributes are detailed in Annex 3 and the perception of a set of attributes according to the experts' experiences in the HTA deliberative process are shown in Figure 5.

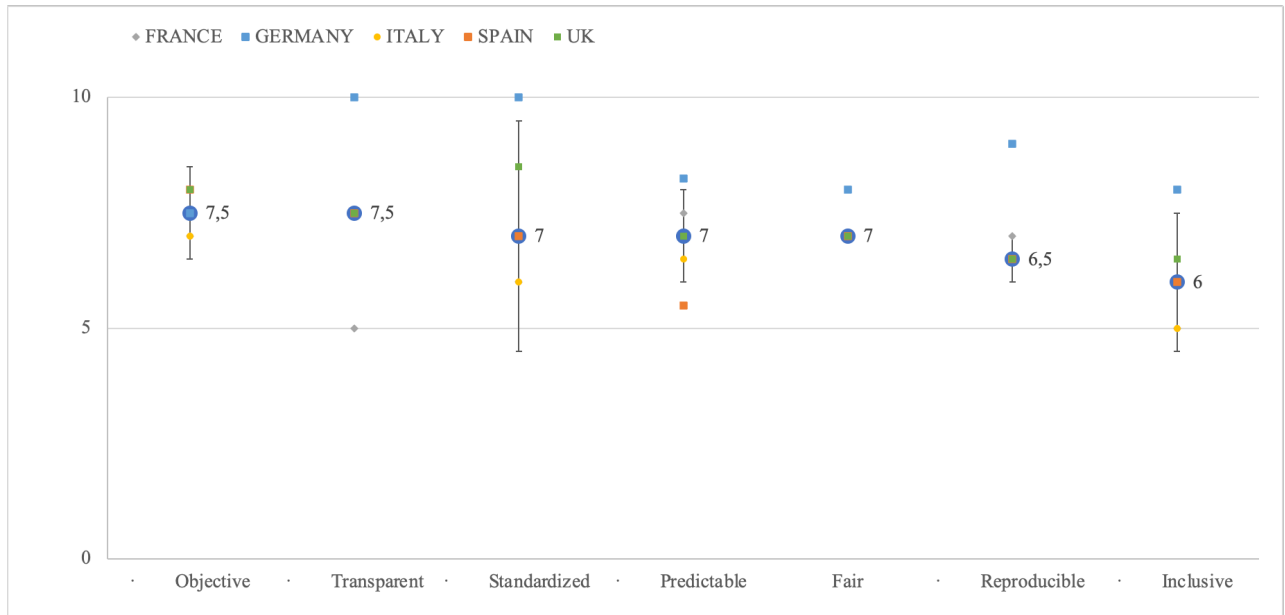


Figure 5. Scores (median and IQR of medians) given by experts to a set of attributes pertaining to the HTA deliberative process.

Overall, the scores for each attribute were similar, being the attributes of “objective” and “transparent” the highest across all the countries (median score 7.5 [IQR 1 and 0]), whereas inclusiveness scored the lowest (median score 6 [IQR 1]). In terms of country-level responses (Annexes 10-14), the experts from Germany had the most positive perception of the HTA deliberative process, with median scores ranging from 7.5 to 10 and scoring the highest in six out of the seven attributes: standardization, reproducibility, objectivity, transparency, predictability, and inclusiveness. France scored lowest in standardization and Italy scored lowest in inclusiveness. Individual responses for each country are reflected in Table S6.

Experts from Spain scored high (≥ 6) all the attributes of the HTA deliberative process except for predictability (5.5).

Experts from France scored high all the attributes except for transparency and inclusiveness (5).

When we look at the responses from the experts from Italy, the dimension that got a low score was inclusiveness (5). Finally, the experts from Germany and UK scored high all the attributes.

Table XI. Quantification of a set of attributes in the HTA deliberative process across countries (median and interquartile range)

Dimensions	Spain	France	Italy	Germany	UK	Median	Interquartile range
Objective	8	7	7	7,5	8	7,5	1
Transparent	7,5	5	7,5	10	7,5	7,5	0
Standardized	7	6	6	10	8,5	7	2,5
Predictable	5,5	7,5	6,5	8,25	7	7	1
Fair	7	7	7	8	7	7	0
Reproducible	6,5	7	6,5	9	6,5	6,5	0,5
Inclusive	6	5	5	8	6,5	6	1,5

6.3.2. Recommendations on how to improve the Health Technology Assessment deliberative process.

The experts were asked to provide recommendations on ways to acknowledge the implicit factors and improve the objectivity, transparency, and standardization of the HTA decision-making process. The recommendations from the experts were classified by the authors into the following categories: inclusiveness, methodology improvement and transparency (Table XIV).

Most of the experts (17/20) agreed on the importance of expanding the stakeholder involvement with external and diverse perspectives to provide a higher number of perspectives and ensure that many values are identified, and their relative importance understood. The range of stakeholders could include patients, caregivers and physicians specialized in the disease to politicians and defense counsels. Manufacturers, representatives of universities and specialized centers in HTA were other suggested actors.

The next category of recommendations provided by the experts (14/20) is methodology improvement. This would include methodologies like MCDA (174), defining and documenting the implicit factors beforehand and assigning weights to them. The cost-utility analysis (CUA) was suggested as another tool that could address the implicit factors affecting the disease perception since this method would allow to have all the diseases under an equal footing.

Anonymous voting was proposed, especially in countries like France where the votes are made by a show of hands. This would reduce influences derived from seeing other committee members votes, notably those who are dominant in the committees.

The last suggestion under this category is related to the need of reassessments of HT in light of new evidence. The HTA should ideally be equitable over time regardless of the committee culture or any other mediatic pressure.

The last category is transparency (7/20). The recommendations to improve transparency strive to improve the communication by making the public involved and allow the stakeholders to assess if the deliberative process and resulting recommendations were fair. To achieve this, minutes of meetings and draft committee reports with the conclusions should be available to the public.

It was also suggested to allocate time to self-reflect to display all conflicts of interest and to reveal the committee members' perspective about equity.

Table XII. Recommendations to improve the HTA deliberative process.

Categories	Ideas	Illustrative comments
Inclusiveness (17/20)	<ul style="list-style-type: none"> • Increase the involvement of external and diverse perspectives. This could be achieved by promoting representative participation of patients and caregivers, physicians specialized in the disease, healthcare manager from regions and hospitals, public, politicians and defense counsel specialized in the disease, 	<p>“There could be the involvement of politicians and a defense counsel specialized in the disease who could come from the side of the pharmaceutical company who is submitting the dossier and on the other hand the Social Security could have another counsel expert in the disease. This would contribute to increase the scrutiny and enhance the debate among the committee</p>

Categories	Ideas	Illustrative comments
	<p>pharmaceutical companies, universities and specialized centers in HTA.</p>	<p>members to reach a fairer decision.” (Expert from France)</p> <p>“In order to bring the implicit factors into consciousness we could give to the experts one minute of silence before the deliberation to reflect about them or by performing an amnesic assessment.” (Expert from France)</p>
<p>Methodology improvement (14/20)</p>	<ul style="list-style-type: none"> • Follow a specific methodology assigning weights to the implicit factors (e.g., MCDA, cost/QALY) • Anonymous voting system • HTA re-assessments in light of new evidence or arguments that were not originally considered 	<p>“The cost/QALY is a rough tool, but it allows to have all the diseases under an equal footing”. (Expert from France)</p> <p>“We could use a similar approach to MCDA, defining the implicit factors or criteria beforehand and introducing them progressively and in a consensual way after having been validated by the different members in the committee and then having weighted them.” (Expert from Spain)</p>

Categories	Ideas	Illustrative comments
		<p>“Every single opinion and vote should have the same weight in the decision. In countries like France where the votes are made by a show of hands, one way to reduce bias from seeing others’ vote is by making the vote anonymous. In all Committee there are members who are dominant and members who are dominated. That is why the vote should be anonymous to avoid any kind of influence. The improvements should be largely psychological: how to reach in a trust way a consensus among individuals without aggregations?” (Expert from France)</p> <p>“We should be able to be so agile in the new assessments as in the re-assessments.” (Expert from Spain)</p>
Transparency (7/20)	<ul style="list-style-type: none"> • Make the meetings available to public to allow stakeholders to judge if the deliberative 	<p>“The process would be more transparent if the deliberative discussions were open to the public with</p>

Categories	Ideas	Illustrative comments
	<p>process and the resulting decision are fair.</p> <ul style="list-style-type: none"> • Post draft committee reports with the conclusions for public comment. <p>Document any conflict of interest, political preferences as well as the committee members' perspective around equity. Allocate time to self-reflect to display all conflicts of interest.</p>	<p>external observers. Then, the discussions would be approached in a different way.” (Expert from Italy)</p>

6.4. Discussion

To the best of our knowledge, the findings of this mixed-methods research suggest that implicit factors play a role in the HTA deliberative process. Our research represents the first published data focusing specifically on the implicit factors influencing the HTA deliberative process in Europe.

These implicit criteria, that do not form part of deliberative process frameworks, cannot be neglected. It has previously been acknowledged that implicit factors such as cognitive biases influence decision-making processes (175). However, the literature on this topic is scarce and current checklists such as the HTAi and ISPOR taskforce do not account extensively for implicit factors. Therefore, HTA practitioners may not always be fully conscious of the presence of these factors and their impact on final recommendations.

Most of the interviewees acknowledged the existence of implicit factors in the HTA deliberative process and concurred that despite the process being defined and the key scientific criteria of the evaluation published, there are implicit criteria that cannot be ignored and that have not been acknowledged so far. Therefore, they have not been integrated as part of the deliberative process framework.

While empirical methods relating to clinical effectiveness, safety, and CE form the major element of the assessment of a HT, value judgments also form a constituent part and permeate all levels of HTA, both in the assessment (i.e., the evaluation of relevant aspects of the technology to form a basis for decision (176)) and appraisal (i.e., recommendation on the implementation of the technology, based on the assessment (176)).

Ignoring these value judgments can lead to situations in which HTA proves to be insufficient. Elements not easily quantified in the clinical and economic assessments such as equity should be documented to make the decision process more rational, better justifiable, and more transparent (16,177–181).

The experts perceived the process as fair, standardized, and reproducible. However, in terms of the perceptions on the standardization, interviewees from France, Italy and Spain scored the process low compared to Germany and the UK. This could be explained by the fact that G-GBA's and NICE's assessments follow a standardized procedure based on evidence-based medicine resulting from their HTA guidelines (87,182).

Burden of disease was scored as having a high influence in the five countries in scope. This dimension is considered an explicit factor in most of the countries except in Italy.

In England, equity and value judgments are factors explicitly considered in the guidelines (183).

Experts from France, Spain and Italy had a high median score in the dimension of professional experience. We can then assume that the professional trajectory is perceived as an influential factor in these countries. However, we did not explore if the likelihood of having higher or lower biases was based on the number of years of experience and exposure of the HTA members to the assessments and appraisals.

When looking at the country-level responses, France and Italy had a high median score of equity and conflict of interests.

In Germany, just two dimensions got a score of 5 for the degree of influence of implicit factors and in both instances, it was the same expert who scored.

The findings of this research highlights three major insights.

The first one is the heterogeneity across countries in the factors influencing the decisions, some being considered implicit by some countries and explicit by others (i.e., equity).

The second key takeaway refers to the intervariability in the perception of degree of influence of implicit factors across countries. We identified a higher degree of influence of implicit factors in Italy, Spain, and France whereas in Germany and UK, the experts reported only burden of disease as a factor having a high influence. However, this factor is explicit in these two countries, hence no implicit factor was deemed as highly influencing decisions in Germany and UK. This heterogeneity may result in different HTA recommendations, which in turn may impact the equity in access to health technologies. Furthermore, it hampers the transparency and legitimacy of HTA.

Lastly, the third major insight comes down to the identification of some trends in the way the scores were given. For example, burden of disease was scored as having a high influence in all countries and professional experience was scored high by France, Italy, and Spain.

Overall, transparency and objectivity were scored high in all countries. However, particularly the finding related to objectivity is not consistent with the scores provided in France, Italy, and Spain in which the influence of implicit factors was reported in a significant way.

Implicit factors may often play an important role in countries such as Spain and Italy given their decentralized healthcare system compared with countries with a centralized system like Germany (184). This in turn would contribute to the inequality in access to innovations across regions (64). Another reason would lie on the methodology and procedures of the HTA bodies in these countries which are different from G-BA's and NICE's.

We could then argue, based on the experts' perception from Germany and the UK, that there may be a plausible association between explicit and implicit factors. Hence, procedures characterized by greater transparency in terms of criteria assessed in the HTA process and higher methodological robustness could lead to a more rational evidence-based decision making with higher application of explicit factors and lower influence of implicit factors (183).

However, the strength of this association between explicit and implicit factors has not been formally established but cannot be ruled out.

Standardized methodologies like MCDA can serve as a tool to collect and document the implicit factors to raise awareness about their influence in the deliberative process. These criteria are weighted based on their relevance to individuals involved in the process. It provides insights into the rationale behind the HTA decision-making process. However, complex methodologies can suppose a hurdle in the agility of decision-making.

Even if the application of a MCDA framework may allow to identify perspectives across different stakeholders when appraising a healthcare intervention, both qualitatively and quantitatively (124), it has also some limitations related to its implementation which may compromise the quality of recommendations. These limitations may be double counting of one or more criteria or not including the deliberative component as part of the MCDA, making it just quantitative (185).

An example of methodology leveraging MCDA is The EVIDEM (Evidence and Value: Impact on DEcision-Making) framework that was developed to support deliberative processes by disentangling scientific judgment and value judgment.

There are other proposals, like the one from the 2020 HTAi Global Public Forum. They agreed that transparency, inclusivity, and impartiality are the core values of deliberative processes for drug coverage decision making (117).

Another approach to structuring and systematizing the HTA deliberation, is evidence-informed deliberative process (EDP), which provides practical and stepwise approach for HTA bodies

based on deliberation between stakeholders. According to this approach, the legitimacy of HTA processes could be improved through implementation of four elements: transparency, evidence-informed evaluation, appeal, and stakeholder involvement. Stakeholder involvement is the key element of EDP, that is ideally realised through the participation of the stakeholders in the deliberation. As this is not always possible, alternative approaches may be stakeholder communication or consultation (178).

Frameworks described above aimed to standardise and structure the deliberative process to ensure that all elements requiring deliberation are addressed and concluded. Structuring and standardizing the HTA deliberative process is key to improve the quality of this process. Another important element that should be improved is capturing the implicit factors influencing the HTA deliberative process and making them explicit.

One of the ways of converging decision-making process is the Delphi Panel Methodology, which is a scientific method used to achieve expert consensus by performing controlled assessment and reassessment (follow-up) using a series of surveys until consensual decision is established. This kind of decision-making process has strengths. For example, it allows the direct communication among experts contributing to the resolution of highly complex problems and explores areas in which controversy or lack of clarity exists. Another strength is that respondents can think about the problem over several rounds, enhancing the validity of the data. Lastly, its flexible methodology considers many applications and variations, which allows the research to adapt the technique to the research context (186)

However, Delphi methodology also presents the several limitations such as results generalization to a wider population. Additionally, it is time consuming (substantial time commitment to complete the process) and laborious both for researchers and participants and this would explain the dropouts. Another limitation lies in the fact that the experts' responses might not be fully independent since they are in contact with each other (186,187).

The importance of engaging with patients and patient organizations along the HTA was frequently highlighted by the interviewed experts. Overall, it is recognized that patient involvement should occur across the entire HTA process to enhance trust in the HTA deliberative process (188).

Other than Germany and the UK, the rest of experts did not perceive that the HTA process was inclusive enough and this explains why stakeholder involvement was recommended to improve transparency, legitimacy, and objectivity. The higher score given by experts from Germany and the UK could be explained by the fact that G-BA and NICE include patients' groups in the board and take into consideration the patients' perspectives in the appraisals at different levels of involvement (189). NICE is one of the pioneers in patient engagement in HTA processes, with active participation of caregivers and patient themselves in the committees' deliberations. Since 2004, patients or caregivers, patient group representatives and advocacy groups have contributed to the G-BA through participation in committees and discussions in which they are entitled to submit petitions (189).

In France, even though patients are involved in the deliberation in TC from 2015, there are areas for improvement regarding their engagement and their influence of their considerations on these deliberations. On the other hand, it is also from 2015 that the representative of the pharmaceutical industry is not involved anymore in the TC as a consultative member (190,191).

In Italy and Spain, there is no patient participation in the HTA process. However, such kind of involvement relies largely on the patient organizations' proactivity (184,189).

There has been a rapidly growing interest in including not just patients but also other stakeholders, and the broader public in deliberative processes in ways that add value to the process and to the parties involved (192). Nowadays, different stakeholders including industry representatives, patients and patient associations and health professionals are part of the HTA process, in some countries. Similarly, health professionals, medical associations and payers are often involved in assessment or appraisal committees (5). The G-BA includes members from associations of physicians, hospitals, and sickness funds, along with patient representatives, as does many of the IQWiG governing boards and advisory panel (193). NICE, HAS and IQWiG established opportunities to engage with industry, healthcare managers, clinicians, and academics to discuss strategic challenges (194).

Preferences, concerns, and perspectives of a range of relevant stakeholders on socio-ethical aspects around the HT should not be ignored in the HTA process like in the case of the use of cochlear implants in deaf children. Although the technology was advocated by some as effective and safe and with additional benefits for deaf individuals, representatives of deaf organizations, objected that the technology represented a negative value judgment on the deaf community. The two different perceptions were partially explained by the fact that both groups defined the

problem from different background theories (9,195). This example showcases the importance of collecting and integrating into the HTA evidence that is not always objective nor easily quantifiable, such as values or norms; hence there is a need to involve stakeholders with different perspectives and values (9,16,110,177,180). Additionally, there are some situation-specific contextual factors that are implicit in certain countries and that influence decision-making. The lack of transparency derived from not disclosing these factors nor the way they influence the decision-making, raise questions on decisions' legitimacy. These factors need to be properly documented (110).

Broad stakeholder participation can serve to identify the full range of interests that the society has by making the process more rational and contributing to the legitimacy of decision-making. A systematic approach and general principles have been described elsewhere (178,181) to facilitate stakeholder participation in the deliberative process. The principles highlighted among others are transparency (explicitly description of the deliberative process including ways of stakeholder involvement) and impartiality (deliberative process free from internal or external influences). It needs to be acknowledged that stakeholder involvement deserves special attention in the HTA reports documenting who were involved in the decision-making as stakeholders, what they proposed and how their feedback was used.

Another way to address transparency could be by conducting the HTA process independently from the institution that will ultimately be responsible for the pricing and reimbursement decision. The HTA bodies in Germany and in the UK have higher autonomy than in France and Spain where these institutions depend on the MOH and there may be political influences (27) . HTA bodies recognize the importance of making the process "independent" from subjective aspects coming from the committee members to increase the fairness and legitimacy of the process (167,179).

The accountability of the assessment and decision-making itself should be well determined to mitigate the influence that biases have in the decision-making. For example, the HTA expert who is part of the assessment should not be part of the team which is responsible of the decision on the HT (180).

In short, the value of stakeholders in the deliberative process is seen as an instance of strengthening the quality of the deliberative process.

There may be further factors influencing the deliberation, not often measured, and therefore omitted from value assessments. While CUA represents a standard methodology to determine

the economic value of a new technology in most of the HTA (196), it has been encouraged to consider potential novel elements of value from a societal perspective (197).

Building upon societal perspective, Tversky and Kahneman identified several consistent biases in the way people make judgments, finding that people often rely on easily recalled information, rather than actual data, when evaluating the likelihood of a particular outcome, a concept known as “availability heuristic”(198). The Nobel laureate and leading behavioral economist, Richard Thaler, brought nudge theory to prominence (199) (200). Nudge was defined as “any form of choice architecture that alters people's behavior in a predictable way without restricting options or significantly changing their economic incentives”, in other terms, any technique used to influence human behavior. This concept is grounded in behavioral economics, which have demonstrated that humans are not entirely rational beings. Thaler described how social and group influences can affect what others think and do and he believes that a way to get around these behaviors are using nudges.

It would certainly be interesting to identify a bridge theory between Thaler’s nudge notion and the economic rationalism, as the latter assumes that human beings make decisions intended to maximize utility without any sort of influence but based solely on research performed by themselves. In the HTA committees there are certainly group influences that can affect the thinking or positioning of other HTA members.

The upcoming European JCA becoming applicable from 2025 (see Chapter 1, section 1), aims to put in place a framework to support Member States cooperation and the harmonization of methodological standards to centralize the clinical assessment of health technologies. This joint work is supposed to address the heterogeneity in HTA appraisal and to ensure a significant level of independence and transparency by putting in place common methodological approaches that encompass evaluation criteria explicitly (201). Still, higher levels of transparency might be achieved when addressing in a systematic way the implicit factors influencing the HTA deliberative process. In this line, one of the legislative acts of the regulation from the EC, states that the JCA should be only factual and exempted of value judgments (201).

6.5. Strengths and limitations

One strength of our interviews is their high response rate (80%), which is above the average of the interviews conducted in the field of HTA ranging from 18 to 90% (188). Another strength lies in the background of respondents which included decision-makers and payer advisors at national and regional level with at least three years of experience in deliberative processes. To our knowledge this is the first qualitative research focused on the implicit factors in the HTA deliberative process.

As per the limitations of this study, the factors that were asked to the experts were previously identified in a SLR (Section 5 of Chapter 2) (168). However, there may be other factors that were not captured in the questions of the interviews and may influence the decision as well (e.g. unmet need, confidential discounts). It is unknown how these other factors may have an impact and downstream in the deliberative process. The findings of this study may not be generalized to other countries in Europe with a less structured HTA processes in which implicit factors could represent a different weight in the deliberative process. Additionally, this research focused on medicines, therefore our findings cannot be extrapolated to other health technologies requiring different processes.

In terms of the population on which the study was conducted, we did not count with a large population as in other contexts. The participants in the HTA decision committees in each country are usually no more than 10 people, although they have much more extensive technical support. For this reason, it was not possible to carry out sample estimation due to the small number of individuals. However, because of this, robust statistics (median, interquartile range, etc.) were used to describe the responses.

Another limitation lies in the fact that five experts did not participate in the interviews, and it is unknown what would have been the impact if they had participated. However, at the same time since the saturation was reached after three interviews per country, additional interviews may not have brought supplementary new information.

Also, there is a potential limitation for selection bias in the recruited sample of participants as the interviews specifically targeted people known to be involved in HTA in the countries in scope. However, this bias may be limited since the experts had a robust experience in the HTA deliberative process and since the data saturation was reached, we don't think we would have found additional information should we had identified other experts.

Recall may be present. However, for the purpose of these interviews the memory bias in the interviews may have been mitigated since a list of implicit factors were called out in the questions.

Self-complacency in some cases may have impacted this research given some likely underestimation of the influence of implicit factors and in turn resulting in an overestimation of the optimal process. This could be perceived in some responses of the experts from Germany. Indeed, its HTA deliberative process may be ahead of the rest of the countries in many aspects. However, the significant high scores versus the other countries led us to think of the presence of biases in some answers.

6.6. Conclusions

The findings from this research expand the understanding of implicit factors and its implications in the HTA deliberative process. This is a call to action for decision makers from countries with established HTA processes where the role that implicit factors play in the deliberative process is still unknown, to reflect on their respective implicit factors in order to mitigate its impact on the HTA decision-making.

Further research may explore options to acknowledge implicit factors systematically to ensure their legitimacy and transparency in the HTA deliberative process. This research may also be completed by deepening the findings in one of the countries in scope and/or by interviewing HTA experts from other countries.

Since in every country HTA process and individuals are unique, we could expect variability in the weight allocated to these implicit factors or even in the identification of additional implicit factors.

7. CONCLUSIONS FROM CHAPTER 2

Decision-making is impacted by several type of factors going from contextual to any kind of cognitive bias. In order to evaluate these kinds of factors we first developed a definition of implicit factors influencing the HTA deliberative process. This is the first time that this concept has been defined and it set the basis of our subsequent research projects. Implicit factors in HTA refer to all non-defined factors that are not explicitly collected or described in the HTA guidelines and that may influence the HTA deliberative process and the subsequent recommendations.

Two pieces of research have been performed to identify and assess the impact of implicit factors in the HTA deliberative process and to determine whether HTA processes in the five European countries of scope incorporate additional criteria beyond economic evaluation or clinical benefit assessment, and, if so, which ones and how they inform the HTA recommendations.

The first research, a SLR, confirmed that implicit factors, being part of the deliberative process, interfere with the HTA recommendations.

It also found a lack of a standardized framework for addressing these factors across the studied countries. For this reason, there is a need to unmask and clarify these factors to increase the transparency, fairness, impartiality, and formality of the process.

Some HTA agencies have used frameworks for specific deliberative processes. However, these frameworks do not account for subjective elements such as behavioural and cognitive aspects that may influence the final decisions.

The second piece of research, a mixed-methods study consisted of interviews with 20 HTA experts from France, Germany, Italy, Spain, and UK (four experts per country) with direct or indirect interactions in the deliberative process over the last 10 years. Semi-structured interviews were conducted to encourage the interviewees to discuss openly their individual approaches to decision-making when assessing medicines. The discussion was divided into two main sections: perceptions on the HTA deliberative process and recommendations to improve this process.

The saturation was reached after three interviews in all five countries.

This research confirmed and expanded the findings from the SLR through interviews with the HTA experts.

Most of them acknowledged the influence of implicit factors in the process.

The implicit factors having an influence on the HTA deliberative process (from higher to lower score) were burden of disease, professional experience, functional role, qualification, equity, committee's culture, value judgments, psychology, politics and society and conflict of interest. The experts perceived the HTA deliberative process being fair, standardized, reproducible, objective, transparent, predictable, and inclusive (from highest to lowest score).

In a second time, the interviewees provided recommendations to control implicit factors, being the stakeholder involvement and the methodology improvement the most frequently mentioned followed by transparency.

This last piece informed us on the importance accorded by the HTA experts on a methodology supporting the HTA process. This in turn led us to the final part of our research consisting of a targeted literature research to identify existing methodologies accounting for implicit factors and the development of a checklist as a solution to improve the HTA deliberative process.

8. ANNEXES FROM CHAPTER 2

Annex 1: Definition of implicit factors

- Ethical issues There are ethical issues stemming from the different types of information patients and other participants bring to an HTA collaboration and the resulting influence that information has within the assessment and decision-making process (140).
- Ethical implications: can be associated to “ethical issues” (141)
- Personality”: associated with human performance. Traits, and particularly conscientiousness and emotional stability, are associated with performance at many different types of work. Personality also appears to influence various aspects of decision-making (144).
- “Opinion”: expert opinion is divided on the effectiveness of the technology and the cost of the technology (145)
- “Political influences “: political values or ideologies influencing health policies. (151)
- “Political pressures”: in some cases assessment recommendations can be reversed in appraisal process, possibly due to political pressure (152).
- “Societal perceptions”: the result from social values and interests on what makes health interventions valuable (116)
- “Cultural values”: what is cultural determined or believed (153).
- “Organizational culture”: It is the story in which people in the organization are embedded, and the values and rituals that reinforce that narrative. It is shaped by and overlaps with other cultures especially the broader culture of the societies in which it operates (202)
- “Individual responsibility”: when the persons have the responsibility to act ethically, both on practical and ethical grounds (154)
- “Power of status”: prestige, honor, esteem, power derived from the social standing in managerial and organizational work (155)
- “Burden of disease“. A comprehensive demographic and epidemiological framework to estimate health gaps for an extensive set of disease and injury causes, and for major risk factors, using all available mortality and health data and methods to ensure internal consistency and comparability of estimates. (156)
- “Unmet need“: availability of adequate alternative treatments (157)
- “Subjective”: perception emerging from a subject’s point of view (146)
- “Training”: systematic acquisition and development of the knowledge, skills, and attitudes required by employees to adequately perform a task or job or to improve performance in the job environment (147)
- “Qualification”: refers to the learning outcomes. Qualifications express what people know, understand and are able to do. They can take different forms such as a (university) diploma or (skills crafts) certificate (148)
- “Precedents for similar previous decisions”: earlier decision being followed in a later case because both cases are the same (149)
- “Experience in previous decision-making”
- “Experience” experience from an individual perspective is a complex interaction between body, sensory input, and neurological processing a relationship with the world as humans encounter, interpret, and shape messages. Experience is a multilayered phenomenon; individuals make sense of experience through cultural, cognitive, subconscious, and personal interpretive layers, by negotiating norms and dominant values, attending to immediate human

relationships, and through an individual's context within larger societal and historical positioning (203).

Annex 2 Search strategy from the SLR

("technology assessment, biomedical"[MeSH Terms] AND ("decision-making"[All Fields] OR "deliberative process"[All Fields] OR ("implicit"[All Fields] OR "implicitness"[All Fields]) OR ("subject"[All Fields] OR "subject s"[All Fields] OR "subjective"[All Fields] OR "subjectively"[All Fields] OR "subjectiveness"[All Fields] OR "subjectives"[All Fields] OR "subjectivities"[All Fields] OR "subjectivity"[All Fields] OR "subjects"[All Fields] OR "subjects s"[All Fields]) OR ("psychologie"[All Fields] OR "psychologies"[All Fields] OR "psychology"[MeSH Subheading] OR "psychology"[All Fields] OR "psychology"[MeSH Terms] OR "psychology s"[All Fields]) OR "value judgement"[All Fields] OR ("inform"[All Fields] OR "informal"[All Fields] OR "informality"[All Fields] OR "informally"[All Fields] OR "informant"[All Fields] OR "informant s"[All Fields] OR "informants"[All Fields] OR "information"[All Fields] OR "information s"[All Fields] OR "informational"[All Fields] OR "informations"[All Fields] OR "informative"[All Fields] OR "informatively"[All Fields] OR "informativeness"[All Fields] OR "informativity"[All Fields] OR "informed"[All Fields] OR "informer"[All Fields] OR "informers"[All Fields] OR "informing"[All Fields] OR "informs"[All Fields]) OR ("emoting"[All Fields] OR "emotion s"[All Fields] OR "emotions"[MeSH Terms] OR "emotions"[All Fields] OR "emotion"[All Fields] OR "emotional"[All Fields] OR "emotive"[All Fields]) OR ("reimbursability"[All Fields] OR "reimbursable"[All Fields] OR "reimburse"[All Fields] OR "reimbursed"[All Fields] OR "reimbursement"[All Fields] OR "reimbursements"[All Fields] OR "reimbursers"[All Fields] OR "reimburses"[All Fields] OR "reimbursing"[All Fields] OR "reimbursment"[All Fields]) OR ("coverage"[All Fields] OR "coverages"[All Fields])) AND (("english"[Language] OR "french"[Language] OR "german"[Language] OR "italian"[Language] OR "spanish"[Language]) AND 2009/01/01:2019/12/31[Date - Publication]) AND ("england"[MeSH Terms] OR "england"[All Fields] OR "england s"[All Fields] OR "englands"[All Fields] OR ("france"[MeSH Terms] OR "france"[All Fields] OR "france s"[All Fields]) OR ("germanies"[All Fields] OR "germany"[MeSH Terms] OR "germany"[All Fields] OR "germany s"[All Fields] OR "germanys"[All Fields]) OR ("italy"[MeSH Terms] OR "italy"[All Fields] OR "italy s"[All Fields]) OR ("scotland"[MeSH Terms] OR "scotland"[All Fields] OR "scotland s"[All Fields]) OR ("spain"[MeSH Terms] OR "spain"[All Fields] OR "spain s"[All Fields]) OR "UK"[All Fields] OR "United Kingdom"[All Fields] OR ("wales"[MeSH Terms] OR "wales"[All Fields] OR "wales s"[All Fields])) AND (english[Filter] OR french[Filter] OR german[Filter] OR italian[Filter] OR spanish[Filter])

Annex 3 Discussion guide

I. INTRODUCTION

The general HTA decision-making process has been partially established based on non-explicit factors. Yet, the importance of using explicit and transparent criteria for coverage decision making in line with health system values has been acknowledged. However, the values of a health system are often not explicitly considered in the HTA process.

Assessment and deliberation performed by HTA agencies may be influenced by subjective and implicit factors that affect the final recommendations and decisions leading in turn to disparities in treatment access. The objective of these interviews is to identify and better understand decision-makers' perceptions on the implicit factors influencing the HTA deliberative process in France, Germany, Italy, Spain, and the UK.

This research is part of a PhD project at the University Claude Bernard Lyon 1 in France on the HTA deliberative processes in Europe.

The first part of this PhD consisted of a Systematic Literature Review on the implicit factors influencing the deliberative HTA process. The second part aims to gather the experts' feedback to complement or validate the findings from this review. Your experience could be extremely helpful in this second phase.

It is important to reinforce that this collaboration is not remunerated since this is part of a research project from the University.

This interview will be recorded, and the key findings will be published. Your responses will be presented in an aggregated way, keeping them separate from your name/contact information and your identity will not be revealed in the final publication.

The estimated time to complete this survey is approximately 60 minutes.

PROFESSIONAL BACKGROUND

Please, provide what is your current role and affiliation.

Can you confirm that you have been involved in HTA deliberative processes for medicines in a direct or indirect way? Please, indicate how long have you been involved in such process and in what time frame.

When you participated in deliberative processes, what was the title of your position and your role?

Please, specify the geographic scope of the deliberative process.

DELIBERATIVE PROCESS: DYNAMICS AND IMPLICIT FACTORS

1. Based on your experience, could you please briefly describe the deliberative process dynamics (how it is conducted) and what are the stakeholders involved?
2. What were the appraisal committee members who were responsible for providing the recommendations?
3. When divergences between the committee members happened during the deliberation, how were they usually handled to reach a decision?
4. Usually, the HTA deliberative process take into consideration different criteria. In your experience, what are the most important criteria?
5. Based on the criteria that you just mentioned, which ones drove the decisions? Meaning, which ones had the highest weight in the decisions? Please, give an example.
6. In your opinion, are there some criteria that you consider could influence the decision-making and that were not explicitly addressed? Please, provide an example.
7. Were they documented?
8. Did your organization have an explicit decision guideline for acceptance/non-acceptance of health technologies?
9. In the case of not having an explicit decision guideline, what do you follow?

10. Do you think that the decision-making process can be based on subjective elements such as opinions, personal considerations?

11. Based on your experience, could you please indicate the degree of importance that you think these criteria may have in the HTA deliberative process? Please, score the degree of influence of the following factors being 0 the least influential and 10 the most influential. Feel free to add any criteria that you think might be missing. Definitions of these criteria are provided below.

- Functional role refers to the role the committee members in the HTA deliberative process
- Psychology refers to all elements related to subjective considerations in the context of HTA; to the perceptions, preferences, opinions and feelings the members have on the disease, the HT or the company commercializing the health technology
- Qualification means the degree and educational background of the committee members or chairs
- Value judgments are understood as judgments about what is good. There are many types of goodness, such as scientific, economic, moral goodness etc.
- Equity is defined as the value of promoting more fair distribution of access to health care.
- Political and social influences allude to the political and social pressure that may influence the HTA recommendations. For example, patient associations may put pressure to have access to a particular therapy and this may influence the HTA bodies in their recommendations of this therapy.

ITEMS	0	1	2	3	4	5	6	7	8	9	10
Functional role											
Psychology/Subjectivity											
Qualification											
Committee culture											
Equity											
Value judgments											
Professional experience											
Conflict of interest											
Political and social influences											
Burden of disease											

12. On a scale from 0 to 10, being 0 the number with the lowest score and 10 the number with the highest, could you please score the deliberative decision-making process based on your experience?

- “Objective” means that the deliberative process is not influenced by personal feelings, opinions or vested interests when considering or assessing a particular medicine.
- “Transparent” refers to the deliberative process visible or accessible through a recording or report by the public. The objectives, modes of stakeholder involvement, the decision reached, and its related argumentation should be explicitly described and made publicly available.
- “Standardized” alludes to an established process with a clear guidance on how the HTA organization is supposed to perform the HTA deliberative process.
- “Predictable” alluding to the fact of being able to expect an HTA outcome.
- “Fair” refers to assessing diseases and/or health technologies without favoritism or discrimination.
- “Reproducible” is defined as obtaining consistent results following the same method.
- “Inclusive” refers to the fact of involving in the HTA deliberative at least one of the relevant stakeholders: patients/patients associations, physicians, public.

ITEMS	0	1	2	3	4	5	6	7	8	9	10
Objective											
Transparent											
Standardized											
Predictable											
Fair											
Reproducible											
Inclusive											

II. RECOMMENDATIONS TO IMPROVE THE DELIBERATIVE PROCESS

- 13. Do you think the deliberative process may benefit of including additional stakeholders?
Which one would you suggest including?

- 14. What do you think of sharing a draft of the conclusions with different stakeholders (e.g., patient groups, health professionals, general public) with rationale underlying final determinations of contentious issues to increase the transparency of the exercise? Do you see your (ex) organization willing to adopt and implement this measure?

- 15. What are, from your perspective, the key actions/measures that should be taken to improve the acknowledgment of the implicit factors to increase transparency of the HTA deliberative process?

- 16. Do you have any recommendation that would help to address the implicit criteria in a systematic and standardized way to make the HTA appraisal more transparent and legitimate?

- 17. If you were asked to develop a checklist supporting the HTA deliberative process, how would you uncover the implicit factors in a way that they are explicitly addressed and properly documented?

Annex 4 Academic and professional background of the interviewed experts

Expert	Country	Current role and institution	Former roles	Education
Expert 1	Spain	Professor in the Health Public School	External advisor to the high-impact drug committee in Andalusia	PhD in Economics; Master in Public Health
Expert 2	Spain	Consultant in health economics and market access	General secretary of the National Transplant Organizations; Counsel and general secretary at the Economics Ministry - Instituto Carlos III	Bachelor in Economics Sciences; Master in Business Administration
Expert 3	Spain	Director at Consorci de Salut i Social de Catalunya (2 years)	Various positions at Consorci de Salut i Social de Catalunya ; Responsible of Pharmaceutical Planning at Catalonia Government	Master in Senior Health Management; Health Economics Certificate; Doctor of Pharmacy; Master in Public Health
Expert 4	Spain	Chief of the Regional Pharmacy Department	Pharmacy Director and subdirector at the Health Regional Department in Valencia subdirector of Pharmacy in the Health Regional Department in Valencia	PhD Business Administration
Expert 1	Italy	Medical Doctor at AdReS Health Economics and Outcomes Research	Medical Director Advanced Research	Medical Doctor
Expert 2	Italy	Research scientist at Institute of Healthcare in Rome; professor of political economics	Researcher at the national centre of HTA in Italy	PhD in Health Economics
Expert 3	Italy	Professor in Economics, Politics and Health Economics	External expert to AIFA	Bachelor in economics

Expert	Country	Current role and institution	Former roles	Education
Expert 4	Italy	Director of HTA department at Italian National Agency for Regional Health Services (<i>Agenzia Nazionale per i servizi sanitari Regionali</i> , AGENAS); Member of the HTAi's Committee	Director at the National Center of HTA; Director of HTA unit at University Hospital	MD
Expert 1	France	Associate Director Medical at Alira Health	MedTech expert consultant (6 years); Project lead at HAS (3 years)	PHD in biomedical engineering; Master's degree in pharmacology
Expert 2	France	Consultant	Member of HAS	MD
Expert 3	France	Independent Consultant in Market Access	President of the Transparency Commission	MD
Expert 4	France	Public Health Professor	Transparency Committee Member	MD
Expert 1	UK	Head of a consulting company on health economics	NHS and NICE Advisor	Bachelor's in health economics, Master in Sciences and PhD
Expert 2	UK	Managing partner and director in a consulting company on health economics and market access	Industry representative on New Drugs Committee of SMC NICE advisor	Bachelor's in economics
Expert 3	UK	Director in a consulting company on health economics and market access	NHS Advisor	PhD in Philosophy and Economics
Expert 4	UK	Professor of Global Health Economics and member of JCVI	Advisor to the MOH	Health economist
Expert 1	Germany	Private Practice (physician)	Former Member of G-BA; Honorary Chairman of the Bavaria National Association	MD (paediatrician and general practitioner)

Expert	Country	Current role and institution	Former roles	Education
Expert 2	Germany	Consultant; Member of the the arbitration board for drug prices in the SHI in Germany.	Managing director of a private company (5 years); Principal at IMS HEOR in Germany, (4 years)	Health economist
Expert 3	Germany	Professor for Health Care Management	Professor and chair of the Institute für Health Care Management; professor for health economics at the school of public health; professor for health insurance; worked in the German MOH	Economist and political scientist by training
Expert 4	Germany	Consultant at Association of Private Health Insurance	Deputy chairman of the working group (4 years); Member of Approval Commission of the Federal Institute for Drugs and Medical Devices (BfArM) Chairman of the Board of Trustees of the German Agency for Health Technology Assessment (DAHTA) (6 years)	Neurologist and psychiatrist

Annex 5 Degree of influence of the implicit factors on the HTA deliberative process: responses by expert from Spain

Dimensions	Expert 1	Expert 2	Expert 3	Expert 4
Functional role	6	6	3	9,5
Psychology	4	0	2	4
Qualification	7	10	3	5
Committee culture	5	0	4	6
Equity	7	8	4	2
Value judgments	4	2	3	3
Professional experience	8	10	3	5
Conflict of interest	2	0	3	5
Political and social influences	1	0	4	8
Burden of disease	6	8	4	8

Annex 6 Degree of influence of the implicit factors on the HTA deliberative process: responses by expert from France

Dimensions	Expert 1	Expert 2	Expert 3	Expert 4
Functional role	2	5	10	3
Psychology	4	2	6	4
Qualification	8	7	6	5
Committee culture	3	8	6	6
Equity	8	7	6	7
Value judgments	8	2	4	4
Professional experience	8	8	8	4
Conflict of interest	3	1	3	2
Political and social influences	2	2	3	3
Burden of disease	7	7	8	4

Annex 7 Degree of influence of the implicit factors on the HTA deliberative process: responses by expert from Italy

Dimensions	Expert 1	Expert 2	Expert 3	Expert 4
Functional role	8	7,5	6	5
Psychology	5	5	8	3
Qualification	8	4,5	4	6
Committee culture	8	5	6	5
Equity	8	8	8	7
Value judgments	9	8,5	10	7,5
Professional experience	8	8,5	5	8
Conflict of interest	5	5	6	5
Political and social influences	8	7,5	6	5
Burden of disease	8	8,5	0	8

Annex 8 Degree of influence of the implicit factors on the HTA deliberative process: responses by expert from the UK

Dimensions	Expert 1	Expert 2	Expert 3	Expert 4
Functional role	8	2	8	3
Psychology	6	3	7	2
Qualification	7	5	6	1
Committee culture	8	4.5	6	1
Equity	3	4	6	8
Value judgments	5	4.5	9	2
Professional experience	8	5	5	5
Conflict of interest	5	0	1	2
Political and social influences	2	8	6	2
Burden of disease	4	5	7	8

Annex 9 Degree of influence of the implicit factors on the HTA deliberative process: responses by expert from Germany

Dimensions	Expert 1	Expert 2	Expert 3	Expert 4
Functional role	0	0	5	2
Psychology	3,5	5	5	0
Qualification	1	5	2	0
Committee culture	2	0	2,5	1
Equity	2	0	5	0
Value judgments	1	5	6	5
Professional experience	0	5	6	1
Conflict of interest	0	0	5,5	1
Political and social influences	1	3	2,5	0
Burden of disease	0	0	5	2

Annex 10 Quantification of a set of attributes in the HTA deliberative process: responses by expert from Spain

Dimensions	Expert 1	Expert 2	Expert 3	Expert 4
Objective	9	9	7	2
Transparent	10	9	6	2
Standardized	8	7	7	2
Predictable	7	5	6	2
Fair	8	9	6	4
Reproducible	8	8	5	4
Inclusive	9	10	0	3

Annex 11 Quantification of a set of attributes in the HTA deliberative process: responses by expert from France

Dimensions	Expert 1	Expert 2	Expert 3	Expert 4
Objective	8	7,5	3	5
Transparent	7	8	5	4
Standardized	6	8	5	4
Predictable	8	8	7	6
Fair	8	7	6	7
Reproducible	6	8	7	6
Inclusive	5	6	2	3

Anex 12 Quantification of a set of attributes in the HTA deliberative process: responses by expert from Italy

Dimensions	Expert 1	Expert 2	Expert 3	Expert 4
Objective	7	9	6	7
Transparent	7	9	3	8
Standardized	6	8	6	6
Predictable	6	8,5	4	7
Fair	7	9	6	7
Reproducible	7	8	5	6
Inclusive	5	7	4	5

Annex 13 Quantification of a set of attributes in the HTA deliberative process: responses by expert from the UK

Dimensions	Expert 1	Expert 2	Expert 3	Expert 4
Objective	5	8	8	10
Transparent	7	8	6	9
Standardized	10	9	6	8
Predictable	7	6	7	7
Fair	8	6	6	10
Reproducible	6	7	6	10
Inclusive	6	6	7	8

Annex 14 Quantification of a set of attributes in the HTA deliberative process: responses by expert from Germany

Dimensions	Expert 1	Expert 2	Expert 3	Expert 4
Objective	9	7	7	8
Transparent	10	10	5	10
Standardized	10	10	5	10
Predictable	8,5	10	5	8
Fair	10	8	5	8
Reproducible	10	9	7	9
Inclusive	9	7	3	9

CHAPTER 3: A SOLUTION THAT ACCOUNTS FOR IMPLICIT FACTORS IN THE HTA DECISION-MAKING

1. Introduction

As described previously (see Chapter 2, Section 3), a deliberative process can be defined as the process enabling, receiving, and exchanging of the information between the group of actors, in order to critically review an issue, and to achieve agreement and subsequently inform decision making (106). Deliberative processes are a well-established element of HTA programs in many high- and middle-income countries. They are believed to provide the best way to bring together complex sets of evidence, values, and perspectives, while allowing these aspects to be identified and discussed, and consequently, making HTA recommendations more transparent, inclusive, and trustworthy (7). Based on the HTAi/ISPOR Taskforce, deliberation in HTA is the informed and critical examination of an issue and the weighing of arguments and evidence to guide a subsequent decision.

However, through this “critical examination” there are additional considerations that are not official because sometimes these are unconscious and therefore can impact the transparency and legitimacy. Based on literature (15,16) and on the findings from our two pieces of research (Sections 5 and 6 of Chapter 2), there are additional factors and biases that are not explicitly reported and influence HTA recommendations.

There are several initiatives and frameworks striving for the transparency, inclusivity, and impartiality in the HTA deliberation and aiming to standardise and structure the deliberative process to ensure that all elements requiring deliberation are addressed and concluded. However, current frameworks do not sufficiently account for implicit factors (116,178).

At the same time, suggestions for policymakers have already been made to support research that seeks to better understand biases by developing tools and lessening healthcare disparities (204).

The above led us to develop a checklist for HTA practitioners and this is what constitutes the objective of this chapter. The checklist that will be presented enables a comprehensive

assessment of the key factors in the HTA process, including implicit factors, that could potentially play a role in the decision-making process and impact the final recommendation or decision.

To develop our checklist, we followed a stepwise approach.

The first step was to undertake a targeted literature review (TLR) to identify existing checklists assisting the HTA deliberative process.

A second step consisted of performing a critical appraisal of the articles identified in the TLR.

The third step was the development of our checklist based on the findings from our SLR (see Chapter 2 Section 5), our mixed-methods research (see Chapter 2 Section 6) and on the areas not covered in the existing checklists identified.

For each of the three steps, we will present the methods and the results separately.

2. Targeted literature review

A SLR is defined as “a systematic, explicit, comprehensive, and reproducible method for identifying, evaluating, and synthesizing the existing body of completed work produced by researchers, scholars, and practitioners. “It follows established guidelines such as PRISMA statement. It is considered the most comprehensive literature review. It typically involves searching multiple predefined electronic databases and grey literature sources.

On the other hand, a TLR is a non-systematic literature review that is meant to be informative rather than all-encompassing review of the literature on a topic. Generally, it does not take a systematic approach to answer the research question. It helps to identify trends and better understand the current context. It may or may not follow a predefined protocol (205,206).

For the purpose of this review, we believed a TLR was the most efficient and suitable approach.

2.1. Methods

The database used to perform this search was PubMed. Retrieval was not limited by publication date. The search was performed in September 2022. No geographic limits were applied.

The search strategy was the following: ("checklist"[Title/Abstract] AND ("HTA"[Title/Abstract] OR "health technology assessment"[Title/Abstract]) AND "deliberat*"[All Fields]) AND (english[Filter] OR french[Filter] OR german[Filter] OR italian[Filter] OR spanish[Filter])

2.1.1. Eligibility criteria

The inclusion criteria comprised:

- Original research publications describing the development or application of a checklist to assist the HTA deliberative process in English, French, German, Italian and Spanish

The exclusion criteria comprised:

- Papers written in languages other than English, French, German, Italian and Spanish

- Papers on review types that are not intended to answer research questions about checklists to support the HTA process
- Systematic reviews and meta-analysis
- Papers focused on specific diseases
- Papers focused on health technologies other than pharmaceuticals

2.1.2. Article selection

The retrieved articles were reviewed by a researcher (CM), and those considered irrelevant or not related to our research question were removed. The remaining articles were further assessed to identify those studies that met the eligibility criteria. Selection criteria was applied to all studies found in PubMed by two reviewers.

2.2. Results

Four publications were retrieved from which one was duplicated.

Among the remaining three, a full-text screening was performed and just one article was included: the joint HTAi/ISPOR Task Force checklist published in June 2022 (135) . The reason for excluding the other two articles (116,207) was that the content did not address the research question and therefore they did not present a checklist assisting the HTA deliberative process.

3. Appraisal of the checklist from the joint HTAi/ISPOR Taskforce

An appraisal of the checklist from the joint HTAi/ISPOR Taskforce was performed and we identified the areas not covered in the tool for the sake of our thesis and to leverage on any section that could potentially address the implicit factors to expand it further in our tool.

3.1. Methods

A thorough evaluation was done by assessing the relevance of the content in accordance with our focus of the thesis, the implicit factors. We checked if it was alluded through different terms: implicit/informal/non-explicit factors.

In all the six sections of the checklist (determining the need for a deliberative process, preparing for a deliberative process, conducting a deliberative process, supporting a deliberative process, development and communication of the output and monitoring, and evaluating a deliberative process), we assessed the strengths and limitations. The relevance of the checklist was also evaluated thanks to the results from the mixed-methods research that was done as a second project of this thesis (see Section 6 of Chapter 2). Its content was mapped against the recommendations collected from this mixed-methods research.

As part of this task, we also checked if the goals of the checklist were addressed in the respective sections.

Two reviewers (CM, MT) followed independently these steps. Then, they reconvened and shared their findings. When discrepancies were found a third reviewer (CC) performed the assessment to reach a consensus by majority.

3.2. Results

The purpose of the HTAi/ISPOR Taskforce checklist (135) was “developing the governance and structure of an HTA program (i.e., deliberation about processes) and managing the various stages of an HTA process (i.e., deliberation within processes).” The checklist was intended to be used prior to designing a deliberative process or during the review of an existing one. However, it is difficult to assess the achievement of the objectives of the checklist as they are not clear or difficult to measure.

For the first objective “developing the governance and structure of an HTA program”, the article states that HTA bodies must consider also broader aspects of governance, such as those “to whom the deliberative group is accountable”. It is unclear how the checklist can help in developing the governance of an HTA program. On the other hand, the second objective “managing the various stages of an HTA process” is not clear in terms of what the authors mean by “manage”.

A contribution of the guidance was the development from the Taskforce of the definitions of deliberation and deliberative process in HTA.

The checklist was divided into six main phases. The strengths and limitations of each section are presented in Table XIII following a detailed assessment of the checklist.

Table XIII. Assessment of the different phases of the HTAi/ISPOR checklist

Phase	Strengths	Limitations
Determining the need for a deliberative process	The scope of the deliberation provides the overall context and proposes two different settings (deliberation about the process and within the process) and outlines the characteristics of each of them. It sets the needs for a deliberative process: reasons to deliberate, desired outcomes and scope of the deliberation. In the reasons to deliberate it considers an implicit factor (“self-interest”).	The ultimate goal of “facilitating participatory decision making” was not included in the reasons to deliberate.
Preparing for a deliberative process	This section describes the contextual factors and guidance to be considered for the implementation. This enables planning and structuration. It also helps HTA practitioners to have consciousness on what can hamper or drive the process.	It is unclear to what extent this phase helps the HTA practitioners to prepare for the deliberative process. It covers a kind of implicit factors (contextual factors). There may be additional implicit factors other than contextual factors (e.g., biases) that play a role in the implementation and that were not considered in the checklist.

<p>Conducting a deliberative process</p>	<ul style="list-style-type: none"> - It reinforces the diversity and the broad spectrum of stakeholders' perspectives. - It reveals the importance of determining the type of membership. - It reveals the importance of transparency (openness of deliberation and type of information shared with the public) - It highlights the importance of defining a way to reach the end of the deliberation (the recommendation) - It remarks the importance of following and placing in the public domain the explicit criteria. 	<ul style="list-style-type: none"> - The perspective on memberships, and the selection of profile characteristics should be part of the previous section ("preparing for a deliberative process") since they should be well defined before conducting the deliberative process. - The authors focus on the contextual factors relevant to the process (internal and external) and on the explicit criteria. There is no dedicated attention to other implicit factors (e.g., ethics, cognitive biases), which is a major limitation of the checklist.
<p>Supporting a deliberative process</p>	<ul style="list-style-type: none"> - It focuses on the type of information and ways to make it available to the HTA participants. A clear understanding of the information is critical to ensure meaningful participation. 	<ul style="list-style-type: none"> - Regarding the type of information that will be made available to the deliberative process, it is rather general (e.g., "all information made available to the HTA body"). - It is not clear how the information will be reviewed and why the distinction between HTA body and participants was made, as the HTA bodies are the target audience. One of the answers to the question "what information will be considered by participants?" was "any information provided by HTA body and participants". There are no questions to check if all relevant information is available

		to the participants or if the information was clearly understood.
Development and communication of the outputs of deliberation	<ul style="list-style-type: none"> - Developing a communication strategy and defining what and how will be shared with the public is key to ensure the transparency of the process. This will enable the understanding of all the elements that were considered for the recommendation. - It focuses on the way to communicate the outputs. 	There is no mention to the timelines associated to the communication of the outputs.
Monitoring and evaluation.	This phase is important to check if the deliberative process is achieving its intended goals. The table shows a list of process and outcomes indicators along with proposed methods that can help the HTA body to assess and evaluate the deliberative process.	The table proposing different indicators and methods is not integrated in the checklist and it is not clear how this information as a part of the checklist is going to be available to those interested.

Additionally, from our perspective there is a step that is missing between the phases of “supporting a deliberative process” and “development and communication of the outputs of the deliberation” and this is the different ways the decision-making can be performed (e.g., consensus, vote...). (See Chapter 2 section 6.3.2)

The checklist provides guidance prior to design a deliberative process or when reviewing an existing one. If we focus specifically on the objectives for which the checklist was created (“developing governance and structure” and “managing the various stages of an HTA process”) it is difficult to determine if the objectives were achieved. It would require most likely a pilot where the checklist is tested and validated.

The introduction states that “well conducted deliberative processes can make explicit the assumptions, arguments and values that are entailed when assessing health technologies”. It is not clear how these elements are going to be explicit if the checklist does not address the implicit factors. This is a major limitation of the checklist, as the implicit factors may influence

the HTA final recommendations in positive and negative ways. For the sake of legitimacy and objectivity, it is important to raise awareness of the implicit factors, so they are properly addressed or mitigated.

3.3. Discussion

As a key takeaway from this assessment, the HTAi/ISPOR Taskforce checklist is a good attempt to facilitate the understanding of the different components of a HTA deliberative process. It provides a guidance for designing and implementing the deliberative processes through questions across the six different phases. The checklist aims to formalize different features of the deliberative process such as how participants will be selected, how the process will be facilitated and whether meetings will be open to public.

Still, it has three main limitations. First, the checklist does not address the implicit factors that may influence the HTA deliberative process. Additionally, some questions are too broad and lack clear guidance. Finally, the length of the checklist may be a hurdle for the implementation. There is a need for a more practical checklist that takes into account these limitations, especially those related to implicit factors.

There was no concordance between this checklist and the insights gathered from the interviews that our research group performed to reveal implicit factors (See Chapter 2, Section 6), which led our research team to develop a new checklist.

4. Development of the RELIANT checklist: a tool to address implicit factors in the HTA deliberative process.

Given the lack of checklists in the literature accounting for the implicit factors influencing HTA recommendations, we developed the RELIANT (**RE**vea**L**ing **I**mplicit **f**actors **i**n **H**TA) checklist.

The RELIANT checklist is presented as the first checklist addressing the implicit factors present in HTA. It is aimed as a practical tool to acknowledge and elucidate the implicit factors present in the HTA deliberative process for pharmaceuticals and the meeting dynamics surrounding this process. In HTA, deliberation takes place from the horizon scanning to the monitoring, assessment, appraisal, and evaluation of the recommendation that has been issued (107).

The ultimate goal is to improve the deliberation by making it more rationale, impartial, legitimate and transparent. For this reason, the objective of the last step of the PhD thesis was to develop a checklist addressing the implicit factors.

4.1. Methods

4.1.1. Development of the first version of the checklist

To develop our checklist, we leveraged the findings from a SLR previously published (Chapter 2, Section 5)(168), the mixed-methods research (Chapter 2, Section 6) described earlier and the results of the assessment of the HTAi/ISPOR checklist (Chapter 3, Section 3).

Two additional articles (112,208) on implicit factors were proposed proactively by one expert at the time of the interviews. These articles were not retrieved as a result of our SLR because one of them was out of the pre-specified time window of publication (2021) and the other did not match the key words of our search strategy. For the definition of cognitive biases, we leveraged on these articles.

The checklist development was based on the “Guidelines for developing evaluation checklists: the checklists development checklist (CDC) by D. L. Stufflebeam” (209).

As a first step, the thesis PhD research team agreed on the objective of the checklist, defined the checklist’s intended users, studied the relevant literature, and clarified the criteria that

should be met by the tool. The objective agreed was to support the HTA practitioners to become aware of the implicit factors that could have an impact on the HTA recommendations.

The checklist had to be easy to understand, easy to implement and reproducible.

We then identified a list of categories that would form the skeleton of the checklist. We focused mainly on the cognitive biases (Chapter 2, Section 1) since these are the implicit factors more subjective likely of bringing biases at the end of the deliberative process and therefore, likely to affect the recommendations.

The selection of these categories was made based on the results from the qualitative research (Chapter 2, Section 6) and on what we considered that was missing in the HTAi/ISPOR checklist vis a vis the implicit factors.

In a third step, we defined the order of these categories going from a more general and objective approach to finalize with the cognitive biases. For each category, we developed a set of questions with the intention to help the HTA practitioner to reflect on the factors that he or she considered in the deliberative process.

We also defined the format of answers with options of “yes/no/sometimes” and “low/medium/high”. We believe this kind of format contributes to the simplicity and to time saving to go through the checklist.

Finally, we agreed on a first version ready to be shared with a group of experts.

4.1.2. Content validity phase

A group of experts was appointed from those interviewees who expressed interest in participating in the development of the checklist. The group was composed by eight experts’ representative of the countries and profiles assessed (Table XIV). There was at least one expert per country and per type of profile. Two rounds of review were performed (November 2022 and January 2023).

Table XIV. Profile characteristics of the eight study participants

Country	Profile in the HTA deliberative committee
France	Chair
France	Committee Member
Germany	External Advisor
Italy	Committee member
Spain	Pharmacy Director
UK	External advisor
UK	Committee member
UK	Committee member

Experts were asked individually via e-mail to provide feedback on the different sections of the first version of the checklist (Table XV), the items, and the place of the checklist in the deliberative process. An open question was asked about their overall perception on the checklist. A follow-up teleconference was proposed to clarify any question. Two out of the eight experts (one from France and one from the UK) accepted this option.

Their comments and suggestions were incorporated leading to a shorter second and final version that was shared for final comments and endorsement. Their responses are detailed in Table XVI.

As a result of the review, all comments were incorporated and a second and final version was consolidated. The main comments were pointed towards further clarification on some section and verbiage and about the length of the checklist.

Once we had the final version (Table XVII), the checklist was called RELIANT (**RE**vea**L**ing **I**mplicit **f**actors **i**n HTA). Reliant is a name that resonates with the objectives of this checklist since its implementation aims to address the potential implicit factors and biases that may compromise the credibility and trust of the HTA deliberation.

4.2. Results

4.2.1. Characteristics of the checklist

The audience for this checklist is HTA experts who have a direct or indirect involvement in the HTA deliberative process.

The checklist has seven sections covering perspectives, objective factors, meeting dynamics, personal interest, previous experience, context, and cognitive biases. It contains 16 questions, each of them having a different range of options of answers.

The first section, section A, aims to gather the perspectives that have been considered in the deliberative process such as the health insurer/payer perspective, the societal perspective or other.

Section B displays a list of objective factors for the HTA expert to calibrate the importance of those in the HTA process. This section starts addressing the factors, that may be explicit or implicit depending on the HTA body and its methodology. These factors are clinical burden, humanistic burden, economic burden (direct and indirect costs), prevalence and incidence, population vulnerability, availability of effective alternatives, innovation of the technology, strength of the evidence, clinical sign of potential value and strong biological hypothesis of efficacy.

The following section, section C “Meeting dynamics”, aims to check on the preparedness for the meeting and clarity of the data and topics for discussion. For example, it asks if the HTA expert in question received all the necessary information to make a decision. It also aims to evaluate if there were any dominant perspectives and if the way of reaching a conclusion may affect the expert performing the checklist’s perspective. This section prompts to the reflection on the way of working.

Section D focuses exclusively on the personal interests and how this can affect the expert’s perception. As opposed to section C that covers the group meeting dynamics, this part focuses on the personal factors that can represent a bias and deserve to be analysed separately.

The next part, section E, is about the previous experiences of the individual reviewing the checklist and their impact on their perception, for example any previous experience with the manufacturer or the disease that could affect his appraisal.

Section F aims to consider any kind of contextual influence that might have affected the recommendation. Any influence from society, culture, media politics, healthcare professionals, manufacturers, health administration should be captured in this section.

Finally, section G, dedicates special attention to the different cognitive biases that might have impacted the expert's judgment. This part takes back the biases that have been presented in the first section of Chapter 2. These are: affect heuristic, anchoring bias, attentional bias, authority bias, automation bias, availability bias, confirmation bias, consistency tendency, false consensus effect, framing effects, groupthink, halo effect, hard/bandwagon effect, in-group conformity, intellectual bias, novelty, optimism bias, overconfidence bias, reductionism bias, scientific inbreeding, specialty bias and thinking inside the box.

Table XV. The RELIANT checklist version prior to the experts' review.

Sections	Questions																
A. Perspectives	<ul style="list-style-type: none"> What are the perspectives that have been considered? (select one or more): <input type="checkbox"/> Health insurer <input type="checkbox"/> Societal <input type="checkbox"/> Other _____ 																
B. Objective factors (explicit or implicit in the HTA framework)	<i>What is the importance that you allocate to these factors?</i>	<i>How much influence did they have in your recommendation?</i>															
<ul style="list-style-type: none"> Clinical burden (e.g. severity of the disease, mortality, frequency of hospitalizations) 	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>				Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<ul style="list-style-type: none"> Humanistic burden (impact on quality of life of patients' and caregivers) 	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>				Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<ul style="list-style-type: none"> Economic burden: direct costs of treatment 	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>				Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<ul style="list-style-type: none"> Economic burden: indirect costs of treatment 	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>				Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<ul style="list-style-type: none"> Prevalence and incidence (rare disease, disease affecting large number of patients) 	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>				Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<ul style="list-style-type: none"> Vulnerability of the population 	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>				Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<ul style="list-style-type: none"> Availability of effective alternatives (on and off-label)/unmet need 	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>				Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<ul style="list-style-type: none"> Innovativeness of the technology independent of the performance 	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>				Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<ul style="list-style-type: none"> Strength of the evidence (robustness of clinical study design and effect size) 	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>				Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<ul style="list-style-type: none"> Clinical sign of potential value, but value not fully demonstrated with evidence (aspirational benefit demonstrated by immature data, surrogate, partially validated endpoints, single arm study)* 	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td>Low</td> <td>Medium</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>				Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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	<p><i>*To be rated only if the strength of the evidence was considered as medium or low</i></p> <ul style="list-style-type: none"> Strong biological hypothesis of efficacy (hypothesis well supported by preclinical research, physiology, pharmacology, disease mechanism) <p><i>*To be rated only if the strength of the evidence was considered as medium or low</i></p>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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C. Meeting dynamics	<i>Did you receive all information necessary to make an informed decision?</i>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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	<i>Could the way the data was presented have affected your perception?</i>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>												
<i>Did you ask all relevant question from your perspective?</i>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>								
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<i>Did you receive clear and unambiguous responses to your questions?</i>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>								
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<i>Did any dominant perspective/opinion prevent alternative view to discussion?</i>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>								
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<i>Could the way the decision was made (for example consensus vs. voting procedure, show if hands) have affected your decision?</i>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>								
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D. Personal interest	<i>Do you believe that your personal interest (e.g., willingness to use the drug by yourself/your friends/your relatives/your patients) could have any impact on your perception?</i>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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E. Previous experience	<i>Was your perception impacted by your previous experience with the manufacturer?</i>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<i>Was your perception impacted by your previous experience with the disease?</i>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>								
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<i>Was your perception impacted by your previous experience with similar type of medication?</i>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>								
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F. Context	<i>Do you believe that the final decision was impacted by any form of pressure listed below?</i>		<i>What impact did it have on the final decision?</i>												
	<ul style="list-style-type: none"> Political 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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	<ul style="list-style-type: none"> Patient groups and caregivers 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<ul style="list-style-type: none"> Healthcare professionals 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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<ul style="list-style-type: none"> Pharmaceutical companies 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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<ul style="list-style-type: none"> Social 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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<ul style="list-style-type: none"> Cultural 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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<ul style="list-style-type: none"> Media 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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<ul style="list-style-type: none"> Administration/ Health authorities 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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<ul style="list-style-type: none"> Moral/ethic (your sense of equity and values) 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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	<ul style="list-style-type: none"> Healthcare system affordability 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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	<ul style="list-style-type: none"> Allocated budget to certain diseases 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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	<ul style="list-style-type: none"> Feasibility (ability of the healthcare system to ensure a right use of treatment) 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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	<ul style="list-style-type: none"> Public health priority 	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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	Other _____		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
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G. Cognitive biases and fallacies (individual and collective)	<i>In an effort to be as objective as possible, do you consider any of these potential biases may have impacted your judgement?</i>		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
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	<ul style="list-style-type: none"> Affect heuristic (decision influenced by subjective feelings) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
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	<ul style="list-style-type: none"> Anchoring bias (focusing on the first picture you learn and staying with the first impression) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
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	<ul style="list-style-type: none"> Attentional bias (paying disproportional attention to some things, over others) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
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	<ul style="list-style-type: none"> Authority bias (having more confidence in a decision that was validated by an authority figure) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
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	<ul style="list-style-type: none"> Automation bias (tendency to accept automated clinical decision advice) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
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	<ul style="list-style-type: none"> Availability bias (making judgments of likelihood based on ease of recall) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
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<ul style="list-style-type: none"> Confirmation bias (focusing on information confirming personal beliefs) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
Yes	No	Sometimes													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
<ul style="list-style-type: none"> Consistency tendency (difficulty in changing a point of view when the change is justified by the new evidence) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> False consensus effect (overestimation on how much other people are aligned with your appreciation) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> Framing effects (perception influenced by the way in which the evidence was presented) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> Groupthink (situation in which the views of the decision-making group become homogeneous and contrary views are discouraged) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> Halo effect (giving disproportionate weight in decision making to the beliefs of eminent individuals) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> Hard/bandwagon effect (choosing based on other people choices) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> In-group conformity (having more confidence in a decision when it is in agreement with others) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> Intellectual bias (becoming closed-minded about a belief) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> Novelty (uncritical acceptance of a new technology) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> Optimism bias (tendency to overestimate the likelihood of favourable outcomes) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> Overconfidence bias (overestimation of personal ability or opinion) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> Reductionism bias (reducing complex scenarios into simpler ideas) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<ul style="list-style-type: none"> Scientific inbreeding (replication of views by the individuals with the same training/educational experience) 		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
Yes	No	Sometimes													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													

• Search satisficing (stopping research once self-satisfying evidence is found)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Specialty bias (form of groupthink, situation when those in a specialty adopt a homogeneous set of beliefs)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Thinking inside the box (inflexibility of thinking within decision-making group)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Fallacy of silence (omission of contradictory evidence)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Planning fallacy (incorrect estimation of the benefits and timing of policies/actions)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Sunk-cost fallacy (making decision based on previously spent effort for the assessment, unwillingness to change the course when too much effort has been invested)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Arguing from ignorance (claiming that a statement is false because we do not know if it is true and vice versa)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Fallacy of diversion (substitution of one argument for another)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Fallacy of division (reasoning applied to a group is confused with reasoning applied to individual)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Appealing to authority (giving inappropriate weight to the argument coming from a source of expertise or authority)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Appealing to popularity (claiming that the argument is valid base on most people's acceptance)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Ad hominem fallacy (directing criticism to a person rather than criticize the argument itself)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Straw man fallacy (attacking a misrepresentation of an opinion)	Yes	No	Sometimes
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4.2.2. Feedback from the group of experts

The group of eight experts (one from Italy, one from Germany, one from Italy, two from France and three from the UK) was asked to provide feedback on the different sections of the checklist, the items, and the feasibility of its implementation as well as the place of the checklist in the deliberative process.

The main comments were about making the checklist a practical tool, short, concise, and easy to deploy (Table XVI).

The experts were asked where they would see the implementation of the checklist in the HTA deliberative process. Six experts shared they would use the tool prior to the appraisal whereas one expert thought it could be used during the deliberation and another expert saw the value of using the tool retrospectively, meaning after the appraisal.

The arguments supporting its use prior to the deliberation were that it would allow to think prospectively on all the implicit factors that can impact the recommendation and therefore this would allow the HTA practitioner to be conscious and thoughtful about them. This in turn could be a way to mitigate their influence.

One expert from UK suggested to define the target audience expected to run this checklist as well as the type of health technology (medicines for the purpose of this research).

The experts acknowledged the need for the validation of the tool.

Overall, the checklist was perceived as a valuable tool, exhaustive and practical with the potential to play a key role in the future HTA process.

Table XVI. Feedback on the RELIANT checklist from the eight HTA experts.

Experts' countries	Main comments on the content	Changes reflected in the updated version of the checklist	Overall perceptions on the checklist	Position of the checklist in the HTA process
Italy	<p>"I am afraid of its length since this could difficult is implementation."</p> <p>"I don't see so much relevance to the part dedicated to fallacies."</p>	The checklist was shortened following the removal of the part focused on "fallacies"	<p>"This tool is very interesting given its exhaustiveness."</p> <p>"I put a face to some of the referred biases."</p>	Pre-appraisal
France	"The part related to fallacies could be removed to shorten the checklist and make it more practical."	The checklist was shortened following the removal of the part focused "fallacies."	<p>"This is a very complete checklist with many considerations on it. It is exhaustive but practical at the same time."</p> <p>"The checklist could be used in some workshops first to make the committee aware of its use."</p>	Pre-appraisal
France	"It would be helpful to make it shorter to facilitate the implementation".	The checklist was shortened following the removal of the part focused "fallacies"	<p>"This checklist is comprehensive and innovative."</p> <p>"I like the fact that both group and individual dynamics are being considered."</p>	Pre-appraisal
Germany	<p>"From a German system's perspective, it would be implemented in the assessment but not in coverage and pricing discussions."</p> <p>"Maybe in Section C, add "committee" "to make it clearer".</p>	The name of Section C was further detailed. It was added "committee" to "meeting dynamics".	"The list is fairly comprehensive."	During the assessment
Spain	"It would be good to specify the context: what are	It was clarified that the checklist it is intended to be	"I found the checklist interesting, and I	Pre-appraisal

	the technologies (drugs, medical devices, vaccines?) subject for the checklist.”	applied only to medicines.	would be eager to see how this is intended to be implemented.”	
UK	<p>“At end maybe add an open space for any more comment – qualitative evidence/ information can often be very useful.”</p> <p>“Is the checklist meant to be completed prospectively or retrospectively?”</p>	<p>A row was added to integrate any additional comment that the expert may have.</p> <p>The intend of use of the checklist was defined (prospectively).</p>	“Very nice tool be self-aware of the biases and other factors present in the deliberative process.”	Post appraisal
UK	<p>“Maybe clarify in introductory notes about the checklist intention for the specific person/ persons completing it.”</p> <p>“Add a row for strength of cost-effectiveness evidence.”</p> <p>“SMC and some other HTA’s may give a different rating to patients and caregivers QoL – consider distinguishing between the two options.</p>	<p>The intended users were defined in the description of the checklist.</p> <p>A row for strength of cost-effectiveness evidence was added in section B).</p> <p>In Section B, the impact in quality of life was distinguished between patients and caregivers</p>	<p>“Nice checklist. It would be good to pilot the checklist with a few intended users of course.”</p> <p>“I find section G (Cognitive bias) a very interesting list “</p>	Pre-appraisal
UK	<p>“Clarify the perspectives of whom (section A of the checklist)</p> <p>“Maybe label Health insurer/payer”</p> <p>“If the checklist is intended to be used</p>	<p>It was added into the first question of the checklist (section A): “What are the perspectives that have been considered by the HTA expert completing the checklist?”</p>	“Very interesting and helpful checklist. If applied in a systematic way, this could make a big difference in the way the HTA is conducted. It would promote a more objective and conscious	Pre-appraisal

	<p>prospectively, use the present tense in the questions instead of past tenses.”</p> <p>“Maybe it needs clarity on what indirect costs means, e.g., everything else than direct cost of treatment e.g. hospital and other resource use costs, caregiver costs, productivity costs, costs on other government sectors?”</p>	<p>In the options of answer in Section A, it was added “payer” along to health insurer.</p> <p>The questions were formulated in present tense.</p> <p>The clarification on what indirect costs mean was added accordingly in the part of economic burden (Section B)</p>	<p>exercise.”</p>	
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Table XVII. Final version of the RELIANT checklist following the experts' review.

Sections	Questions						
A. Perspectives	<i>What are the perspectives that have been considered by the HTA expert completing the checklist? (select one or more):</i> <input type="checkbox"/> Health insurer/payer <ul style="list-style-type: none"> <input type="checkbox"/> Supra-national <input type="checkbox"/> National <input type="checkbox"/> Regional <input type="checkbox"/> Societal <input type="checkbox"/> Other _____						
B. Objective factors (explicit or implicit in the HTA framework)	<i>What is the importance that you allocate to these factors?</i>			<i>How much influence do they have in your recommendation?</i>			
	• Clinical burden (e.g., severity of the disease, mortality, frequency of hospitalizations)	Low	Medium	High	Low	Medium	High
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	• Humanistic burden: impact on quality of life of patients	Low	Medium	High	Low	Medium	High
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	• Humanistic burden: impact on quality of life of caregivers	Low	Medium	High	Low	Medium	High
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	• Economic burden: direct costs of treatment	Low	Medium	High	Low	Medium	High
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	• Economic burden: indirect costs of treatment (everything else than direct cost of treatment such as caregiver costs productivity costs or costs on government sectors)	Low	Medium	High	Low	Medium	High
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	• Prevalence and incidence (e.g. rare disease, disease affecting large number of patients)	Low	Medium	High	Low	Medium	High
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Vulnerability of the population	Low	Medium	High	Low	Medium	High	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
• Availability of effective alternatives (on and off-abel)/ unmet need	Low	Medium	High	Low	Medium	High	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
• Innovativeness of the technology independent of the performance	Low	Medium	High	Low	Medium	High	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
• Strength of the clinical effectiveness evidence (robustness of clinical study design and effect size)	Low	Medium	High	Low	Medium	High	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
• Strength of the cost-effectiveness evidence	Low	Medium	High	Low	Medium	High	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
• Clinical sign of potential value, but	Low	Medium	High	Low	Medium	High	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

	<p>value not fully demonstrated with evidence (aspirational benefit demonstrated by immature data, surrogate, partially validated endpoints, single arm study)* <i>*To be rated only if the strength of the evidence was considered as medium or low</i></p>														
	<ul style="list-style-type: none"> Strong biological hypothesis of efficacy (hypothesis well supported by preclinical research, physiology, pharmacology, disease mechanism) * <i>*To be rated only if the strength of the evidence was considered as medium or low</i> 	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
Low	Medium	High													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
C. Committee meeting dynamics	<i>Did you receive all information necessary to make an informed decision?</i>		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
	Yes	No	Sometimes												
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>												
	<i>Could the way the data was presented have affected your perception?</i>		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
	Yes	No	Sometimes												
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>												
<i>Were you able to ask all relevant question from your perspective?</i>		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
Yes	No	Sometimes													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
<i>Did you receive clear and unambiguous responses to your questions in the meeting?</i>		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
Yes	No	Sometimes													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
<i>Did any dominant perspective/opinion prevent other views to be discussed?</i>		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
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<i>Could the way the decision was made (for example consensus vs. voting procedure, show if of hands) have affected your decision?</i>		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
Yes	No	Sometimes													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
D. Personal interest	<i>Do you believe that your personal interest (e.g., willingness to use the drug by yourself/your friends/your relatives/your patients) could have any impact on your perception?</i>		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
Yes	No	Sometimes													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
E. Previous experience	<i>Was your perception impacted by your previous experience with the manufacturer?</i>		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
	Yes	No	Sometimes												
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<i>Was your perception impacted by your previous experience with the disease?</i>		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
Yes	No	Sometimes													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
<i>Was your perception impacted by your previous experience with a similar type of medication?</i>		<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
Yes	No	Sometimes													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
F. Context	<i>Do you believe that the final recommendation could be impacted by any form of influence listed below?</i>		<i>What impact could it have on the final recommendation?</i>												
	• Political influences	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>												
	Low	Medium	High												
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>												
	• Patient groups and caregivers	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Low	Medium	High													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
• Healthcare professionals	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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• Pharmaceutical companies	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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• Social influences	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
• Cultural influences	<table border="1"> <thead> <tr> <th>Yes</th> <th>No</th> <th>Sometimes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Yes	No	Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Low</th> <th>Medium</th> <th>High</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Low	Medium	High	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Yes	No	Sometimes													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													
Low	Medium	High													
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>													

	• Media	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Low <input type="checkbox"/>	Medium <input type="checkbox"/>	High <input type="checkbox"/>
	• Administration/ Health authorities	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Low <input type="checkbox"/>	Medium <input type="checkbox"/>	High <input type="checkbox"/>
	• Moral/ethic (your sense of equity and values)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Low <input type="checkbox"/>	Medium <input type="checkbox"/>	High <input type="checkbox"/>
	• Healthcare system affordability	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Allocated budget to certain diseases	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Feasibility (ability of the healthcare system to ensure a right use of treatment)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Public health priority	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Other _____	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
f) Cognitive biases (individual and collective)	<i>In an effort to be as objective as possible, do you consider any of these potential biases may impact your judgement?</i>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Affect heuristic (decision influenced by subjective feelings)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Anchoring bias (focusing on the first picture you learn and staying with the first impression)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Attentional bias (paying disproportional attention to some things, over others)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Authority bias (having more confidence in a decision that was validated by an authority figure)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Automation bias (tendency to accept automated clinical decision advice)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Availability bias (making judgments of likelihood based on ease of recall)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Confirmation bias (focusing on information confirming personal beliefs)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Consistency tendency (difficulty in changing a point of view when the change is justified by the new evidence)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• False consensus effect (overestimation on how much other people are aligned with your appreciation)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Framing effects (perception influenced by the way in which the evidence was presented)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Groupthink (situation in which the views of the decision- making group become homogeneous and contrary views are discouraged)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Halo effect (giving disproportionate weight in decision making to the beliefs of eminent individuals)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Hard/bandwagon effect (choosing based on other people choices)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• In-group conformity (having more confidence in a decision when it is in agreement with others)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Intellectual bias (becoming closed-minded about a belief)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Novelty (uncritical acceptance of a new technology)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Optimism bias (tendency to overestimate the likelihood of favorable outcomes)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Overconfidence bias (overestimation of personal ability or opinion)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>

	• Reductionism bias (reducing complex scenarios into simpler ideas)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Scientific inbreeding (replication of views by the individuals with the same training/educational experience)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Specialty bias (form of groupthink, situation when those in a specialty adopt a homogeneous set of beliefs)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
	• Thinking inside the box (inflexibility of thinking within decision-making group)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Sometimes <input type="checkbox"/>
Additional observations				

5. Discussion

In an attempt to assist HTA practitioners in their individual and collective assessments and appraisals, we developed the RELIANT checklist, the first checklist tool to support the HTA deliberative process by guiding the HTA practitioner to reflect on the implicit factors that may be influencing the process.

The findings of our previous mixed-methods research suggest that implicit factors may play a role in the HTA deliberative process. However, current guidelines do not account for implicit factors and in consequence their impact has not been minimized in a systematic way.

There are other initiatives aimed to support shared-decision making when multiple treatment options are available (210,211). The ASCO guideline (210) introduces explicit and quantifiable criteria for the assessment of net health benefit in oncology. However, these are clinical value frameworks that have a narrower scope (clinical efficacy, safety in oncology), different users (patients and oncologists versus HTA practitioners) and different objectives (selection of an oncology therapy vs. HTA recommendation to inform further therapy's positioning and pricing and reimbursement decisions). Moreover, the final decision may not be exempted of implicit factors coming from the oncologist and patients.

The RELIANT checklist represents the first attempt to raise awareness and provide a tool to reveal the implicit factors influencing the HTA recommendations.

It fills the existing gap on the implicit factors that other checklists have not addressed so far (135). While the objectives of the HTAi/ISPOR Force checklist focus on the governance and the stages of an HTA process, the RELIANT checklist focus mainly on the implicit factors. It aims to make the HTA practitioners aware and acknowledge the implicit factors present in the HTA deliberative process for pharmaceuticals.

Based on the HTAi/ISPOR Task Force, “well conducted deliberative processes can make explicit the arguments that are entailed when assessing health technologies”. We believe that to make explicit these arguments, implicit factors must be called out. Bond K. et al. propose a list of key principles and associated actions that can be used to guide the development of a HTA process (44). One of the principles stays “The link between HTA findings and decision-making processes needs to be transparent and clearly defined”. One associated question to this principle asks if the organization have an explicit decision rule for the acceptance of HT. The

author encourages the use of checklists by the chair and committee members as an explicit approach to ensure there are no criteria overlooked.

On a similar note, Bond K. et al. stated that HTA should be an unbiased and transparent exercise and raise a question about the practice adopted by the committee to mitigate the influence of cognitive biases.

The importance of the development of methods to address biases and in consequence improve decision-making has been pointed out by the laureate Nobel Prize in Economics, D. Kahneman in his book “Thinking, fast and slow” (119) in which he proposes a simplified model on the way our brain processes information, leading to two modes of thinking. The author explains mental life by the metaphor of two agents called System 1 and System 2 which drive the way we think and make choices. System 1 is fast, intuitive, and emotional. It has biases. System 2 is the conscious and reasoning self that has beliefs. It is slower, more deliberative logical and controls thoughts.

System 1 comes along with the biases of fast thinking and the persuasive influence of intuitive impressions on our thoughts. One of the limitations of System 1 is that it cannot be turned off. What can be done about biases? How can we improve judgments and decisions? The short answer that D. Kahneman provides is that little can be achieved without considerable effort, so he invites organizations to develop useful checklists in order to control these biases and improve decisions. For the author the identification of judgment mistakes is a diagnostic element that will lead to better choices (119).

As an extension of D. Kahneman’s approach, revealing the implicit factors (in particular the cognitive biases) influencing the HTA deliberative process and discussing about them is a way to mitigate their impact and to improve HTA recommendations. HTA practitioners may not be fully aware of the presence of these factors and their impact on the final recommendations.

Under the European regulation on HTA (36), the upcoming JCA process will follow a stepwise approach. Firstly, any evidence required for the JCA will be submitted once at the Union level. However, Member States will be able to carry out assessments on the added value and to perform complementary clinical analyses of the HT concerned. Additionally, in accordance with the founding principles of the EU, the organization of health services, allocation of resources as well as pricing decisions will remain under sovereignty of the member states.

The RELIANT checklist acts as a prompt for the various implicit factors to consider during the undertaking of an HTA. It comes to fill a void by addressing the need towards seeking a better understanding of biases by the development of a solution (204). Our checklist is aimed as a practical tool to acknowledge and elucidate the implicit factors present in the HTA deliberative process for pharmaceuticals and the dynamics surrounding this process.

We envision the checklist implementation as follows. The RELIANT checklist should be used prospectively by any HTA practitioner directly or indirectly involved in the HTA deliberation, prior to reaching a final recommendation to increase awareness of potential implicit factors that may jeopardize the transparency and legitimacy of the process. The HTA Committees should allow for some time to consult this checklist and reflect on the factors.

At national and regional levels, HTA deliberation seems to be heterogeneous and not fully explicit. Because of this, our checklist may serve as a tool to increase the legitimacy of the process.

The RELIANT checklist might be a vehicle to further harmonize the appraisal step, revealing and acknowledging the role of implicit factors in addition to the classic criteria.

At a supra-national scale, the role that the EU will play in relation with the future JCA will be exempt of value judgements in order to respect the responsibilities of Member States pursuant to Article 168 (36). In this sense, the RELIANT checklist is a valuable tool that if systematically used by those responsible for JCA, might contribute to achieve the objective of delivering a European standardized assessment for which value judgements (among other factors) would be identified and hence, controlled.

The authors recommend that HTA practitioners become familiar with the entirety of the checklist prior to the first use. For this, it would be beneficial to share the tool with the rest of the Committee involved in the deliberation and be used in internal trainings as part of continued education within the HTA bodies at the HTA commission level aiming to reflect on the HTA process and on factors that influence this process.

The checklist remains nonetheless aimed at all HTA practitioners with the hopes that it will increase awareness of implicit factors.

Hence, the RELIANT checklist has the potential to support the HTA deliberative processes at a national, regional, or local level prior to the HTA appraisal.

The validation of the checklist could showcase its usefulness in a real-life setting involving HTA bodies across different countries. This validation could be performed through a succinct and simple questionnaire focused on the utility and feasibility of implementation of the checklist. Once RELIANT will have been validated, we envision to make a formal proposal to the HTA agencies for its integration in the national and sub-national guidelines.

Since the first part of the validation (content validation) was already undertaken and this led us to the actual version of our checklist, we plan to perform a second part of validation by a pilot test based on an application of the checklist in HTA agencies followed by a survey to get critical feedback following its application in real settings.

Strengths and Limitations

Our checklist is the first one that accounts for the potential implicit factors happening in the HTA deliberative process.

It has been built upon the findings from two previous research projects and it has been reviewed and endorsed by different experts from the countries in scope.

The checklist has the potential to support the HTA deliberative processes at a national, regional, or local level prior to the HTA deliberation.

As per the limitations of the checklist, since the tool has been built upon previous research focused on specific countries and in medicines, the applicability in other countries and other HT may need to be tested. However, we do not expect much variability since the HTA process is largely common across technologies.

A formal SLR was not performed to inform the development of the checklist, therefore we may have missed relevant existing literature. In this sense, one expert brought to our attention two articles that were not retrieved as a result of our SLR because one of them was out of the pre-specified time window of publication (2021) and the other one did not match the key words of our search strategy.

The development of our checklist was not done based on a SLR. Nevertheless, the information extracted from the interviews was relevant and comprehensive to the extent that the experts who reviewed and provided feedback on RELIANT considered it an interesting and optimal tool to be used in their countries.

The checklist was tested in a limited number of experts (8) and at the same time all these experts participated previously in the interviews (Chapter 2, section 6), therefore their review may have been biased. Nevertheless, the validation phase that we propose would mitigate this assumption.

Additionally, testing this tool in different disease areas and geographies would contribute to its further validation.

Finally, the implicit factors that the checklist captures could differ should the scope of this thesis had been broader including additional geographies and/or other health technologies.

6. Conclusions from Chapter 3

There is scarcity of tools accounting for the existence of implicit factors in the HTA deliberative process. The HTAi/ISPOR checklist, the only checklist we identified in the literature is a good attempt to facilitate the understanding of the different components of a HTA deliberative process. Still, it has some limitations, being not addressing the implicit factors the most relevant for the object of this thesis. Additionally, there is a need for a practical checklist that includes implicit factors.

The RELIANT checklist is the first checklist proposed to address the implicit factors in the HTA process and it arises from the assessment of the existing checklist assisting the HTA process and the incorporation of the findings from our mixed-methods research.

The checklist was developed following a stepwise approach. Once the objective was defined by the PhD thesis team, we identified the categories focusing on the implicit factors that were highlighted in the interviews and those that were not present in the HTAi/ISPOR checklist. These categories constitute the core of the checklist. The selection of these categories was made based on the results from the qualitative research and on what we considered that was missing in the HTAi/ISPOR checklist vis a vis the implicit factors. We then defined the order of these categories going from a more general and objective approach. For each category, we developed a set of questions with the intention to help the HTA practitioner to reflect on the factors that he or she considered in the deliberative process, and we also defined the format of answer for the questions.

Finally, we agreed on a first version ready to be shared with a group of experts that consisted of eight experts from the five countries in scope. These experts participated previously in the interviews that constituted the second piece of research of this PhD thesis.

This group was asked to provide insights on the different sections of the checklist, the items, and the feasibility of its implementation as well as the place of the checklist in the deliberative process.

The main comments were about making the checklist a practical tool, short, concise, and easy to deploy.

The experts perceived the tool comprehensive and valuable for the HTA deliberative process. Most of them positioned the tool ahead of the appraisal. All concurred in the utility and importance of the checklist to contribute to a more objective, conscious, and transparent

decision-making process. A new version of the checklist was developed following the HTA experts' comments.

HTAi/ISPOR checklist focuses on the governance and the stages of an HTA process whereas the RELIANT checklist focuses mainly on the implicit factors. The checklist we proposed aims to make the HTA practitioners aware and acknowledge the implicit factors present in the HTA deliberative process for pharmaceuticals.

Our checklist could be further enhanced by an empirical validation substantiating its applicability in regular HTA processes and its ease of use.

To validate it, we propose its implementation by some HTA agencies from the countries in scope. Through a questionnaire we could collect the insights from the experts on the capacity of the tool helping to mitigate the implicit factors and on the feasibility of its implementation. Additional research could go towards other types of factors not addressed in this thesis, such as public health benefit, place in therapeutic strategy or innovation level that are factors not systematically considered in an explicit way by all the countries (27).

Looking forward, the application of the checklist and its methodology could be explored in other HT such as medical devices and adapted in other countries that could benefit as well from this tool.

It could be interesting to apply it in some emerging countries where there is a lower level of HTA institutionalization, higher influence of certain stakeholders in the process and where HTA mechanism and structures are not established (212).

Finally, the RELIANT checklist fills a void in this area since to our knowledge it is the first tool to support the HTA deliberative process by guiding the HTA practitioner to reflect on the implicit factors that may be influencing the process. By doing this, the checklist is intended to contribute to the legitimacy, objectivity, and transparency of the HTA appraisal.

GENERAL CONCLUSIONS

The key research questions in this thesis were to identify and understand the implicit factors influencing the HTA deliberative process in Europe and the development of a tool to address them. The overall aim of this thesis is structured into four main pieces of research: an SLR and a mixed-methods research (Chapter 2), a TLR to identify relevant checklists and a checklist (Chapter 3) that fed into the development of our main output: the RELIANT checklist.

In Chapter 1, we discussed the heterogeneity of the HTA appraisals in Italy, France, Germany, Spain, and the UK. This heterogeneity has led to numerous projects with the objective to harmonise the assessment of new technologies, the most recent one being the proposal of the EC on the JCA expected to be implemented in 2025 (36). Although various initiatives have been launched in recent years, variability across countries in the HTA process still exist even for the same drug and indication leading to issues on equity and fairness (27) (213). By ensuring all factors (explicit and implicit) are well understood, we can propose solutions to mitigate the implicit factors and subsequently the disparities derived from them.

In the second chapter of this thesis, we developed a definition of implicit factors in the HTA process. Implicit factors refer to all the non-defined factors that are not explicitly collected or described in the HTA guidelines and that may influence the HTA deliberative process and the subsequent recommendations. We believe this is a significant contribution to the evidence behind HTA conceptual frameworks (214,215), since to our knowledge this concept has not been formally defined before. We trust that the definition of implicit factors will facilitate their understanding and assessment and put in practice ways to control them.

The results presented in this PhD thesis contribute to the scarce literature identified in our SLR. The objective of this SLR was to identify and categorize implicit factors involved in the HTA deliberative process of medicines in France, Germany, Italy, Spain, and the UK. This piece of research highlighted three key findings.

The first one is that there is a scarcity of literature around the implicit factors and their impact on the HTA decision-making from a general and country level perspective.

The second finding is that implicit factors, being constitutive of the HTA deliberative process, might exert an influence on the HTA decision-making and recommendations.

The third one is that there is a lack of a standardized methodology for addressing these factors across the countries in scope. For this reason, there is a need to unmask and clarify these factors to increase the transparency, fairness, impartiality, and formality of the process and to strive for a more explicit deliberative process.

To expand the findings of this SLR, we performed a mixed-methods research to analyze the impact of the implicit factors in the HTA deliberative processes from the standpoint of HTA practitioners in the countries in scope. This research represents the first published data, to our knowledge, of primary data collection focusing specifically on the implicit factors influencing the HTA deliberative process in Europe.

Semi-structured interviews were conducted online with 20 HTA experts from the countries in scope based on a discussion guide and an interview checklist. The interview guide was divided into two main sections: perceptions on the HTA deliberative process based on the experts' experience and their recommendations on how to improve the deliberative process. In the first section, respondents were asked to score the degree of influence that 10 factors may play in the HTA deliberative process, as well seven attributes related to the HTA deliberative process.

As per the main findings of this research, most of the interviewees acknowledged the existence of implicit factors in the HTA deliberative process despite the process being defined and the key scientific criteria of the evaluation published and available in the public domain. It would be beneficial to acknowledge these factors to make the decision-making process more objective and transparent. This would help to understand the rationale behind the HTA recommendations.

The experts perceived the process as fair, standardized, and reproducible. However, in terms of the perceptions on the standardization, interviewees from France, Italy and Spain scored the process low compared to Germany and the UK.

The importance of patient involvement along the HTA was highlighted by the interviewed experts.

Overall, it was recognized that a multi-stakeholder approach (patients, caregivers, physicians, politicians, defense councils) should occur across the entire HTA process. Other than Germany and the UK, the rest of experts did not perceive that the HTA process was inclusive

enough and this explains why stakeholder involvement was recommended to improve transparency, legitimacy, and objectivity.

The last recommendation was pointed towards transparency by improving the communication of the outputs from the appraisal or minutes of the meetings and by making the public involved in the HTA process.

This mixed-methods research is a call to action for decision makers from countries with established HTA processes where the role that implicit factors play in the deliberative process is still unknown, to reflect on their respective implicit factors in order to mitigate its impact on the HTA decision-making.

The interviewed experts also highlighted there is a need to develop transparent methodologies addressing the implicit factors and by reinforcing the anonymous votes in the deliberative process in countries like France.

In Chapter 3, we leveraged the findings from our two previous pieces of research, to build a tool accounting for the implicit factors in a standardized way. We performed a TLR and we identified one checklist that was recently published, the HTAi/ISPOR checklist (135). A critical appraisal of this tool was performed, identifying its strengths and limitations. The HTAi/ISPOR checklist identified in the TLR represents a good attempt to facilitate the understanding of the different components of a HTA deliberative process. Still, several limitations were identified. The key limitation for the purpose of this research is that even though the HTAi/ISPOR checklist was perceived as a good attempt to facilitate the understanding of the different components of a HTA deliberative process, it does not address the implicit factors that may influence the HTA deliberative process. Additionally, some questions are too broad and lack clear guidance. Finally, the length of the checklist may be a hurdle for its implementation.

The findings of this appraisal led us to develop the RELIANT checklist, a practical tool that acknowledges and elucidates the implicit factors present in the HTA deliberative process for pharmaceuticals and the meeting dynamics surrounding this process. To the best of our knowledge, our checklist represents the first tool to support the HTA deliberative process by

guiding the HTA practitioner to reflect on the implicit factors that may be influencing the process.

By doing this, the checklist is intended to contribute to the legitimacy, objectivity, and transparency of the HTA appraisal.

The checklist was developed leveraging the findings from the SLR previously published (210), the previous qualitative research, the results of the appraisal of the HTAi/ISPOR Taskforce checklist and additional evidence based on a TLR.

This checklist was fine-tuned following two rounds of review performed by eight HTA experts who participated in the qualitative research previously performed. Experts were asked individually to provide feedback on the different sections of the checklist and the feasibility of its implementation in their respective HTA organizations as well as the place of the checklist in the deliberative process.

Their comments and suggestions were incorporated leading to a shorter second and final version that was shared for final comments and endorsement.

The target audience for this checklist is HTA experts who have a direct or indirect involvement in the HTA deliberative process.

The RELIANT checklist has the potential to support the HTA deliberative processes at national, regional, or local level prior to the HTA appraisal.

The ultimate goal of the checklist is to improve the deliberation by making it more rationale, impartial, legitimate and transparent.

This checklist would support the use of transparent methodologies that allow the explicit consideration of factors influencing the appraisal and subsequent recommendations. We believe this will lead to a more rational evidence-based decision-making, which could improve the efficiency of resource allocation decisions while on the same time raising public confidence and the perceived fairness of decision outcomes.

Our checklist could be further enhanced by an empirical validation substantiating its applicability in regular HTA processes and its ease of use.

The RELIANT checklist was the result of a research focused on medicines in five European countries. No matter what kind of HT is being assessed, there may be implicit factors in those deliberative processes and the evaluators and decision-makers among the HTA practitioners are human beings and are not free of cognitive biases.

This PhD thesis presented significant progress in the identification and comprehension of implicit factors (with a special focus on the cognitive biases) influencing the HTA deliberative process in the countries in scope and in the development of a tool aiming to control these factors and subsequently to make the process more objective and transparent.

In the grand scheme, our proposal aims to legitimate the HTA deliberative process, leading to enhance access to health technologies and ultimately, improve population health.

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