A Work Project presented as part of the requirements for the Award of a Master's degree in International Development and Public Policy from the Nova School of Business and Economics.

The Role of Real-World Evidence in Health Technology Assessment Decision-Making:

What differences between RWE and randomised controlled trials (RCTs) are highlighted in HTA guidelines, and how do these differences impact the assessment of effectiveness and safety?

A Systematic Literature Review

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17/12/2024

Abstract

This Systematic Literature Review (SLR) investigates the integration of Real-World Evidence (RWE) into Health Technology Assessment (HTA) processes to address the limitations of Randomized Controlled Trials (RCTs) in healthcare decision-making. The SLR examines methodological, data quality, and regulatory factors influencing RWE adoption across diverse healthcare systems. The findings reveal significant variability in HTA practices across countries, highlighting barriers such as inconsistent frameworks and limited interoperability. By synthesising evidence, this research underscores RWE's potential to complement traditional evidence, improve patient access, and inform reimbursement decisions, supporting global efforts to optimise HTA methodologies and promote equitable healthcare policies.

Keywords: *Real-World Evidence, RWE, Health Technology Assessment, HTA, Randomized Controlled Trials, RCTs, RWE Integration, Decision-Making, Reimbursement, Reimbursement Decision, Policy Recommendations, Best Practices, Case Studies, Guidelines, Frameworks, Standards, International Health Systems, Healthcare Systems, Methodological Challenges, Evidence-Based Decision-Making*

This work used infrastructure and resources funded by Fundação para a Ciência e a Tecnologia (UID/ECO/00124/2013, UID/ECO/00124/2019 and Social Sciences DataLab, Project 22209), POR Lisboa (LISBOA-01-0145-FEDER-007722 and Social Sciences DataLab, Project 22209) and POR Norte (Social Sciences DataLab, Project 22209).

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Acknowledgements

We thank João Leite, IQVIA Health Economics Consultant at IQVIA, for his support and cooperation during this Work Project. Moreover, we thank Prof. Pedro Pita Barros, our supervisor, for encouraging us and providing his full support during this project.

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List of Abbreviations

The following table outlines the significance of various abbreviations and acronyms throughout the thesis, along with the page numbers where each is defined or first used.

Abbreviation	Meaning	Page
RWE	Real-World Evidence	2
HTA	Health Technology Assessment	2
SLR	Systematic Literature Review	2
RCT	Randomized Controlled Trials	2
RWD	Real-World Data	11
QALY	Quality-Adjusted Life Years	17
NICE	National Institute for Health and Care Excellence	19
HAS	Haute Autorité de Santé	19
IQWiG	Institute for Quality and Efficiency in Health Care	19
EHR	Electronic Health Records	20

FDA	Food and Drug Administration	22
CDA	Cancer Drugs Fund	25
SNDS	French National Health Data System	25
EUnetHTA	European Network for Health Technology Assessment	26
CADTH	Canadian Agency for Drugs and Technologies in Health	26
PMDA	Pharmaceuticals and Medical Devices Agency	26
AIFA	Agenzia Italiana del Farmaco	26
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios	26
TLV	Swedish Dental and Pharmaceutical Benefits Agency	26
PBAC	Pharmaceutical Benefits Advisory Committee	27
PMS	Post-marketing surveillance	28
AGREE	Appraisal of Guidelines for Research and Evaluation	30
JA3	Joint Action 3	30
REA	Rapid Evidence Assessment	30
NHS	National Health Service	31
EC	External Control Arm	32
CT	Transparency Committee	32
CEESP	Committee for Economic and Public Health Evaluation	32
CDISC	Clinical Data Interchange Standards Consortium	33
PICOS	Population, Intervention, Comparator, Outcomes, Study Design	35
RQ	Research Question	44
RoB	Risk-of-Bias tool	45
TRUST	Transparent Uncertainty Assessment Tool	48
EHDS	European Health Data Space	51
MEA	Managed Entry Agreement	51
SAT	Single Arm Trial	59
DiGA	Digital Health Applications	65
ICERs	Incremental Cost-Effectiveness Ratios	71

PSA	Probabilistic Sensitivity Analysis	73
DataSAT	Data Suitable Assessment Tool	76
PROs	Patient-Reported Outcomes	77
HES	Hospital Episode Statistics	87
HERQoL	Health-related quality of life	89
CEA	Cost Effectiveness Analysis	93
JCA	Joint Clinical Assessment	123

Disclaimer

This SLR represents a collaborative group effort. Sections designated as individual work are identified by the name and student ID of the contributing author indicated alongside the respective section or title. All other content reflects joint contributions and collective analysis conducted as part of the group work.

1. Introduction (Group Work)

The introduction will present the topic of RWE in HTA based on previous research, followed by a problem statement, after which the study's significance will be displayed. Finally, the research question, objective, and outline of this SLR will be shown.

1.1 Context and Relevance

Integrating RWE into HTA processes has become crucial in shaping the decision-making of healthcare systems regarding the reimbursement and accessibility of innovative therapies. As more drugs are approved for use in specific patient populations and at earlier stages of diseases, traditional methods of generating evidence from clinical trials face significant challenges. These challenges include restricted participant availability and the time required to produce reliable results (Graili et al. 2023a). In cases where clinical trial data does not sufficiently demonstrate the value of an intervention, RWE can provide additional supporting evidence for its assessment (IQVIA 2022). This shift has led to an increasing focus on how RWE complements clinical trial data to address uncertainties in HTA processes (Curtis et al. 2023a).

For stakeholders, including policymakers, payers, and patients, understanding how various healthcare systems incorporate RWE into their HTA frameworks is critical to assessing its effects on reimbursement decisions and patient access to new treatments (Claire, Elvidge, et al. 2024).

Regulators and HTA bodies have acknowledged this importance by publishing guidance on using external controls derived from Real-World Data (RWD) to generate RWE (Curtis et al. 2023a).

Incorporating RWE into HTA has significant implications. It addresses the limitations of RCTs, such as limited generalizability due to stringent eligibility criteria and controlled conditions. Additionally, RWE also provides valuable insights into long-term outcomes, adverse effects, and patient-reported outcomes, often not captured in clinical trials. By leveraging RWE, HTA frameworks can offer more holistic evaluations of a technology's value, enable nuanced reimbursement decisions, and potentially accelerate patient access to innovative therapies. The outcomes of HTA, which are informed by RCT and RWE data, are critical in determining whether a new therapy will be reimbursed and made accessible to patients (IQVIA 2022). Positive HTA outcomes lead to full reimbursement and market access, whereas adverse outcomes may restrict access or limit availability to specific patient groups.

The use of RWE, however, also comes with trade-offs and risks. These include bias and confounding risks, data quality variability, data standardisation challenges and analytical complexity. Because, unlike RCTs, RWE relies on pre-existing datasets, which may lack specificity and control. Therefore, the extent to which RWE is considered in HTA assessments varies across countries, reflecting differences in how HTA bodies approach its integration. This variability significantly impacts decision-making, mainly when traditional trial data is insufficient (Thokagevistk et al. 2024). These limitations often arise due to RCTs' inability to fully capture real-world clinical scenarios' complexity. However, while some HTA bodies demonstrate greater acceptance and reliance on RWE, others remain cautious. This variation underscores the need for robust methodological guidelines and clear acceptance criteria to ensure RWE is effectively leveraged in decision-making.

Consequently, as mentioned before, this paper conducts a structured and methodical SLR. By synthesising existing evidence, the SLR provides stakeholders with a comprehensive understanding of RWE's role in HTA, its impact on reimbursement decisions, and its potential to harmonize practices across healthcare systems.

1.2 Research Question and Objectives

This SLR aims to explore the integration of RWE into HTA processes across different healthcare systems and its implications for decision-making outcomes such as reimbursement approvals. Through a SLR, this research seeks to answer the following research questions:

1. What factors influence the integration of RWE into HTA processes across different countries and healthcare systems, and what are the implications for decision-making outcomes such as reimbursement approvals?
2. What recommendations can be derived from successful case studies of RWE implementation in HTA to inform the development of robust methodologies and global health policy frameworks?
3. What are the key methodological challenges in developing robust RWE for HTA decision-making, and how do different health systems address these challenges?
4. What differences between RWE and randomised controlled trials (RCTs) are highlighted in HTA guidelines, and how do these differences impact the assessment of effectiveness and safety?
5. How do international HTA bodies harmonise evidence requirements for RWE, and what are the most effective methodologies and frameworks for supporting reimbursement decisions?

1.3 Problem Statement

The integration of RWE into HTA processes has become essential for addressing the limitations of RCTs in healthcare decision-making. RWE offers essential insights into effectiveness, safety, and patient outcomes; moreover, its implementation could be more consistent across nations due to disparities in methodology, data availability, and stakeholder acceptance. These disparities affect reimbursement approvals and patient access, highlighting the necessity for standardised global protocols and comprehensive methodology.

International HTA agencies exhibit varying responses to RWE, with some showing increasing acceptance and others maintaining a cautious stance, mainly depending on RCTs. These inequalities underscore significant challenges, including the establishment of methodological standards, the assurance of data interoperability, and the promotion of stakeholder trust. This thesis examines the factors affecting RWE integration, identifies methodological barriers, and considers solutions to align evidence needs and enhance decision-making.

1.4 Significance of study

This SLR offers a comprehensive evaluation of the role of RWE in HTA processes, which is essential for ensuring fair and evidence-based access to innovative therapies. Addressing the five research questions enhances understanding of the factors affecting RWE integration, identifies practical barriers, and presents recommendations for harmonisation across healthcare systems.

The findings contribute to knowledge about the role of RWE in decision-making and its impact on reimbursement outcomes and patient access. By systematically analysing these challenges and

offering evidence-based recommendations, this research supports global efforts to optimise the use of RWE in HTA and refine healthcare decision-making processes.

1.5 Thesis Structure Overview

This SLR systematically addresses the research question by following a structured six-chapter approach, ensuring clarity and rigor in its analysis. The thesis starts with an introduction, which provides an overview of the research topic, the problem statement, the significance of the study, and the research question. Chapter Two reviews all the relevant literature related to the ideas explored in this thesis. In Chapter Three, the methodology outlines the SLR approach used, including data collection, screening, and analysis processes. Chapter Four illustrates the results, focusing on the analysis and findings specific to the research questions, supported by relevant examples and case studies. Chapter Five discusses the findings, integrating key insights, implications for the field, and thesis limitations. Finally, Chapter Six concludes the study with a summary of all the key findings, including an answer to the research question and an outlook for further studies. A detailed thesis structure is illustrated in Figure 1.

Figure 1 – Thesis Structure
Source: Constructed by author

This thesis ensures a transparent, comprehensive, and stringent answer to the research question by systematically addressing each component of the research process.

2. Literature Review (Group Work)

This chapter presents previous theories supporting the research and research question while introducing the current situation of relevant subjects and related literature in those fields more explicitly.

2.1 HTA and its Role in Healthcare Decision-Making

2.1.1. Definition and key facts of HTA

HTA is defined as "a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner" (EUnetHTA 2007) . More in-depth, HTA aims to give an interdisciplinary approach to evaluating the value of health technology throughout its lifecycle while informing decision-making to enable an equitable, efficient, and high-quality health system (IQVIA 2022). It is frequently utilised in the drug reimbursement and pricing decision-making processes (Nicod et al. 2020). The term HTA was first described by the U.S. Office of Technology Assessment in 1976. Nowadays, HTA is deployed in more than 30 countries worldwide (Guidelines International Network, n.d.). Technologies in the context of HTA can be pharmaceuticals, medical devices, diagnostic methodologies, surgical procedures, and public health interventions.

The principal aim of HTA is to inform decision-making by thoroughly assessing the medical, economic, social, and ethical ramifications associated with the introduction and utilisation of health interventions within healthcare systems (European Commission 2024b). Furthermore, HTA ensures that decisions are based on evidence, characterised by transparency, and enacted equitably by bridging clinical evidence with policy frameworks.

In addition to these factors, it is essential to consider that HTA is commonly applied at the national level, with each country implementing its own distinct HTA systems. Thereby, numerous countries have set up their own HTA agencies and created guidelines to enhance transparency and efficiency in resource allocation (Wang et al. 2021). Consequently, HTA utilises varying assessment methods and criteria across different nations. National frameworks and guidelines are also crucial in the cross-national decision-making process regarding HTA (Nicod et al. 2020).

2.1.2. Dimensions of HTA

Before the HTA process is covered, the six dimensions of HTA will be presented and explained. HTA considers six dimensions through a multidimensional evaluation of a technology's value, as shown in the following figure.

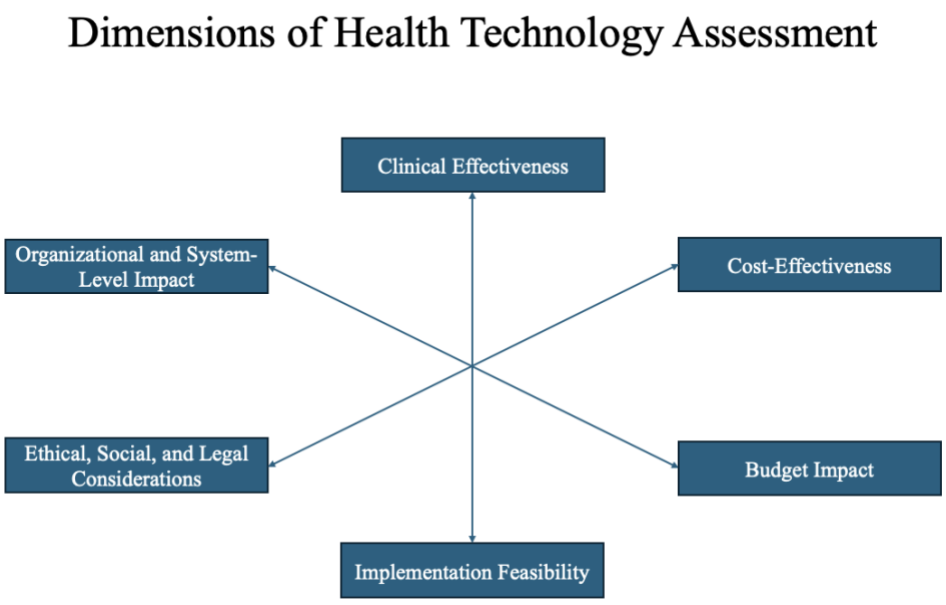

Figure 2 – Dimensions of Health Technology Assessment
Source: Constructed by author

The first dimension is clinical effectiveness, which evaluates the therapeutic advantages of a technology in relation to current treatments. It emphasises outcomes such as survival rates, symptom relief, and safety profiles (Maywald 2008).

The second dimension is cost-effectiveness, which assesses whether a technology's health and therapeutical benefits warrant its costs. Therefore, Quality-Adjusted Life-Year (QALY) metrics can be supportive (Angelis, Lange, and Kanavos 2018).

The third dimension is the budget's impact, as HTA estimates the financial repercussions of adopting technology within a healthcare system and budget, facilitating a balance between affordability and access (Fontrier, Visintin, and Kanavos 2022).

The fourth dimension is implementation feasibility. Thereby, the dimension examines whether a healthcare system possesses the necessary infrastructure, resources, training, and capacity to support technology's effective and widespread adoption (Vis et al. 2020).

The fifth dimension assesses ethical, social, and legal considerations, emphasising the broader societal impacts of technology, which encompass ethical issues, social acceptance, and legal concerns (Draborg et al. 2005).

The sixth dimension pertains to the organisational and system-level impacts, analysing how technology influences healthcare delivery models and system efficiency workflows (Segur-Ferrer et al. 2022).

2.1.3. Decision-making process

In the following section, the decision-making process of HTA will be presented. The decision-making process follows a systematic six-step evaluation model and can be grouped into three

phases: assessment, appraisal, and decision-making. This process is illustrated in the following figure.

Figure 3 – Decision-Making Process of Health Technology Assessment
Source: Constructed by author

The initial step involves formulating the assessment question that the HTA system aims to address. Consequently, it's essential to establish the HTA's objective as well. In the second step, significant data collection occurs by gathering information from a variety of sources, such as clinical trials, RWD, economic studies, and patient-reported outcomes. In the third step ,the data collected has to be analysed using economic modelling, statistical methods, and clinical evaluation. In the fourth step, evidence should be integrated by merging the collected data. This creates a comprehensive perspective on the influence of technology on healthcare due to the HTA. In the next step, guidelines and recommendations must be developed based on the evidence and analysis. Thereby, the four dimensions of HTA mentioned above play a crucial role. These guidelines are typically directed at healthcare policymakers, clinicians, and payers, focusing on the appropriate use, reimbursement decisions, or limitations of the technology. In the last step, the recommendations and results will be reported and presented in a transparent and accessible way for the stakeholders.

The six steps in the explained decision-making process in HTA can be divided into three phases. Therefore, steps one to four can be grouped as the assessment phase. In this phase, scientists will collate and critically review scientific evidence. The second phase is the appraisal, which summarises the process in step five. In this phase, the output of the assessment will be reviewed in the context of other factors that influence the decision-making for health technology and policy. In

the final phase of decision-making, the recommendations and guidelines will be provided and published to the population. This phase is shown in process step six. These three phases engage with three distinct areas: science, policy, and population (EUPATI 2015).

Finally, it has to be noted that HTAs guide critical decisions regarding the allocation of healthcare resources by providing stakeholders and policymakers with rigorous evidence (World Health Organization, n.d.). This process optimises resources to improve healthcare delivery and patient care by balancing innovation, cost-efficiency, and effectiveness (Curtis et al. 2023a). Nevertheless, the decision-making process, involvement, and every step of the process can be different for different HTA bodies (EUPATI 2015).

2.1.4. Multidimensional evaluation and decision-making process

This multidimensional evaluation of a technology's value and the decision-making process resulting from HTA is also crucial for prominent HTA bodies. Notable organisations such as the National Institute for Health and Care Excellence (NICE) in the UK, the Haute Autorité de Santé (HAS) in France, and the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany employ HTA frameworks to inform stakeholders, decision-makers, manufacturers, patients, and researchers about evidence-based reimbursement decisions (Thokagevistk et al. 2024). In these contexts, HTA findings directly influence the approval of technologies for public funding. Moreover, integrating RWE into HTA frameworks strengthens the connection between clinical practice and policymaking. The practices of these organisations, particularly in their use of RWE, will be described in greater detail in later sections of this paper.

2.2 RWE and its Role

RWE is defined as “the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD” (U.S. Food & Drug Administration 2024). All data that is collected routinely from different sources of health data that are not part of RCTs are defined as RWD (Dang 2023a). Primary sources of RWE can include data from Electronic Health Records (EHRs), patient registries, pharmacy details, laboratory results, insurance claims, and observational studies (Sherman et al. 2016; Canada’s Drug Agency 2024). Thereby, RWD can be gathered and analysed using various study designs. These include case-control studies, both prospective and retrospective cohort studies, and pragmatic clinical studies. A common type of RWE is post-marketing surveillance in the context of generating pharmacovigilance data (Berlin, Glasser, and Ellenberg 2008). It provides a more comprehensive view of a therapy's performance under everyday clinical practice conditions, which can differ significantly from controlled trial environments (Oortwijn 2018) (D. Yang, MD and L. Nguyen, MD, MBA, 2022). In addition, awareness and acceptance of RWE have grown among various healthcare stakeholders. Thus, several regulatory bodies, such as the EMA, have established frameworks and guidelines for implementing RWE in HTA (Dang 2023a).

RWE is increasingly essential in the healthcare decision-making process due to its ability to address several limitations of traditional clinical trials. This is due to the increased usage of healthcare technology and the possibility of collecting large data sets of RWD. The following section will discuss the importance of RWE in the healthcare decision-making process and afterwards, the challenges RWE aims to overcome in clinical trials will be presented.

RWE is essential for healthcare decision-making as it offers a broader patient representation. RCTs, which are a part of traditional clinical trials, use strict inclusion and exclusion criteria, which can limit the generalizability of their findings to the broader patient population. Another essential aspect of RWE is that it is collected from real-world settings and can therefore provide insights into the long-term safety and effectiveness of interventions. This represents an advantage over RCTs, which have limited durations and sample sizes.

Furthermore, RWE facilitates the comparison of various treatment options in real-world settings, assisting clinicians and researchers in making informed choices about the most effective interventions for specific patient populations (Chodankar 2021). Additionally, RWE is essential for healthcare decision-making as after a health technology is approved, RWE can be used to conduct post-launch surveillance regarding a health-technologies long-term safety and effectiveness (Dang 2023a).

In comparison to traditional clinical trials, RWE addresses multiple challenges, such as summarised generalizability, cost and time efficiency, flexibility in the study design, and real-world treatment insights. As RCTs are conducted under controlled conditions and specified for a selected population, it can occur that their results do not fully reflect real-world scenarios. Therefore, RWE supports bridging this evidence gap by providing real-world everyday data from diverse sources like EHR, databases, and registries (Dang 2023a). The mentioned cost and time efficiency are also crucial in this context, as RCTs can be quite time- and resource-consuming. In comparison to that, RWE studies use RWD, which can be less time-consuming in terms of collecting and processing the data. Furthermore, in contrast to the rigid protocols of RCTs, RWE studies can adopt more adaptable research methods to tackle specific clinical inquiries or regulatory requirements.

2.3 Integration of RWE into HTA

Current practices integrating RWE into HTA are advancing globally, yet its broader utilisation varies across countries. Its importance and usefulness have already been recognised widely, mainly when it comes to increasing the speed of pharmaceutical approval and reimbursement operations (Pulini et al. 2021). Even so, its potential has not been fully realised, in part due to the decision-makers lack of confidence in its application for important reimbursement decisions (Akehurst et al. 2023). Thus, several specific applications have been identified with the aim of assessing multiple purposes. RWE can help close some evidence gaps in traditional clinical trials, where HTA agencies can improve their upfront and post-launch evaluations. By expanding the evidence base beyond the limitations of a clinical trial, RWE enhances the understanding of the safety and effectiveness of a therapy, assesses its long-term impact, and supports reimbursement decisions. It also provides access to data from populations that are often excluded from traditional clinical trials. (Graili et al. 2023).

HTA ensures that limited healthcare resources are allocated to technologies offering the greatest value to stakeholders (Shi et al. 2023). With no uniform global HTA framework, countries vary in their adoption of RWE. Emerging trends underscore the importance of addressing three key dimensions:

- Generating local evidence to complement clinical trial data
- Assessing effectiveness and safety under real-world conditions
- Supporting cost-effectiveness and budget impact analyses

These three dimensions represent the importance of RWE in relation to HTA (EUPATI 2015). Regulatory bodies, including the EMA and FDA (Food and Drug Administration), increasingly use RWE to assess post-marketing safety and explore its application in decision-making. However, challenges related to quality, acceptance, and methodological standards persist, highlighting the need for greater collaboration among HTA bodies, industries, and researchers (Berger et al. 2017; Graili et al. 2023b). This concern is also due to potential risks in collecting RWD, such as data quality and global variability. RWD is often used for purposes different from those it was initially collected for, which can lead to gaps in critical information. Its quality can be affected by errors in how data is recorded or collected, as well as variability across different sources. To ensure reliability, these issues must be carefully addressed through documentation, cleaning, and pre-processing of the data (Liu and Panagiotakos 2022). Based on this, RWE's contributions address various dimensions of HTA, from clinical effectiveness to organisational and system-level impacts. It shows how effective and safe treatments are in everyday use, compares different drugs, identifies which patients benefit the most, and includes feedback from patients about their experiences (Roberts and Ferguson 2021). Furthermore, it can contribute to the cost-effectiveness dimension by providing exact, RWD on healthcare resource utilisation and expenditures. It helps the evaluation of treatments in typical clinical practice conditions, resulting in more accurate cost-effectiveness ratio predictions. On top of that, it has the potential to make economic evaluations more robust and adaptable to real-world contexts, allowing for comparisons between populations and national healthcare systems (He, Fang, and Wang 2023).

In terms of budget impact, cost estimates can also be more accurate when adapted to real-world settings. By including RWE in HTA, decision makers are able to provide a better resource allocation with a better perspective on the efficacy and efficiency of a health-technology (Jaksa et

al. 2022). Also, RWE supports the evaluation of infrastructure and the capacity of healthcare systems to integrate new technologies effectively (Naidoo et al. 2021). This also includes bringing a deeper understanding of patient behaviours and preferences, which is strictly related to the capability of RWE to address ethical and social considerations in HTA (Rand et al. 2019).

In conclusion, RWE plays a vital role in advancing HTA practices by addressing gaps in traditional methodologies and enhancing decision-making frameworks. Despite challenges related to data quality and global variability, its potential to improve healthcare sustainability and patient outcomes remains significant.

2.3.1 Comparative approach of leading European HTA bodies

HTA agencies adopt different positions in the integration of RWE. Such different approaches are well illustrated by looking at three of three leading European bodies: NICE in the United Kingdom, HAS in France, and IQWiG in Germany. NICE can be identified as a leading agency regarding the integration of RWE in HTA. In 2022, NICE published explicit guidelines on the use of RWE to improve healthcare decision making especially in areas, where clinical trials frequently cannot provide all the information needed to support comprehensive HTA (Bullement et al. 2020). While RCTs remain the gold standard, they are often impractical due to ethical, financial, or technical constraints. In such cases, NICE prioritises high-quality RWD to inform economic models, develop digital health technologies, and address health inequalities, particularly for populations underrepresented in trials (NICE 2022). A study was conducted in the UK to quantify the contribution of RWE in NICE application processes aiming to identify technology appraisal (TA) programs published by NICE's website before and after the guidance framework was released. The results show that oncology HTAs included RWE more than any other disease area, and related to the utilisation post-framework, the proportion of TAs using RWE to support clinical effectiveness

remained unchanged. This was potentially driven by challenges in conducting RCTs for rarer tumour types, along with regional discrepancies, which favoured the use of RWD sources, including the Cancer Drugs Fund (CDF), a reliable funding source for cancer drugs in England. However, the use of RWE for indirect treatment comparisons rose after the framework's introduction, from 17% to 26%, but a more extended period could be required to evaluate the framework's actual effect on RWE usage (Green et al. 2024). When assessing the level of acceptance, NICE is at the forefront, as demonstrated by the growing number of study submissions, supported by the robust potential of the UK primary care database (Leahy, Ramagopalan, and Sammon 2020).

Another important framework on the use of RWE in HTA was published by HAS. While the British framework focuses on early integration and diverse applications, HAS utilizes RWE mainly for the long term evaluation of health technologies post launch (Bolton, Rusher, and Bustamante 2020). The essential foundation in setting the stages for the broader integration of RWE in French HTA was laid in 2017, when access to the French National Health Data System (SNDS) was made available, providing high-quality data on nearly 66 million patients (Scailteux et al. 2019). Subsequently, in 2021, HAS published its methodological guidelines, to drive the progress of RWE integration into HTA processes in France (Judith 2021).

Among the three above-mentioned agencies, IQWiG adopts a rather conservative approach regarding the integration of RWE in HTA. German HTA processes still heavily favour RCTs due to their ability to deliver robust causal results (De Pouvourville et al. 2023). IQWiG sets quite stringent criteria for evidence acceptance, demanding high certainty of results and often limiting RWE use, unless its quality matches that of RCTs (IQWiG 2020). Recent studies proved the lack of confidence that the German institute has towards integration of RWE. In the research by Doran

et al. in 2023, it was observed that no submissions to German HTA agencies, such as IQWiG, incorporated RWE during the three-month review period, compared to other European agencies that used RWE in several appraisals, including NICE and HAS (Toomey, Banks, and McEntee-Richardson 2023). However, Germany is already considering its integration in limited circumstances and is showing a willingness to improve on this side, also by joining initiatives like the European Network for Health Technology Assessment (EUnetHTA), a collaborative plan aimed at improving the quality, efficiency, and consistency of HTA processes across European countries (Garrett, Imaz-Iglesia, and Willemsen 2022).

2.3.2 Integration practices across selected countries

However, RWE is increasingly being integrated into routine operations of numerous agencies across the globe. The Canadian Agency for Drugs and Technologies in Health (CADTH) has developed specific guidelines and actively advocates for its application through various publications (Raven 2023). RWE is also becoming progressively more significant in southern Europe, as shown by the Italian and Spanish agencies, the Agenzia Italiana del Farmaco (AIFA), and Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), each with a distinct focus. Italy utilizes RWE extensively in oncology alongside the Swedish agency TLV (Swedish Dental and Pharmaceutical Benefits Agency), and Spain integrates it into post-market evaluations. Furthermore, Japan has demonstrated proactive engagement in the integration of HTA within its regulatory frameworks. The Pharmaceuticals and Medical Devices Agency (PMDA) has conducted research aimed at evaluating decision-making processes related to medication safety, utilising data derived from the Japanese electronic medical database (Kajiyama et al. 2024).

2.4 Challenges and Benefits of Using RWE in HTA

It is evident, that RWE is becoming increasingly relevant in HTA processes. RWE's importance was further demonstrated during the COVID-19 pandemic when it was crucial in evaluating population health and assisting with vaccine research (Schad and Thronicke 2022). During that time the benefits of RWE were evident, because researchers we able to utilise sources such as EHRs, insurance claims, selected data from social media or patient registries to advance the understanding of the virus and deliver useful health technologies to contain the pandemic.

In the following section, both the benefits and challenges of integrating RWE in HTA will be discussed. Addressing RWE´s shortcomings is crucial to unlock its full potential. In this context, RWE's advantages cannot be underestimated, from supplying numerous data collected from the needs of individual patients to providing a broader perspective into healthcare decision-making processes. What follows is an examination of these advantages.

2.4.1. Enhancing decision-making through the utilisation of RWE in patient care

RWE is a valuable way to complement data from traditional RCTs by picturing the sample's actual representation more accurately (Villines, Cziraky, and Amin 2020). Its primary strength in supporting decision-making is the capability to offer context-specific insights on the individual patient, reflecting the clinical situation and overcoming demographic challenges. Moreover, using RWE in patient care helps evaluate how treatments and interventions work in real-world settings, offering a more complete picture of patient health (Zisis et al. 2024). For instance, studies conducted during the COVID-19 pandemic, through the DARWIN EU platform assessed the effectiveness of vaccines. These studies provided valuable RWD on vaccine safety and efficacy, including monitoring age-specific incidence rates and impacts on populations ("EMA" 2024a).

This data demonstrated the power of RWE in driving significant choices and delivering prompt actions during a serious public health emergency.

2.4.2. Long-term Outcomes and Reimbursement Decisions

RWE can be used to reevaluate technologies that have already received funding and approval during the post-marketing surveillance (PMS). Thereby, PMS monitors the drug safety of a particular product, making sure that it keeps beneficial features after being placed on the market (Huang, Moon, and Segal 2014). To assess how these technologies function in real-world settings over an extended period, HTA bodies can use RWE. This ensures that the technologies continue to deliver positive outcomes for patients. Consequently, this ability can play a fundamental role in the reimbursement decision process (Maruszczyk et al. 2022). In an ideal scenario, HTA bodies and payers can make more informed and accurate evaluations of new and existing treatments.

However, after discussing the advantages of incorporating RWE into HTA, it is equally important to address the challenges that come with its implementation. One of the primary drawbacks inherent to RWE data is its nature, which is characterized by limitations such as variability in quality, lack of consistency across countries, and privacy concerns (Grimberg et al. 2021). This exemplifies the dual nature of RWE - the very characteristics that make it valuable are also the ones that create its limitations.

2.4.3. Data Limitations and Infrastructure Gaps

RWE relies on diverse data sources, notably the previously mentioned EHRs and patient registries. The former are generally used as tools for physicians to document clinical information and lack of regularity. The latter are standardised most of the time but also excessively costly. Therefore, the risk is that the level of detail and accuracy provided varies substantially across physicians

(Kamphuis et al. 2018). This inevitably leads to selection bias and lower data quality compared to RCTs in various countries (Zisis et al. 2024). Fragmentation issues also complicate the integration of RWE data since there is no standardised structure that can reduce their heterogeneity. Finally, privacy concerns might limit RWE by restricting access to detailed patient data due to strict regulations, which often require anonymisation (Bhatt 2024).

2.4.4. Credibility of RWE and Stakeholders' Acceptance

Unlike RCTs, which follow strict protocols and standardised methodologies, RWD comes from diverse sources, and it is not always easy to assess its accuracy and reliability (Naidoo et al. 2021). This factor, combined with the increasing concerns around observational studies, makes it difficult for stakeholders to fully accept RWE as strong evidence. Stakeholders struggle to accept RWE due to misalignment between evidence providers and users, variation in quality standards, and inconsistency. Observational studies and registries may not provide the necessary transparency, standardisation, and essential data sets for payers and regulators to make informed decisions (Jandhyala 2021).

2.5 Global Guidelines for RWE in HTA

As RWE becomes increasingly integrated into HTA processes, more HTA agencies are establishing structures and frameworks to ensure its appropriate utilization. Consequently, numerous organizations have developed guidelines for incorporating RWE into HTA. For the countries restricted by the defined PICO criteria, key regulatory and HTA guidelines available in English include those from the EMA, Germany's IQWiG, France's HAS, Sweden's TLV, the UK's NICE, Canada's CADTH, Australia's TGA, and Japan's PMDA. These guidelines provide insights

into regulatory frameworks, clinical and cost-effectiveness assessments, and decision-making criteria for healthcare interventions. The subsequent section will examine these key national guidelines in detail while incorporating global perspectives, including recommendations from international organizations like the EMA, to provide a comprehensive understanding of both global and regional approaches.

Global guidelines exhibit prevalent themes concerning data quality, transparency, and relevance (Capkun et al. 2022). Most adhere to internationally recognised standards, such as the Appraisal of Guidelines for Research and Evaluation (AGREE), which was developed in 2003. This evaluative tool addresses the variability inherent in guideline quality by assessing the methodologies of development, the validity of recommendations, and the factors influencing practical application. Nevertheless, guidelines still diverge in terms of their focus, scope, and application (NICE 2024).

The EUnetHTA guidelines for HTA aim to integrate RWE with the goal of creating a sustainable European HTA model that reduces duplication and increases patient access to health technologies. According to the European Commission: “Thirty HTA organisations from 19 EU countries [...] indicated that they use elements of EUnetHTA joint assessments in their national HTA processes” (European Commission 2024). The guidelines emphasise procedural changes from the Joint Action 3 (JA3) initiative to increase usability, transparency, and inclusiveness in Rapid Evidence Assessments (REAs), encouraging stakeholder involvement from health technology developers, patients, and healthcare professionals. Transparency is a key focus, requiring accessible data for unbiased assessments, while feedback mechanisms ensure factual accuracy (Willemsen et al. 2022). The EUnetHTA methodological guidelines specifically address challenges faced by assessors in evaluating the relative effectiveness of both, pharmaceutical and non-pharmaceutical health

technologies. Summing up, the guidelines promote collaboration across European countries and resolve methodological differences to strengthen the use of RWE in HTA (Hausner et al. 2019).

Established in 1999 in the UK, NICE addresses inconsistencies in the availability and quality of treatments and care within the National Health Service (NHS). From its inception, NICE has focused on developing guidance that ensures treatments not only meet quality standards but also provide good value for money (NICE 2022). NICE publishes guidelines in four key areas - the use of health technologies within NHS, clinical practice, guidance for public sector workers on health promotion and ill-health avoidance, and guidance for social care services and users (Mitchell 2020a). These guidelines cover a wide range of topics, including preventing and managing conditions, improving health outcomes, and organising care services. By integrating research, clinical expertise, and patient perspectives, NICE delivers reliable recommendations for diagnosing, treating, and preventing conditions. NICE's frameworks for RWE focus on gathering data from routine clinical practices, patient registries, and observational studies while engaging stakeholders to ensure relevance (NICE 2022).

The IQWiG guidelines for HTA emphasise a systematic and transparent approach to evaluating health technologies, with a focus on RWE. While IQWiG primarily relies on RCTs for their internal validity, they acknowledge their limitations. Therefore, they are open to incorporating RWE when RCTs are unavailable or not feasible. In addition, IQWiG offers flexibility in study design, considering the proximity of trial conditions to routine care, and evaluates RWE based on established methods that are updated annually (Fricke and Dauben 2009). The types of RWE considered include outcomes, resource use, and the values of resources. Transparency is maintained through a review process involving both internal IQWiG employees and external experts (IQWiG 2020).

HAS, founded in 2004, evaluates the value of medicinal products and medical devices in terms of medical, economic, and public health aspects (HAS 2021a). These evaluations guide public authorities on funding decisions for health products under the national health insurance system, as well as their appropriate use in prevention, diagnosis, and treatment strategies. Specialised committees, such as the Transparency Committee (CT) and the Committee for Economic and Public Health Evaluation (CEESP), primarily rely on clinical trials to assess product efficacy. Recognising the growing importance of real-world studies, HAS updated its methodology guide in June 2021 to address challenges in quality and validity, integrating RWD alongside clinical trials (Massetti et al. 2015). These updates are influenced by better access to health data and the inclusion of patient perspectives. HAS also works with agencies such as EUnetHTA to improve the effectiveness of HTA and promote international cooperation. The HAS guidelines propose using RWE as an external control arm (EC) when RCTs are unavailable and encouraged conducting pragmatic trials, such as cohort-based, registry-based, contactless, or direct-to-patient trials (Judith 2021).

The Canadian guidelines, issued by CADTH, aim to standardize and promote transparency in the reporting of RWE, ensuring its credibility and reliability in healthcare decision-making. The guidelines were created through a comprehensive three-phase process. In phase 1, environmental scans were conducted to identify existing documents and recommendations related to RWE reporting. Phase 2 involved a modified Delphi process with an expert panel to refine and select final recommendations, ensuring that the guidelines reflect a broad range of expert opinions specific to the Canadian context. Phase 3 included public consultation to gather feedback and improve the guidelines. While the guidelines are tailored to the Canadian healthcare system, they

are informed by international best practices and are generally applicable to other jurisdictions, although some recommendations may be less relevant outside of Canada (CADTH 2023b).

The PMDA in Japan integrates RWE into its regulatory processes, particularly when RCTs are not feasible. RWE is used for post-market surveillance, utilising data from EHRs, patient registries, and claims databases to monitor long-term safety and outcomes. The agency also uses early access programs based on RWE, allowing faster access to therapies with limited clinical trial data, subject to post-market monitoring. To ensure consistency and quality, PMDA follows Clinical Data Interchange Standards Consortium, CDISC, standards in its RWE studies (PMDA 2024).

These variations in global guidelines show the challenges and opportunities associated with using RWE in HTA. The heterogeneity of guidelines reflects regional differences in healthcare priorities, data infrastructure, and policy objectives, making harmonisation complex but worth trying. Data quality and interoperability remain universal challenges, as the integration of RWD into HTA requires standards and methodologies. Ethical and privacy concerns also pose significant challenges, particularly in the context of global data sharing and collaboration.

3. Methodology (Group Work)

This SLR will adhere to the guidelines from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2021). By applying these methods, our goal is to ensure the minimisation of bias, a transparent methodology, and the reproducibility of our findings. The steps outlined below detail our approach.

3.1 Systematic Literature Review Process

The SLR process began with the identification of the topic of interest. The topic of interest was defined in cooperation with IQVIA and revolves around the use of RWE in HTA. The primary objective of this research is to provide an in-depth overview of how RWE can be utilised in HTA and to address five specific research questions. Through this process, the study aims to understand the benefits, drawbacks, and limitations of including RWE in HTA decision-making.

To achieve these objectives, the SLR followed a structured and transparent methodology, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2021) and is designed to minimise bias, ensure transparency, and maintain reproducibility throughout all stages of the review.

The SLR process is divided into several key stages. Each one is documented in detail to ensure the validity and reliability of the findings.

The first stage is the definition of research questions. Therefore, the topic of interest for the review was closely defined through internal team discussions, as well as discussions with IQVIA, to ensure both academic and practical relevance. By doing so, five specific research questions were formulated to guide the review process. One of these questions will be picked up in Chapter 4 to be investigated in detail.

Subsequently, a search strategy was developed to identify studies in alignment with the PICOS framework, which is described in detail in Chapter 3.2. The search strategy is based on the utilisation of PubMed as a database, which allows for the use of search strings to be able to achieve an iterative refinement of the body of literature for this review, as well as manual literature searches.

A comprehensive description of the search strategy is given in Chapter 3.3. After the identification of suitable literature, data extraction was conducted. Therefore, a standardised data extraction form (see Appendix D) was developed to collect relevant information systematically. The extracted data was then synthesised to answer the research questions. An in-depth explanation of the data extraction process is given in Chapter 3.5.

This study adheres strictly to a predefined protocol to minimise bias, maintain transparency, and ensure reproducibility. The protocol (see Appendix F) guided all stages of the review, from study selection to data extraction. This protocol ensured consistency and reduced the risk of subjective decision-making. For the screening process, a dual review approach was adopted in which both the abstract and full-text screening stages involved two independent reviewers to reduce individual bias. In case of discrepancies in the assessment of a source, a third team member who was previously not involved resolved the conflict to reach the decision over including or excluding the source.

In order to maintain transparency and reproducibility of the review, all stages of the review process were comprehensively documented. This includes all decisions, such as reasons for inclusion/exclusion and modifications to the search string. The documentation is included in the Appendices.

3.2 Eligibility Criteria (PICOS Framework)

To ensure a systematic and transparent approach to the literature review, this work adopts the PICOS framework to define the inclusion and exclusion criteria for the studies considered. As mentioned in Chapter 3.1, the use of the PICOS framework is an important cornerstone of the review since it facilitates a structured and reproducible selection process by clearly delineating the

scope and boundaries of the review. Additionally, restrictions on publication language, date, and geographic scope are applied to maintain relevance and focus.

PICOS	Inclusion	Exclusion
Population	Any	Not applicable
Intervention	Any	Not applicable
Comparator	Not applicable	Not applicable
Outcomes	Positive reimbursement decision Negative reimbursement decision Recommendations on RWE	Other outcomes
Study Design	Case Studies Guidelines	E.g., RCTs, cohort studies, observational studies
Restrictions	Studies published in English within the last 5 years for the following countries: UK, Germany, France, Spain, Italy, Sweden, Australia, Canada, Japan	Any other language, any older study, any other country

Figure 4 - PICOS Criteria
Source: SLR Protocol (Appendix)

(P) Population: The review includes studies that examine any patient population, with no regard for disease area, demographics or clinical setting. The review aims to understand the general application of RWE in diverse HTA contexts. Therefore, the focus lies on studies that address the integration of RWE in HTA processes. No exclusions were made based on population characteristics. Studies that do not address the integration of RWE into HTA are excluded.

(I) Intervention: Any study that involves interventions incorporating or evaluating the use of RWE within HTA processes is included. By setting this criterion rather broadly, the review ensures the inclusion of various intervention types, such as therapeutic strategies, diagnostic tools, or health

policies, provided RWE is a core component. In the same manner as for the population criterion, studies that do not explicitly involve or evaluate the use of RWE in HTA processes are excluded.

(C) Comparator: For the inclusion of a study, there is no specific comparator required. As the objective is to investigate the application/evaluation of RWE into HTA rather than a comparative analysis. Comparators are, therefore, also not a factor for study exclusion.

(O) Outcomes: Only studies which directly report outcomes related to HTA processes are included. The relevant outcomes investigated in this review include:

- Positive reimbursement decisions where RWE played a role in the approval.
- Negative reimbursement decisions where RWE influenced the denial or limitation of approval.
- Recommendations on the integration, use, or methodological considerations of RWE in HTA.

Studies which reported other outcomes unrelated to HTA processes, such as purely clinical outcomes without any link to HTA, were excluded.

(S) Study Design: The review focuses on case studies and guidelines as primary sources of evidence since these study designs provide practical and methodological insights into the use of RWE in HTA. However, studies with other designs, such as RCTs and Cohort studies or observational studies, were excluded unless they explicitly integrated RWE into HTA processes that carried clear HTA implications.

Restrictions: To further refine the scope and relevance of the review, a number of restrictions are applied. Only studies published in English are included, ensuring accessibility and consistency in

interpretation. Additionally, only studies published within the last five years are included to ensure the review reflects current practices and trends in the use of RWE in HTA. Furthermore, only studies from the United Kingdom, Germany, France, Spain, Italy, Sweden, Australia, Canada, and Japan are included due to their established and functional HTA and processes and Agencies. An overview of these countries' HTA decision-making authorities is provided below in Figure 5.

Any other language, any older study, from any other country, is excluded to maintain focus on the latest evidence and methodologies from countries that provide established HTA processes and an active exploration of RWE integration.

Country	HTA Agency
Spain	Provincial HTA Committees
Italy	AIFA – Italian Medicines Agency
Germany	IQWiG – Institute for Quality and Efficiency in Health Care G-BA – Federal Joint Committee
France	HAS – French National Authority for Health
Sweden	TLV – Swedish Dental and Pharmaceutical Benefits Agency
United Kingdom	NICE - National Institute for Health and Care Excellence
Canada	Canadas Drug and Health Technology Agency
Australia	TGA – Therapeutic Goods Administration
Japan	PMDA – Pharmaceuticals and Medical Devices Agency

Figure 5 - Agencies by country

Source: Constructed by author

3.3 Information Sources and Search Strategy

This research paper uses a structured approach to identify relevant literature and guidelines by combining database searches with supplementary hand searches to ensure a comprehensive review.

The primary focus was on using PubMed as the main database to capture documents and insights related to RWE in HTA since it allows for the utilisation of search strings to filter results. The development and refinement of these search strings played an essential role in this process.

PubMed was chosen as the primary database due to its extensive collection of biomedical literature, comprising over 37 million citations and abstracts. It offers so-called Boolean operators, which are critical for constructing targeted queries. These Boolean operators, which include AND, OR, and NOT, were used to structure the search strings:

- AND ensures that results include all specified terms.
- OR retrieves results that contain at least one of the specified terms.
- NOT excludes specific terms, helping to refine the focus of the search.

For instance, PubMed interprets “RWE HTA” as “RWE AND HTA” by default but allows manual customisation of queries using Boolean operators. This functionality was essential in developing the search strings used to identify the literature for this study.

The search strings were crafted iteratively to capture studies that align closely with the research objectives whilst also avoiding irrelevant results. The terms were selected based on their relevance to the PICOS framework to best ensure their alignment with the inclusion criteria and save time during screening.

The initial search strings included broad terms to identify a wide range of studies. Over multiple iterations, the search strings were refined to exclude irrelevant results and incorporate alternative keywords, synonyms, and field-specific terms. The Boolean operators were used to combine or

exclude terms logically to ensure a balance between the sensitivity and specificity of the search string.

Each iteration of the development process for the search strings was thoroughly documented in a Microsoft WORD and can be found in Appendix D. This documentation enhances the transparency and reproducibility of the search strategy. The final versions of the search strings are included in Appendix A and serve as the foundation for identifying the primary literature for this study.

To complement the database search, two additional manual searches were conducted to ensure a comprehensive review. The first one being a hand search on PubMed, and the second one being a manual web search for documents originating from official HTA agencies that document guidelines for HTA and the use of RWE within it.

For the hand search on PubMed a targeted phrase search using the term “RWE in HTA” was conducted on PubMed. This search yielded 21 additional studies that were not captured by the initial search strings but were deemed relevant to the research focus. These results are catalogued under the designation "HS" in Appendix E.

For the HTA agency guidelines, a manual web search was performed to locate official guidelines published by HTA agencies. The goal was to identify currently valid official guidelines on how agencies evaluate RWE and incorporate it into their decision-making processes for HTA. This search identified eight additional documents that were published by official HTA Bodies and provided key insights into current practices and standards for HTA. These documents are also included in Appendix E.

3.4 Study Selection and Screening Process

For the screening process, the studies that could be identified by applying the previously described search strategy were imported into Microsoft Excel for organisation and further evaluation (see Appendix E). After removing duplicates from the data, the selection process was conducted in two stages: abstract screening and full-text review, both carried out by two independent reviewers to ensure academic rigour and reduce bias in the inclusion of studies.

In the abstract screening, all abstracts of all identified studies were reviewed independently by two reviewers. During this stage, the inclusion/exclusion criteria, as defined by the PICOS framework, were applied to exclude studies that do not fit the scope of this review and include promising sources to later be read through in detail in the full-text screening. When discrepancies arose between the assessment of a source between the first and second reviewer, a third review was conducted by a team member to resolve the conflict. This first stage screening was able to narrow down the 3973 sources to ca. 113 promising sources.

During the full-text screening, the 113 studies that passed the abstract screening were subjected to a detailed full-text review. As with the abstract screening process, two independent reviews were conducted in which each reviewer evaluated the source in detail with regard to its compliance with the predefined PICOS criteria. Discrepancies in the evaluation between two reviewers were solved in the same way as in the abstract screening phase to maintain consistency throughout the review process.

All steps of this selection process, including the reasons for exclusion at both the abstract and full text screening stages are documented in Appendix E. This processes ultimately produced 20 sources which fit the PICOS and were ready to proceed to data extraction, which is closely

described in Chapter 3.5. The selection process is visualised in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement flow diagram presented in the Appendix. It displays the study selection process, including the number of records identified, included, and excluded throughout the screening process. PRISMA is a stringent, evidence-based framework to ensure transparency and precision in selecting studies for systematic reviews (Page et al. 2021).

The PRISMA flow diagram consists of four fundamental stages:

1. Identification: This stage involves comprehensive database searches to capture relevant records. Additional searches of grey literature and reference lists of included studies are also conducted to ensure completeness.
2. Screening: Titles and abstracts of identified records are screened against predefined eligibility criteria. During this phase, duplicates and irrelevant studies are excluded.
3. Eligibility: Full-text articles of potentially relevant studies are retrieved and evaluated for relevance, quality, and alignment with the research question.
4. Inclusion: Studies that meet all inclusion criteria are incorporated into the final data extraction and synthesis review.

The PRISMA framework improves the transparency of the research selection process, ensuring that every decision is thoroughly documented and reproducible. This systematic review, using PRISMA guidelines, seeks to reduce bias, ensure consistency, and yield reliable and complete results (Page et al. 2021).

3.5 Data Extraction

Data extraction is essential in any systematic review or structured research procedure, as it guarantees consistent, accurate, and transparent collection of relevant data from the included studies. This study's data extraction procedure meets the standards specified in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2021). It integrates best practices from comparable methodological frameworks (Waffenschmidt et al. 2019).

3.5.1. Objective of Data Extraction

The data extraction process aims to systematically gather all information relevant to the research questions and document any recommendations and thoughts provided by the authors. The studies were categorised as case studies, guidelines, or other papers to address the five research questions thoroughly. Additionally, a subsequent evaluation of each study was conducted to guarantee that each study was systematically extracted and recorded. This multi-level approach aligns with established systematic review standards (Higgins et al. 2021).

3.5.2. Data Extraction Review

Data extraction is still essentially a manual process. In the data extraction stage, errors are rarely detected by editors, peer reviewers, or users of systematic reviews. Therefore, to reduce potential bias and minimise errors during the data extraction process, it is recommended that more than one person extracts data from every report. However, disagreements may occur when multiple authors extract data from the same reports. It is essential to compare the responses of two or more extractors to ensure consistency and identify disparities. Any unresolved disagreement should be reported in the review (Higgins et al. 2021).

3.5.3. Data Extraction Template

The data extraction template was designed in collaboration with IQVIA, whose expertise provided insights into structuring the template to align with industry standards and academic research objectives. The template included the following fields, as recommended by systematic review frameworks (Higgins et al. 2021). Figure 7 summarises the fields used in the data extraction template.

Field	Case Study	Guideline	Other
Country	x	x	x
Intervention assessed	x		
Assessment Outcome	x		
Limitations	x	x	x
Strengths	x		x
Recommendations	x	x	x
Organisation		x	
Comparison vs. RCT		x	
Type of RWE used			x
Suitable for RQ Nr.	x	x	x

Figure 6 - Data Extraction Template
Source: Constructed by author

3.6 Quality Assessment

The quality of included studies will be systematically assessed through a structured evaluation process to ensure the reliability and validity of findings, providing an accurate answer to the research question.

3.6.1 Validity

Validity is a fundamental quality criterion in SLRs. It ensures that the findings accurately address the research question and are grounded in reliable and relevant evidence.

In this study, all included studies were double-screened by two independent reviewers to ensure relevance to the research question. This approach minimises subjectivity and enhances the validity of the screening process. A third reviewer will be included if there is a disagreement to ensure methodological stringency and reduce the potential for subjective bias (Higgins et al. 2021).

As no randomised controlled trials (RCTs) were included in the review, tools like the Risk-of-Bias (RoB) tool or the ROBINS-I checklist were not utilised. Instead, relevance and methodological quality were assessed qualitatively, focusing on the applicability and reliability of the evidence to address the research objectives (Sterne et al. 2016).

3.6.2 Reliability

Reliability in an SLR refers to the consistency of the review process, guaranteeing that comparable results can be achieved if different researchers employ the same methodology under comparable conditions (Page et al. 2021).

Additionally, a dual review enhances reliability by guaranteeing that the same results and decisions can be reached if the review is reproduced under similar conditions (Higgins et al. 2021).

Another critical measure involves using a pre-defined SLR protocol. This protocol, developed following PRISMA guidelines, provides a structured framework for study selection, data extraction, and synthesis. The protocol includes specific criteria for inclusion/exclusion, search terms, and data extraction procedures, ensuring that all steps are transparent and reproducible.

Finally, comprehensive documentation enhances reliability by including a systematic review process, which guarantees the reproducibility of other researchers' findings (Page et al. 2021).

4. Results (Group Work/ Individual Work)

This section will answer the five research questions, with each student contributing to one research question. Each student will analyse the studies related to their question and summarise their findings.

4.1 Inclusions (Group Work)

As mentioned above, the systematic selection of studies is based on predefined eligibility criteria and included a combination of database and hand searches to ensure comprehensiveness.

A total of 4,109 records were identified through database searches and organisational registers. After removing 157 duplicates, 3,952 records were screened based on their titles and abstracts. During the screening phase, 3,860 records were excluded based on predefined PICOS criteria, leaving 92 records sought for full-text retrieval. Out of these, 10 could not be retrieved due to the text's unavailability. Consequently, 82 reports were assessed for eligibility. Of these, two were excluded based on population, 4 based on intervention, 55 based on outcomes, and two based on study design. This process resulted in the inclusion of 19 studies from the database and register searches. In addition to these records, 28 studies were identified via hand searches. All 28 were retrieved and assessed for eligibility, with 20 excluded based on study design. As a result, eight additional studies from the hand search were included.

The final review included 27 studies, 19 from database and register searches and 8 from hand searches. These studies provide a robust evidence base for addressing the research objectives, ensuring comprehensiveness by integrating systematic and additional hand searches.

4.3 Research Question 4 – Elena Lialina

What differences between RWE and randomised controlled trials (RCTs) are highlighted in HTA guidelines, and how do these differences impact the assessment of effectiveness and safety?

HTA is an essential process because it evaluates the economic, ethical, social, and medical implications of modern health technologies continuing to revolutionise the health sector. Two major sources of evidence used in this process are highlighted: RWE and RCTs (Brönneke et al. 2023c). In this regard, an in-depth mastery of the distinctions between these sources gives essential background knowledge of determining the safety and effectiveness of the measured interventional to inform its use.

Gomes et al. (2024) agreed that HTA guidelines underscore essential distinctions between RWE and RCTs, impacting the assessment of the efficacy and safety of medical interventions. Further, it was observed that RCTs are tailored to eradicate structural bias and confounding variables using the randomisation strategy. Randomised Control Tests are characterised by strict procedures and monitoring processes that recognise the credibility and accuracy of results (Gomes et al. 2024). Therefore, the RCT methodological stance gives it the privileged or the gold standard status in evaluating the safety and effectiveness of medical treatments (see section 1.1). According to Mitchell (2020), data gathering in RCTs is standardised and controlled, which ensures relative reliability and high data quality that influence objective outcomes and perspectives. Data is awarded preliminary integrity, guaranteed by predetermined protocols and strict adherence monitoring (Mitchell 2020a). Information is generally collected at fixed intervals after rigorous procedures to make results as accurate and consistent as possible. Through such a controlled orientation, the hazards of data errors are countered, with the results being accurate and impartial

as well, and drawing out discrete, objective analyses of interventions' effectiveness and efficacy becomes possible (Tadrous et al. 2024). To eradicate bias, RCT harnesses the blinding (single and double-masked) technique, whereby study participants are unaware they are receiving the placebo or the treatment in a single-masked trial. In a double-masked study, the researchers and participants are unaware of the group assignment, ensuring that the results are not influenced by the researchers' and participants' prior expectations (Zong et al. 2024a). In addition, RCTs utilize predefined secondary and primary outcome measures to assess the safety and efficacy of medical interventions. These outcomes are keenly identified and monitored during the study. Specifying outcomes in advance fosters researchers to offset incidents of selective reporting, thus contributing to reliable and objective results (Franklin et al. 2020).

Conversely, RWE tests are premised on observational studies upon which they are informed and might not engage the rigorous randomisation intrigues (Eichler et al. 2011). They are based on data extracted from the physical context derived from insurance claims, EHR, observational studies, and patient registry data, which are already available in clinics. RWE is susceptible to confounding elements and prejudice since they are derived from data not accrued in a controlled setting (LoCasale et al. 2021). RWE is a constellation of data extracted from routine health care settings. EHRs constitute detailed data concerning patients' diagnoses, demographics, treatment, and care outcomes that are digitally recorded for easier retrieval (Claire, Cresswell, et al. 2024). Details in patient registries include information concerning patient services, such as surgeries, costs, and treatments. This data provides crucial information regarding the use and efficiency of clinical technologies and treatments.

Whereas RCTs are considered the gold metrics for assessing the safety and efficacy of medical interventions, their findings may not necessarily apply to universal contexts because of their

controlled nature (Daigl et al. 2024). Strict exclusion and inclusion criteria employed in RCTs may limit the study population's diversity, and therefore, findings may not holistically mirror how interventions affect diverse populations. RCTs are also time-consuming and may require substantial financial resources to administer rigorous protocols, thus making them implausible for interventions with limited funding.

Regulatory and HTA bodies have increasingly championed the role of RWE in promoting reimbursement and regulatory decisions. RCTs have been utilised as the core source of evidence for reimbursement decisions and regulatory approvals. Nonetheless, RCT shortcomings, including short duration and generalizability, have inspired attention to RWE in policy making (Bhatia 2024). RWE offers complimentary evidence supporting the approval of new medical interventions, reimbursement, and pricing decisions and informs post-market surveillance. This constant surveillance identifies new safety concerns and promotes value delivery to healthcare systems and patients. Therefore, RCTs cannot be wholly discarded but rather used complementarily with RWE to produce meaningful perspectives on the effectiveness and safety of medical interventions. While EMA and NICE accept RWE as supportive evidence, they prioritise RCT data to establish clinical efficacy and safety. Similarly, HAS is selective in considering clinical evidence from single-arm trials and includes RWE mainly in risk management plans. G-BA applies stricter scrutiny than EMA or NICE, favouring RCTs for benefit assessments, reflecting the need for rigorous methods to address confounders when using RWE as formal comparators (Zong et al. 2024a). For instance, according to NICE guidelines, “RCTs are the preferred source of evidence on the effects of interventions” due to all the mentioned characteristics. However, it is not always available: when it is unethical, unfeasible, or not enough funds, for instance. In that case, it is recommended to

implement RWE (NICE 2022a). This point of view is shared by other major guidelines. Here is a comparative table of attitudes toward RWE and RCTs, based on current guidance and practices:

HTA Agency	RCTs	RWE	Notes
HAS (France)	Strong preference for RCTs as the gold standard	Increasing acceptance, especially for supplementing RCT data. Commonly used in cases like rare diseases or single-arm trials where RCTs are challenging.	RWE often used for assessing safety and effectiveness, especially when RCTs are not feasible. Typically complements rather than replaces RCT evidence
IQWiG (Germany)	Strong reliance on RCTs for decision-making	Limited use of RWE, mainly for supporting data when RCTs are not possible (e.g., orphan drugs).	Prefers high-quality RCT data for clinical effectiveness evaluations. Rarely considers RWE, emphasizing methodological rigor
NICE (UK)	Recognizes RCTs as the primary evidence source.	Increasing focus on RWE, especially to address evidence gaps. Published a framework in 2022 to guide the use of RWE.	RWE is encouraged for ongoing assessments, such as the Cancer Drugs Fund. Actively developing methods to integrate RWE into technology appraisals

Figure 9 7 - HAS, IQWIG, NICE

Source: Constructed by author

These insights show varying degrees of RWE acceptance, with most agencies still prioritising RCTs. IQWIG, which sticks to RCTs, states that most of the time only them are suitable for demonstration of causality. The grouping arrangement enhances the variability of the participants and thus helps the researchers to determine whether the intervention or the extraneous factors lead to the variability. Therefore, the above multiple-layered plan ensures that internal validity is maintained in the study (IQWIG 2023). Interestingly, RWE can be generated from RCTs, according to UK MHRA. It has recently published a guidance on how to produce it. Probably it will lead to a combination of internal validity and generalisability of data in future research based on it (MHRA 2024).

4.5.1 Observational Studies

Observational studies are equally quintessential sources of RWE because they observe and assess care outcomes without manipulating study environments, thus rendering useful information concerning how therapeutic and care interventions work in daily practice (Klein et al. 2022). As a result, RWE is a rich source of essential insights because it mirrors the experiences and realities of more diverse and broader patient demographics, including older patients, those from unique socioeconomic extractions, and those with comorbidities, making RWE a source of holistic and balanced perspectives. On the contrary, the design needs of RCTs constitute distinct limitations on the study population and may isolate patients benefiting from the intervention. Norburn, Laura, and Lizzie Thomas (2021) also emphasize that RWEs are essential because they illuminate the experiences of more diverse patient groups, including those unable to meet RCTs' tight inclusion criteria. Thus, integrating RWE will enhance policymakers' and researchers' ability to acquire a nuanced view of the safety and effectiveness of medical interventions (Norburn and Thomas 2021). This disposition makes RWE studies reasonably portable to a physical environment and, as such, provides clear insights into the efficacy and safety of interventions in the care sector through the lens of the various populace (Bowrin et al. 2019). Wide-ranging data capture of patients helps RWE understand how the interventions are faring out in other populations within diversified clinical contexts.

For instance, an assessment of patients with 12 common malignancies enrolled in the Alberta Cancer Registry demonstrated that 38% of 125000 patients on record were deemed trial ineligible (Kim, Lee, and Kim 2018). Eligibility assessment was premised on exclusion criteria dominant in oncology trials: older adults aged above 75, presence of co-morbid cardiovascular disease, anaemia,

and history of immuno-suppression. RWE can be tailored to complement RCT's findings on more inclusive demographics constituting patients illegible for RCTs.

Nonetheless, RWE is flawed when viewed through the lens of the vast volume of data needed for correct assessment and complex data quality management required to address biases. Various methodological frameworks can be adopted to mitigate biases in RWE. The choice of a specific framework is governed by the interventions under examination or the research question. For instance, patients that a particular treatment is going to address may be different from those who are not in some way that is relevant to the results of the study the intervention will deliver. Based on this line of reasoning, the investigators are left with no option other than to use sensitive statistic tools, including the multi-variable regression analysis and propensity score matching, to strengthen the prima facie evidence postulated to support the findings that may otherwise differ from those that do not in ways that impact on the results.

Propensity scores highlight patients' likelihood of obtaining specific treatment based on their unique dispositions and have emerged to become the basis for confounding adjustments in various observational studies (Thokagevistk et al. 2024). Utilizing PS-powered methods allows researchers to focus on causal inference in observational studies by weighing the distinctions in outcomes between reference and treated populations. Propensity scores comprise stratification, matching, weighting, and adjustment as a regressor. Whereas propensity scores were dominantly used in the past, they are limited because they discard unmatched observations like those in control groups. In addition, propensity scores also demand a considerable volume of participants in the control setting, rendering it sub-optimal when studying rare outcomes or anomalous exposure (Patel et al. 2023). Other propensity score methods can escape these constraints. Weighting, unlike matching, provides greater precision by monitoring observations and can enhance better reporting of the balance

between reference and treatment groups. Weighting is relatively more flexible. In the case of pragmatic studies that follow the comparative character of RCTs through real-world methods, a new model called new user, active comparator design was developed to mitigate confounding bias (Curtis et al. 2023).

EMR-based clinical research has been shown to improve the quality of studies and increase clinician satisfaction worldwide. Depending on the study's goals and design, EMR research can use different types of data, such as medication prescriptions, treatment decisions, disease management, and clinical research information. Because of this, EMR data is seen as highly reliable and one of the best sources of RWD. Furthermore, deep learning-based AI requires a large amount of data to work effectively. With EMR systems now widely used in hospitals, there is a big opportunity to analyse this data for clinical research quickly, having access to real-time data, which RCTs lack. However, most deep learning projects using EMR data have not achieved the expected results. The main problem is poor data quality. Algorithms often fail when they are trained on unprocessed or low-quality data, making it hard to get useful or reliable results. To solve this issue, hospitals are working to improve access to data and ensure it is cleaned and well-organised before use. This improvement may lead to an increase in RWE usage (Kim, Lee, and Kim 2018). Castanon et al. (2024) also define how the completeness and quality of data vary at different reporting intervals and often include chances for data inconsistency and inaccuracy (Castanon, Tsvetanova, and Ramagopalan 2024). For example, electronic clinical records may contain wrong or missing information, and insurance claims contain missing information. In such circumstances, the researchers may be compelled to apply complex statistical techniques mentioned before to transform the data set and make the results valid.

One of the included studies by Efthymiadou, Olina, and Panos (2021) in the UK investigates the implementation of RWE in the assessment of oncology therapies through MEAs (see section 4.6.3). The research highlights significant disparities in the uptake of MEAs across countries, influenced by various HTA decision-making variables. The analysis reveals that RWE was utilized to address uncertainties surrounding the cost-effectiveness and clinical outcomes of high-cost oncology therapies. Specifically, the study found that in the context of MEAs, 72% of cases raised concerns regarding cost-effectiveness, compared to only 39% in cases without MEAs. Furthermore, 42% of MEA cases raised issues related to utilities, while only 4% did so in the non-MEA group. This indicates a substantial reliance on RWE to inform HTA decisions when MEAs were in place. Moreover, the authors stress that accumulating a massive amount of data creates vital confidentiality and privacy concerns that cannot be ignored. The authors also state the need to safeguard participants' data by anonymising it and eradicating identifiers that are likely to result in the identification of participants. Guaranteeing privacy protection is vital in establishing and maintaining the cooperation and trust of service users and care providers. Thus, confidentiality and privacy must also be addressed, and standardised research protocols must be adopted to achieve higher reliability of RWE findings (Efthymiadou and Kanavos 2021).

Brönneke et al. (2023) identified that, in RCTs, overall medical operations' safety is assessed based on the secondary and primary outcomes defined beforehand. Such outcomes are purposefully selected and controlled throughout the study (Brönneke et al. 2023c). For example, an RCT trialling a new technology from high blood pressure may consider changes in blood pressure as a primary measure of the outcome but list occurrences of aggravated events as secondary results. Such a predefined orientation contributes to study relevance because the study will contain clinically relevant endpoints. In RWE studies, potential outcomes are not necessarily limited to standard,

objective clinical measures but may include outcomes reported by patients (Zisis et al. 2023). This affords a total appreciation of the intervention's alteration in patients' management and daily regular lives. For example, when conducting health assessments, RWE may include variables such as quality of life, patients' compliance with medication, sustainable health outcomes, and many others. Expanding the approach to outcome measures allows for consideration of broader quantitative results of interventions that would be beneficial in assessing efficacy and safety more comprehensively.

4.5.2 **Impact of RCT and RWE Differences on Effectiveness and Safety Assessment**

RCTs are the core of evidence concerning the effectiveness and safety of clinical applications, interventions, and therapies. On the one hand, the limitations of RCTs stem from the designs that include selective study groups that restrict the subjects to tight therapeutic regimens, and time-bound studies mean they do not offer comprehensive information about intervention effectiveness and safety (Curtis et al. 2023b). The strengths established in the RWE offer an alternative to the polymorphism of the offer that radically relates to the expansion of the evidence base of RCTs in working with policymakers.

Through the lens of cost-efficiency, RWE studies are less costly and time-consuming than RCTs because they do not need the rigorous processes of enrolling and recruiting participants experienced in RCTs. They also help address distinct research questions that RCTs cannot answer, like those engaging high-risk cohorts (Azoulay 2022). For example, the study by Moler-Zapata is focused on the implementation of RWE in emergency surgery for two acute gastrointestinal conditions. The research utilised data from the Hospital Episode Statistics (HES) linked to Office for National Statistics mortality data, allowing for a comprehensive analysis of resource use, hospital stay

duration, and survival outcomes. The study aimed to emulate a target trial framework to mitigate biases commonly associated with observational studies, such as immortal time bias, which can significantly affect the validity of findings. The results indicated that the average total duration of hospital stay was 7 days, with a 30-day mortality rate of 5%. The study estimated that the cost-effectiveness of ES was approximately £18,500 per QALY, falling within NICE threshold of £20,000 per QALY, thus supporting the economic viability of the intervention. Despite the successful application of RWE in this context, challenges were noted, particularly regarding the completeness and accuracy of the HES data. While the study minimised concerns about attrition and reporting bias, the lack of health-related quality-of-life data post-surgery limited the comprehensiveness of the analysis. Furthermore, the reliance on published studies for quality of life weights introduced potential variability in the estimates (Moler-Zapata et al. 2023b).

The increasing adoption of RWE is embedded in the realisation that they detect less frequent side effects and offer quick access to data, rendering them more essential for follow-up studies after RCTs to monitor the long-term effects of medical interventions. Randomised Control Tests are administered over a limited span, implying that the evidence captured might not reflect long-term outcomes and safety prospects. The length of an RCT is often defined by logical constraints such as inadequacy of funding and the necessity to obtain results in one way or another (Curtis et al. 2023b). Although short-term effects are important, they may not always provide for a systems view of the interventions' effectiveness and safety attributes over the years. Nonetheless, RWE yields data on sustainable (long-term) safety and effectiveness by monitoring service users over a prolonged duration. This is eminent, especially in the context of chronic illnesses and medical interventions with long-term results.

For example, the study by Wang et al. explores the differences in long-term survival estimates derived from RCTs versus RWE in the context of advanced non-small cell lung cancer. The real-world cohort consisted of patients from the Flatiron Health database who received similar treatment to the RCT participants, specifically docetaxel monotherapy after platinum-based chemotherapy, between 2011 and 2019. Using parametric survival models, the study found that extrapolating survival data from the RCT overestimated long-term survival compared to real-world outcomes. For instance, the RCT estimated a mean overall survival of 19.2 months, while the RWE cohort showed a mean survival of 14.4 months. Similarly, the 5-year survival rates were 5.4% in the trial group compared to 3.7% in the real-world group. These results highlight the potential for RCT extrapolations to overstate long-term benefits when applied to routine clinical practice. The authors conclude that using RWE alongside RCT data can provide a more accurate reflection of real-world outcomes and better inform HTAs (Wang et al. 2021).

Regarding practical insights, Kalf et al. (2021) argued that RWE evidence provides valuable insights into how interventions are routinely applied in clinical contexts. This study analysed public online forums to identify key HRQoL (Health-related quality of life) concerns for melanoma patients. Posts revealed that 35–45% of discussions focused on HRQoL, with mental health and uncertainty being the most common themes. Concerns included fear, anxiety, and adverse effects. The authors agreed that RWE can reflect how patients comply with prescribed therapies, how dosing regimens are adjusted in practice, and how care plans respond in various care settings (Kalf et al. 2021b). These are essential insights for policymakers and care providers when formulating decisions concerning adopting and utilising new medical technologies. Mastering how interventions are utilised in the physical world helps stakeholders to establish possible impediments to implementation, maximise treatment protocols, and scale up patient outcomes (Bhatia 2024).

The rationale for strict inclusion criteria, partly inherent to RCTs, is to reduce the risk that participants experience (Toledo-Chávarri et al. 2021). Therefore, the reported rates of adverse events in RCT evidence should be lower among patients. However, the detailed assessment of the relative safety of health care interventions using RWE is promoted. This encourages clarity on the expected frequency of adverse events while identifying and quantifying rare ones.

Enormous RCTs are unemployable in specific contexts, like rare diseases. Yet, considering time limitations, finding an adequate number of individuals to represent RCT for such groups is usually a challenge. Consequently, RWE proves essential in evaluating therapies and interventions in such contexts. A dominant approach to this case scenario is conducting a single-arm open-label survey of the investigatory therapy, utilising a control arm from a real-world setting (Baumfeld Andre et al. 2020). In addition, RWE plays a considerable role in cases where studies are deemed to be unethical. For instance, a researcher cannot design an RCT with a placebo arm in clinical contexts where participants are likely to be mistreated or subjected to harm.

The study by Pomey et al. (2020) conducted in Canada investigates the implementation of RWE through the co-construction of HTA recommendations with patients. The initiative aimed to enhance patient involvement (PI) in the evaluation process, traditionally dominated by healthcare professionals. A SLR identified 15 relevant articles on patient experiences and quality of life-related to implantable cardioverter-defibrillators, underscoring the need for patient perspectives. Three committees were formed: an expert patient committee, an expert healthcare professional committee, and a co-construction committee that included both groups. This collaborative structure facilitated the integration of patient insights into the recommendations. The project highlighted the importance of patient-related literature and the necessity for primary data collection when existing literature is lacking. Rigorous patient selection ensured diverse representation, supported by

healthcare providers and outreach platforms. However, challenges arose, such as limited feedback from healthcare professionals, with only two out of six clinicians participating (Pomey et al. 2020).

Summing up, the distinctions between RCTs and RWE significantly impact their roles in evaluating medical interventions' effectiveness and safety. RCTs are considered the best type of studies because these investigations are designed with extreme caution, maximize internal validity, and control all confounding variables to minimise bias. In contrast, RCTs can be highly artificial, have low external validity, and be brief regarding follow-up periods. RWE can be gathered from RWE studies, and it enriches RCTs by presenting long-term results, a diversity of patients, and practical use. By combining the best features of both research approaches, HTAs can improve the understanding of medical procedures and products that can be used in organising a proper, effective, safe, and affordable care delivery system.

5. Discussion (Group Work/ Individual Work)

This chapter analyses the findings presented in the previous chapter in the context of the research question and objectives outlined earlier. By synthesising key insights from the results, this chapter seeks to explore the broader implications of integrating RWE into HTA processes.

5.1.1 Key Findings – Research Question 4 – Elena Lialina

What differences between RWE and randomized controlled trials (RCTs) are highlighted in HTA guidelines, and how do these differences impact the assessment of effectiveness and safety?

This research question discusses the differences between RWE and RCTs, two key sources of evidence used in HTA. Several key findings were made regarding the role of RWE in assessing the effectiveness and safety of medical interventions. One of the primary insights is that RWE provides

a comprehensive understanding of therapeutic outcomes by reflecting the experiences of diverse patient populations, including those often excluded from RCTs due to strict inclusion criteria. This diversity allows for a more holistic view of how interventions perform in everyday clinical settings, particularly for older patients and those with comorbidities.

Moreover, the study highlights the importance of safeguarding participant data to maintain confidentiality and trust among service users and care providers. Anonymising data and eliminating identifiers are crucial steps in ensuring privacy protection, which is essential for the reliability of RWE findings.

Another significant finding is the complementary nature of RCTs and RWE. While RCTs are considered the gold standard for establishing the safety and effectiveness of interventions, their design limitations often restrict the breadth of data collected. RWE, on the other hand, captures long-term outcomes and safety profiles by monitoring patients over extended periods, which is particularly valuable for chronic conditions. For instance, a study comparing survival estimates from RCTs and RWE in advanced non-small cell lung cancer revealed that RCTs may overestimate long-term survival rates compared to real-world outcomes.

Additionally, RWE sheds light on HRQoL concerns, as evidenced by an analysis of online forums for melanoma patients. This analysis revealed that a significant portion of discussions focused on mental health and the uncertainties surrounding treatment, indicating that RWE can provide insights into patient experiences that are often overlooked in traditional clinical trials.

The integration of RWE into HTA is also examined in the context of regulatory frameworks. It reviews recent studies that highlight the growing acceptance of RWE by regulatory agencies and HTA bodies. These organisations recognise the value of RWE in informing decisions about the

reimbursement and adoption of new health technologies. This shift indicates a trend towards more flexible regulatory processes that can adapt to the complexities of real-world healthcare. However, it identifies several barriers to effectively using RWE in HTA. These barriers include concerns about data quality, methodological challenges, and the need for standardised frameworks for generating and evaluating RWE.

5.1 Collaborative Discussion (Group Work)

5.2.1 Cross-Study Comparison

This section compares how RWE is utilized by the reviewed HTA agencies, namely NICE (UK), IQWiG (Germany), HAS (France), CADTH (Canada), PBAC/TGA (Australia), PMDA (Japan) and TLV (Sweden). While all agencies recognise RWE's potential to complement RCTs, their implementation strategies highlight both shared principles and distinct practices.

NICE has developed a comprehensive RWE Framework in the United Kingdom to integrate RWE into decision-making. NICE emphasises methodological rigour, requiring data transparency, quality assurance, and advanced statistical techniques to address biases (NICE 2022a).

In comparison, IQWiG (Germany) follows a more conservative approach. IQWiG primarily uses RWE as supplementary evidence, emphasising RCTs as the gold standard. The agency integrates routine practice data cautiously, often limiting RWE to post-market surveillance or cases where RCTs are not feasible. IQWiG's General Methods stress methodological stringency, particularly in mitigating bias and ensuring data reliability. Unlike other agencies, IQWiG does not require cost-effectiveness analyses, focusing instead on comparative clinical effectiveness. This narrower scope reflects Germany's unique HTA priorities but limits RWE's broader application in decision-making (IQWIG 2023). In France, HAS strikes a balance between the two previous approaches,

by extensively incorporating RWE into both initial and post-market evaluations. HAS's 2021 methodological guideline outlines specific criteria for data quality, emphasizing the importance of national health datasets like the French National Health Data System. RWE is used to reassess technologies approved through RCTs, providing insights into long-term effectiveness, adherence, and treatment patterns. HAS well aligns its guidelines with dynamic healthcare needs, and illustrates a flexible yet rigorous approach to RWE integration (HAS 2021b). In Canada, CADTH collaborates with Health Canada and provincial HTA bodies to harmonize RWE practices. CADTH incorporates RWE into CEAs and post-market evaluations, focusing on data standardization and inter-agency cooperation. Australia's TGA adopts a similar approach to IQWiG in that they use RWE primarily in post-market evaluations, particularly for monitoring long-term safety and performance. TGA incorporates RWE as supplementary evidence in economic evaluations and focuses on using RWE for regulatory decisions, particularly for medical devices and high-risk interventions. Sweden's TLV only vary sparingly uses RWE for reassessing cost-effectiveness post-market. Other parts of their HTA processes remain uninfluenced by RWE. Ultimately in Japan, the PMDA, not unlike HAS in France, focuses on post-marketing surveillance and drug safety evaluations when considering RWE for HTA. Like NICE, the PMDA places a strong emphasis on ensuring data validation and methodological rigour to address the challenges of bias and confounding.

The analysed literature reveals a number of shared principles, as well as a number of distinct approaches when integrating RWE into HTA. All reviewed guidelines, as well as case studies and other studies, share the critical importance of data quality, transparency in methodologies, and robust measures to mitigate biases and confounding factors. These shared principles clearly indicate a universal commitment to integrating RWE into HTA to enhance decision-making. This

cross-agency comparison highlights the need for harmonised global guidelines to improve RWE's applicability and reliability in HTA, improve healthcare delivery, and ensure equitable access to innovative therapies.

5.2.2 Implications for Policy

This review demonstrates that RWE offers significant benefits to HTA. This is a perspective that is broadly recognised and shared among all investigated agencies. A clear trend toward the increasing use of RWE in HTA is evident in the literature, reflecting its growing importance in addressing gaps left by RCTs. This chapter will explore the policy implications of these findings, derived from the varying approaches to RWE integration observed across countries and agencies.

One critical insight is that the integration of RWE into HTA varies significantly between agencies, as all agencies have tailored their use of RWE to align with their healthcare systems. These differences highlight the need for a more harmonised global approach to RWE in HTA while respecting local contexts.

One such step was taken by the EMA, which has put forward a landmark effort to standardise and enhance the use of RWE across the European Union by publishing the 2024 RWE Framework. This framework seeks to harmonise data practices, improve access to diverse datasets through federated networks like DARWIN EU, and establish clear standards for methodological rigour. It especially stresses the transformative potential of RWE in several critical areas namely, post-market surveillance, regulatory decision-making and rare diseases and complex therapies. In post-market surveillance, RWE plays a pivotal role in monitoring long-term safety and effectiveness, particularly for therapies where RCT data is sparse. In the realm of regulatory decision-making, the framework seamlessly integrates RWE into the lifecycle of evidence generation, thereby

enabling regulatory bodies to adapt to the complexities of real-world healthcare delivery. Additionally, in the context of rare diseases and complex therapies, the EMA underscores the significance of RWE in situations where the conduct of traditional clinical trials is not feasible or raises ethical concerns. Building on the EMA's framework and the insights from this thesis, several key recommendations are proposed to enhance the integration of RWE into HTA:

Recommendation 1: Harmonisation of Data Standards

The first recommendation is the harmonisation of data standards. One major barrier to RWE integration is the variability in data collection, coding, and variability porting across countries. Universal data standards are essential to ensure consistency and comparability. The EMA's initiatives, such as the development of phenotype libraries and standardised datasets through DARWIN EU, provide a strong foundation for achieving this harmonisation, which could be further expanded upon. HTA bodies should aim to adopt standard data models to streamline RWE aggregation and analysis, to better facilitate cross-border collaboration.

Recommendation 2: Improvement and Ensurement of Data Quality and Transparency

The second recommendation is to improve and ensure data quality and transparency. The case studies investigated have shown that reliable RWE relies on high-quality data. Agencies such as NICE, HAS, and IQWiG strongly emphasise rigorous criteria for data reliability and provenance, but broader global adoption of these principles is necessary. Policymakers should mandate transparent data collection and reporting to foster trust and credibility in RWE-based findings, thereby enhancing their acceptance of HTA.

Recommendation 3: Further advancement of Methodological Innovation

The third recommendation emphasises the need for further advancement in methodological innovation. To effectively mitigate biases, including confounding and selection bias, that are inherently present in RWE, the application of advanced analytical techniques is essential. Techniques such as propensity score matching, target trial emulation, and modelling have the potential to significantly enhance the reliability of RWE studied, thereby establishing them as standard practice in RWE applications within HTA. Consequently, it is imperative to develop training programs for researchers and analysts to ensure the rigorous application of these methodologies.

Recommendation 4: Promotion of Dynamic HTA Frameworks

The fourth recommendation is to advance the implementation of dynamic HTA frameworks. The case study conducted by Brönneke et al. (2023) clearly demonstrates that dynamic HTA frameworks are pivotal for optimising RWE throughout the lifecycle of health technologies. Post-market reassessments, exemplified by the HAS utilisation of RWE for the re-evaluation of health technologies after a period of five years, yield critical insights into the long-term implications of these interventions. Furthermore, these frameworks should integrate iterative evidence generation, in alignment with the EMA's emphasis on continuous assessment and adaptation.

Recommendation 5: Continuously Incorporation of Patient-centered Outcomes

The fifth and final recommendation is to consistently integrate patient-centered outcomes. It is crucial to acknowledge the significance of patient-reported outcomes and real-world quality-of-life metrics in HTA to capture the patients' perspectives. As those who receive healthcare, their well-being is central to HTA. Clear guidelines for collecting and validating PROs should facilitate their inclusion in decision-making frameworks. Additionally, efforts to involve underrepresented

populations in RWE studies can enhance the generalizability of findings and ensure equitable healthcare policies for all recipients.

Summary and Relevance of Recommendations:

By implementing these recommendations, policymakers and HTA agencies can address critical gaps in traditional evidence generation and promote more comprehensive and equitable healthcare decisions. In this context, the EMA's framework serves as a valuable reference and illustrates that a supranational body, such as the EMA, is well-equipped to lead initiatives in harmonising practices across national HTA agencies. The literature clearly supports the notion that harmonised standards, robust methodologies, and active stakeholder engagement are vital to maximising the transformative potential of RWE in HTA. These coordinated efforts would ensure that healthcare systems remain adaptive, evidence-based, and patient-centred, effectively meeting the demands of an increasingly advanced, complex, and dynamic global health landscape.

5.2.3 Limitations

This SLR faced multiple limitations that must be acknowledged when interpreting its findings. Factors include selection bias, variability in study quality, and systemic challenges in integrating RWE into HTA processes across healthcare systems.

First, selection bias occurred due to excluding grey literature and non-peer-reviewed studies, which may have omitted practical insights. The reliance on English-language studies further narrowed global representation, favouring high-income countries with advanced data infrastructures and established HTA systems. This directly led to the non-inclusion of Spanish and Italian guidelines on the use of RWE in HTA, as none could be retrieved in the English language. Also, variability

in study quality presented challenges, as many studies depended on observational data susceptible to confounding factors and incomplete information.

Second, data availability and infrastructure disparities further constrained the analysis. Centralised systems like those in the United Kingdom enable robust longitudinal analyses, whereas fragmented systems in Germany hinder RWE generation. These systemic differences highlight barriers to leveraging RWE effectively across diverse settings. The review's geographic focus on high-income countries also limits the generalizability of findings to regions with distinct challenges, such as resource constraints and varying regulatory landscapes.

Third, stakeholder trust in RWE remains a critical issue despite efforts like NICE's RWE Framework and the TRUST tool to enhance transparency; scepticism persists, particularly in agencies like IQWiG, prioritising RCTs over RWE. Inconsistent stakeholder engagement and methodological standards exacerbate these challenges.

Lastly, the review emphasises HTA processes within structured regulatory frameworks, which may not reflect the dynamic nature of RWE integration in practice. Political, economic, and social factors, often central to implementation, were not fully explored, limiting the findings' applicability to less mature HTA systems.

In conclusion, while offering valuable insights into integrating RWE into HTA processes, these limitations underline the need for cautious interpretation and acknowledgement of systemic challenges.

5.2.3 Future Research

This review underscores the significant advancements made in the application of RWE within HTA. Nevertheless, numerous underexplored areas remain that present abundant opportunities for future inquiry. Building on the findings of this thesis, several avenues could be pursued to further enhance the utility of RWE in addressing existing challenges in HTA.

The review highlights initiatives such as the EMA's RWE Framework, which aims to achieve international harmonisation of standards for using RWE in HTA. Nonetheless, it also reveals that substantial variability persists in data collection, reporting, and methodological standards across different countries. As such, future research could concentrate on the development of universally applicable guidelines for RWE generation. This could involve comparative studies that analyse the implementation of existing frameworks, such as DARWIN EU, NICE's RWE Framework, and CADTH's initiatives or exploring mechanisms to align practices across diverse healthcare systems, considering regional needs and constraints.

Another promising direction would be the pursuit of advanced methodological approaches for the utilisation of RWE in HTA. This review has made it clear that RWE is inherently susceptible to biases and confounding factors, necessitating the adoption of robust analytical methods. Future research could thus explore the development of innovative statistical techniques aimed at enhancing causal inference in observational studies or assess the efficacy of emerging methodologies, such as target trial emulation and machine learning, in strengthening the reliability of RWE-based HTA.

Furthermore, longitudinal studies evaluating the impact of RWE represent a salient topic of interest for all stakeholders involved, given that the long-term effects of integrating RWE into HTA

processes remain inadequately understood. Consequently, future research could focus on conducting longitudinal studies to assess the influence of RWE on decision-making, reimbursement policies, and patient outcomes over time or to examine the economic and clinical implications of RWE-informed HTA decisions, particularly concerning rare diseases and emerging therapies.

In summary, future research should build upon the foundational work established by HTA agencies. It should address the prevailing methodological challenges, enhance collaboration, and foster innovation among HTA agencies, researchers, and policymakers. By investigating these areas, the potential of RWE to complement traditional evidence and transform HTA processes can be fully realised, ultimately leading to more effective and equitable healthcare decisions on a global scale.

6. Conclusion (Group Work)

This SLR highlights the transformative role that RWE plays in advancing HTA processes globally. All the examined HTA agencies acknowledge RWE's significance as a complementary source of evidence that addresses critical gaps in traditional methodologies. While RCTs offer unparalleled internal validity, they often do not capture the complexities of real-world healthcare delivery. In contrast, RWE provides valuable insights into real-world applicability, long-term safety, patient adherence, and broader population-level outcomes, making it an essential component of modern healthcare decision-making.

The findings of this study illustrate that RWE is gaining acceptance across HTA agencies but is integrated to varying degrees depending on national contexts and regulatory priorities. All reviewed agencies have developed unique frameworks for incorporating RWE, reflecting the diverse healthcare systems they operate within. A structured overview is presented in Figure 12.

HTA Agency	Approach to RWE integration	Key Practices	Strengths	Limitations
NICE ***(UK)***	Proactive integration of RWE at all stages of HTA	Utilizes the RWE Framework and DataSAT Encourages MAAs and pragmatic trials	Strong guidance for RWE integration Early-phase and lifecycle evaluations	Reliance on robust data systems can challenge settings with weaker infrastructure
IQWiG (Germany)	Conservative approach Prioritizes RCTs over RWE	Incorporates RWE only to complement RCTs Focuses on high-quality observational data when necessary	High emphasis on internal validity and methodological rigor	Limited use of RWE reduces flexibility in evidence acceptance
HAS ***(France)***	Balanced approach integrating RWE with traditional frameworks	Uses RWE for post-marketing surveillance and to complement RCTs Employs the SNDS for robust data sources	Strong integration of patient-reported outcomes and national health data	Limited emphasis on early-phase integration
CADTH (Canada)	Structured guidelines for RWE use in HTA	Promotes transparency and standardization Employs stakeholder consultations	Tailored to the Canadian healthcare system Emphasizes credibility.	Less relevant for global contexts outside Canada
TLV ***(Sweden)***	Focus on cost-effectiveness and pricing	Combines RWE with economic modelling Evaluates budget impact and health economic data.	Transparent integration of RWE into reimbursement decisions	Limited focus on broader stakeholder engagement
PMDA ***(Japan)***	Regulatory-driven use of RWE, especially for post-market surveillance	Uses claims databases, EHRs, and registries for early access pathways	Strong emphasis on safety and long-term monitoring	Limited alignment with traditional HTA frameworks
EMA **(EU)**	Collaborative and harmonized integration	Uses JCAs and the HTA Core Model Promotes transparency across EU countries	Encourages cross-border collaboration and reduces duplication	Implementation complexities due to regional differences

Figure 8 12 - Overview of HTA agencies approach to integrating RWE in HTA

Source: Constructed by author

This SLR also reveals that significant challenges that hinder the full integration of RWE into HTA still persist. Especially data heterogeneity, lack of standardisation, and methodological variability remain critical barriers. The key findings addressing the research questions are summarized and depicted in figure 13. The Review shows, that the absence of a unified international framework further amplifies the mentioned issues, limiting the comparability and scalability of RWE across jurisdictions. Additionally, the biases inherent in observational data, such as confounding and selection bias, have the potential to critically undermine the reliability of RWE if not addressed through advanced statistical methods.

Furthermore, this SLR contributes to the ongoing discourse on RWE by analysing successful case studies and deriving actionable recommendations for improving its integration into HTA. The identified key policy implications include the need for harmonised data standards, investment in robust methodological frameworks, and fostering international collaboration. The EMAs RWE framework is recognised as a valuable reference for global efforts by offering guidance on data interoperability, methodological rigour, and iterative evidence generation.

The recommendations outlined in Chapter 5.1.2 aim to address the challenges associated with RWE integration in HTA. The harmonisation of data standards among agencies is essential for minimising variability and enhancing comparability. Furthermore, the adoption of advanced methodologies, such as propensity score matching and target trial emulation, serves to mitigate potential biases. Moreover, it is imperative to incorporate patient-reported outcomes and real-world quality-of-life metrics to ensure that healthcare decisions are aligned with patient needs and priorities.

Furthermore, the integration of RWE into HTA has far-reaching implications for global healthcare systems. By leveraging RWE, HTA bodies can support evidence-based policies that ensure equitable access to innovative therapies, optimise resource allocation, and improve overall healthcare delivery. RWE is particularly valuable in addressing the unique challenges of rare diseases, complex therapies, and digital health innovations, where traditional RCTs may be infeasible or insufficient. Moreover, the adoption of dynamic HTA frameworks that incorporate iterative reassessments can enhance the adaptability of healthcare systems to emerging evidence.

Overall, RWE has the potential to transform HTA by providing a more comprehensive and patient-centred understanding of healthcare interventions. While significant progress has been made, challenges remain that require coordinated efforts from policymakers, HTA agencies, and stakeholders. By implementing the recommendations outlined in this thesis and building on existing frameworks such as those of the EMA, the full potential of RWE can be realised. These efforts will ensure that healthcare systems remain adaptive, evidence-based, and equitable, ultimately improving outcomes for patients worldwide. This study serves as a step toward achieving these goals, contributing to the development of robust methodologies and global health policy frameworks for the effective integration of RWE into HTA.

Research Question	Key Take Away
What factors influence the integration of RWE into HTA processes across different countries and healthcare systems, and what are the implications for decision-making outcomes such as reimbursement approvals?	RWE complements RCTs by addressing gaps in long-term safety, diversity, and rare diseases. RWE integration varies widely, with well-defined frameworks (NICE) and more conservative adaptations of RWE in HTA (IQWiG). High data quality and robust methodologies are essential for reliable evidence.
What recommendations can be derived from successful case studies of RWE implementation in HTA to inform the development of robust methodologies and global health policy frameworks?	The integration of RWE in HTA is successful when paired with high-quality datasets, and alignment with agency guidelines. RWE facilitates dynamic HTA which leads to improved health technology outcomes. Evidence collection should adhere to one universal international standard, in order to allow for data sharing among HTA agencies.
What are the key methodological challenges in developing robust RWE for HTA decision-making, and how do different health systems address these challenges?	Four key methodological challenges: Data quality and validity, data heterogeneity, study design and methodological rigour, and integration with traditional evidence frameworks. HTA agencies establish guidelines that are tailored to their national health system. Approaches vary across countries reflecting the degree to which RWE is integrated into national HTA. Imperative to improve data standards, promote methodological innovation and global harmonisation of evidence requirements.
What differences between RWE and RCTs are highlighted in HTA guidelines, and how do these differences impact the assessment of effectiveness and safety?	RCTs remain the gold standard for initial regulatory approval, while RWE enhances post-market evaluations. RWE addresses gaps left by RCTs, such as long-term safety, real-world diversity, and treatment adherence, while RCTs provide unmatched internal validity.
How do international HTA bodies harmonize evidence requirements for RWE, and what are the most effective methodologies and frameworks for supporting reimbursement decisions?	International HTA agencies face challenges in harmonising evidence criteria, showing how RWE recognition varies across countries. International cooperation is essential, as publishing guidelines alone is insufficient and, in this context, global initiatives, like the EUnetHTA, are needed to establish a unified approach. RWE frameworks can support reimbursement decisions, as instruments to create information for CEA, with MEA as implementation format and dynamic HTA as a tool for reassessment.

Figure 9 13 – Key Take Aways

Source: Constructed by author

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Appendix A: Search Strategy Documentation

Country	Search string	Hits
United Kingdom	**Search:** ((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("United Kingdom"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) **Filters:** in the last 5 years, English	891
Germany	**Search:** ((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Germany"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) **Filters:** in the last 5 years, English	179
France	**Search:** ((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("France"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) **Filters:** in the last 5 years, English	126
Spain	**Search:** ((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Spain"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) **Filters:** in the last 5 years, English	235
Italy	**Search:** ((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies	335

	as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Italy"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) **Filters:** in the last 5 years, English	
Sweden	**Search:** ((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Sweden"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) **Filters:** in the last 5 years, English	141
Australia	**Search:** ((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Australia"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) **Filters:** in the last 5 years, English	1,048
Canada	**Search:** ((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Canada"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) **Filters:** in the last 5 years, English	1,014
Japan	**Search:** ((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Japan"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) **Filters:** in the last 5 years, English	171
All countries		**4.140**

Appendix B: Included Studies from Data Extraction

No.	REF ID	Author	Title	Year
1	*59YKFVY5*	*Brönneke, Jan B.; Herr, Annika; Reif, Simon; Stern, Ariel D.*	*Dynamic HTA for digital health solutions: opportunities and challenges for patient-centered evaluation.*	*2023*
2	*F3TX4NWK*	*Kalf, Rachel R. J.; Delnoij, Diana M. J.; Ryll, Bettina; Bouvy, Marcel L.; Goettsch, Wim G.*	*Information Patients With Melanoma Spontaneously Report About Health-Related Quality of Life on Web-Based Forums: Case Study.*	*2021*
3	*A2KWDURE*	*Moler-Zapata, Silvia; Hutchings, Andrew; O'Neill, Stephen; Silverwood, Richard J.; Grieve, Richard*	*Emulating Target Trials With Real-World Data to Inform Health Technology Assessment: Findings and Lessons From an Application to Emergency Surgery.*	*2023*
4	*4NYCI442*	*Nicod, Elena; Maynou, Laia; Visintin, Erica; Cairns, John*	*Why do health technology assessment drug reimbursement recommendations differ between countries? A parallel convergent mixed methods study.*	*2020*
5	*AWYI5CMM*	*Appiah, Katherine; Rizzo, Maria; Sarri, Grammati; Hernandez, Luis*	*Justifying the source of external comparators in single-arm oncology health technology submissions: a review of NICE and PBAC assessments.*	*2024*

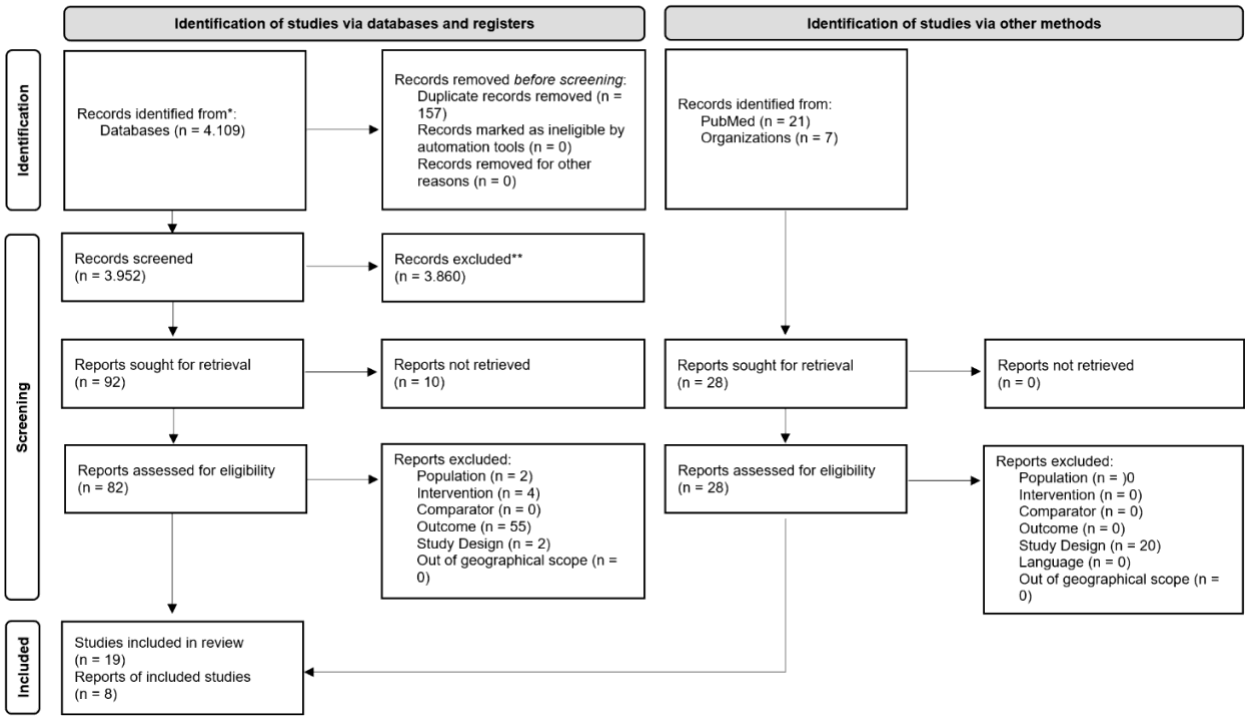
6	*UULVHFL9*	*Nabarette, Hervé; Chastenay, Marie-Hélène; Dupont, Jean-Claude K.; Ganache, Isabelle; Single, Ann N. V.*	*Patient and citizen participation at the organizational level in health technology assessment: an exploratory study in five jurisdictions.*	*2023*
7	*XRBV3H64*	*Buyukkaramikli, Nasuh C.; Wigfield, Peter; Hoang, Men Thi*	*A MEA is a MEA is a MEA? Sequential decision making and the impact of different managed entry agreements at the manufacturer and payer level, using a case study for an oncology drug in England.*	*2021*
8	*EZPF6ZQ7*	*Mitchell, Andrew*	*A NICE perspective on computable biomedical knowledge.*	*2020*
9	*T6M6BGEK*	*Grimm, Sabine E.; Pouwels, Xavier; Ramaekers, Bram L. T.; Wijnen, Ben; Knies, Saskia; Grutters, Janneke; Joore, Manuela A.*	*Development and Validation of the TRansparent Uncertainty ASsessmenT (TRUST) Tool for Assessing Uncertainties in Health Economic Decision Models.*	*2020*
10	*J54ZEM9I*	*Thokala, Praveen; Dodd, Peter; Baalbaki, Hassan; Brennan, Alan; Dixon, Simon; Lowrie, Kinga*	*Developing Markov Models From Real-World Data: A Case Study of Heart Failure Modeling Using Administrative Data.*	*2020*
11	*SYGF5DFG*	*Norburn, Laura; Thomas, Lizzie*	*Expertise, experience, and excellence. Twenty years of patient involvement in health technology assessment at NICE: an evolving story.*	*2020*

12	*X9S3TWI5*	*Ciminata, Giorgio; Geue, Claudia; Wu, Olivia; Deidda, Manuela; Kreif, Noemi; Langhorne, Peter*	*Propensity score methods for comparative-effectiveness analysis: A case study of direct oral anticoagulants in the atrial fibrillation population.*	*2022*
13	*57NLXEC7*	*de Pouvourville, Gérard; Blin, Patrick; Karam, Pierre*	*The contribution of real-world evidence to cost-effectiveness analysis: case study of Dabigatran etexilate in France.*	*2020*
14	*V4QAV42Q*	*Toledo-Chávarri, Ana; Gagnon, Marie-Pierre; Álvarez-Pérez, Yolanda; Perestelo-Pérez, Lilisbeth; Triñanes Pego, Yolanda; Serrano Aguilar, Pedro*	*Development of a decisional flowchart for meaningful patient involvement in Health Technology Assessment.*	*2020*
15	*E6KKW6HX*	*Angelis, A.; Linch, M.; Montibeller, G.; Molina-Lopez, T.; Zawada, A.; Orzel, K.; Arickx, F.; Espin, J.; Kanavos, P.*	*Multiple Criteria Decision Analysis for HTA across four EU Member States: Piloting the Advance Value Framework.*	*2020*
16	*DQZYKTF6*	*Ruggeri, Matteo; Cadeddu, Chiara; Roazzi, Paolo; Mandolini, Donatella; Grigioni, Mauro; Marchetti, Marco*	*Multi-Criteria-Decision-Analysis (MCDA) for the Horizon Scanning of Health Innovations an Application to COVID 19 Emergency.*	*2020*
17	*24GBFQ7X*	*Gao, Yuan; Laka, Mah; Merlin, Tracy*	*Is the quality of evidence in health technology assessment deteriorating over time? A case study on cancer drugs in Australia.*	*2023*

18	*TGI9PDPL*	*Badaiki, Winifred; Pyper, Evelyn; Lester, Kendra; Skeard, Janelle; Penney, Michelle; Shin, Janey; Fisher, Brenda; Hew, Huong; Gulliver, Susanne; Gulliver, Wayne; Rahman, Proton*	*Laying the foundation for Real-world evidence studies: a case study from Newfoundland and Labrador.*	*2022*
19	*PRIZK5ME*	*Pomey, Marie-Pascale; Brouillard, Philippe; Ganache, Isabelle; Lambert, Laurie; Boothroyd, Lucy; Collette, Caroline; Bédard, Sylvain; Grégoire, Alexandre; Pelaez, Sandra; Demers-Payette, Olivier; Goetghebeur, Mireille; de Guise, Michèle; Roy, Denis*	*Co-construction of health technology assessment recommendations with patients: An example with cardiac defibrillator replacement.*	*2020*
20	*F3GIJ5NL*	*Zong, Jihong; Rojubally, Adina; Pan, Xiaoyun; Wolf, Birgit; Greenfeder, Scott; Upton, Alexander; Gdovin Bergeson, Joette*	*A Review and Comparative Case Study Analysis of Real-World Evidence in European Regulatory and Health Technology Assessment Decision Making for Oncology Medicines*	*2024*
21	*/*	*IQWIG*	*General Methods*	*2023*
22	*/*	*HAS*	*Real-world studies for the assessment of medicinal products and medical devices*	*2021*
23	*/*	*NICE*	*NICE real-world evidence framework*	*2022*
24	*/*	*TLV*	*How should we assess and pay? Health-economic assessments and*	*2021*

			payment models for precision medicines and ATMPs	
25	*/*	*Canadas Drug and Health Technology Agency*	*Real-world studies for the assessment of medicinal products and medical devices*	*2023*
26	*/*	*TGA*	*Real World Evidence Regulatory considerations for Medical Devices*	*2024*

Appendix C: PRISMA Flow Diagram



Appendix D: Data Extraction Table

The full data extraction table used for this study is too large for display. It has been included as a supplementary Excel file accessible via:

Appendix E: Search String Word File

Search String Documentation

This document includes different versions of our search string, detailing the iterative process of refining our literature search strategy. Each version represents adjustments made to enhance the precision and relevance of search results. This provides a comprehensive and transparent record of the search development process.

This document is divided into four sections detailing the development of our search strategy. The first section includes the search string for all target countries. The second section provides separate search strings for each country. The third section focuses exclusively on European countries, and the fourth section contains all initial drafts and iterations that contributed to the final search strings.

Table of Contents

1. Search String Documentation (including all the chosen countries)

This version contains all the suggested changes. The publications are reduced to the last 5 years and filtered to only show English publications in the chosen countries: USA, UK, Germany, France, Spain, Italy, Sweden, Australia, Canada, and Japan. Before, we used the MeshTerm Europe to only show publications regarding Europe. This MeshTerm has now been removed from the search string and exchanged by the countries mentioned before. The filters are added as the last step to show how many results were given before. The results show 6,997 publications, which will have to be narrowed down. How can this be done? Should we exclude some countries? If we had only searched for publications in the US, we would have gotten 3,120 hits. If we excluded the US, we would get 3,983 hits. If we had only chosen the European countries from our list, we would have gotten 1,833 hits. We also have the search strings with each country listed individually below.

Research Questions:

1. What are the most common types of RWE used in HTA submissions, and how effective are they in supporting positive reimbursement decisions?
2. How do different methodological approaches in RWE affect the robustness and credibility of HTA outcomes?
3. What global guidelines exist for using RWE in HTAs?
4. What successful case studies show the use of RWE in HTAs?

Concept 1: Real-World Evidence (RWE)

Keywords: Real-World Evidence, RWE

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR “Real-World Evidence”[tw] OR “RWE”[tw]

Concept 2: Health Technology Assessment (HTA)

Keywords: Health Technology Assessment, HTA

Mesh: "Technology Assessment, Biomedical"[Mesh]

Complete: "Technology Assessment, Biomedical"[Mesh] OR “Health Technology Assessment”[tw] OR “HTA”[tw]

Concept 3: Global Guidelines

Keywords: Global guidelines, international standards, best practices

Mesh: “Reference Standards”[Mesh], "Guidelines as Topic"[Mesh]

Complete: "Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh]

OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]

Concept 4: Case Studies

Keywords: case stud*, case example*, best practice*

Mesh: "Single-Case Studies as Topic"[Mesh]

Complete: "Single-Case Studies as Topic"[Mesh] OR “case stud*”[tw] OR “case example*”[tw] OR “best practice*”[tw]

Concept 5: Chosen Countries

Keywords: USA, UK, Germany, France, Spain, Italy, Sweden, Australia, Canada, Japan

Mesh: "United States"[Mesh] OR "United Kingdom"[Mesh] OR "Germany"[Mesh] OR "France"[Mesh] OR "Spain"[Mesh] OR "Italy"[Mesh] OR "Sweden"[Mesh] OR "Australia"[Mesh] OR "Canada"[Mesh] OR "Japan"[Mesh]

Complete: "United States"[Mesh] OR "United Kingdom"[Mesh] OR "Germany"[Mesh] OR "France"[Mesh] OR "Spain"[Mesh] OR "Italy"[Mesh] OR "Sweden"[Mesh] OR "Australia"[Mesh] OR "Canada"[Mesh] OR "Japan"[Mesh]

Final Version		
Number	**Search String**	**Results**
#8	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("United States"[Mesh] OR "United Kingdom"[Mesh] OR "Germany"[Mesh] OR "France"[Mesh] OR "Spain"[Mesh] OR "Italy"[Mesh] OR "Sweden"[Mesh] OR "Australia"[Mesh] OR "Canada"[Mesh] OR "Japan"[Mesh])** Filters: **in the last 5 years, English**	6,997
#7	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("United States"[Mesh] OR "United Kingdom"[Mesh] OR "Germany"[Mesh] OR "France"[Mesh] OR "Spain"[Mesh] OR**	38,385

	"Italy"[Mesh] OR "Sweden"[Mesh] OR "Australia"[Mesh] OR "Canada"[Mesh] OR "Japan"[Mesh])	
#6	Search: **"United States"[Mesh] OR "United Kingdom"[Mesh] OR "Germany"[Mesh] OR "France"[Mesh] OR "Spain"[Mesh] OR "Italy"[Mesh] OR "Sweden"[Mesh] OR "Australia"[Mesh] OR "Canada"[Mesh] OR "Japan"[Mesh]**	2,856,738
#5	Search: **((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])**	199,130
#4	Search: **"Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw]**	196,450
#3	Search: **"Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]**	739,449
#2	Search: **"Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]**	18,421
#1	Search: **"Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]**	1,333,439

2. Search String Documentation (by country)

This version contains all the suggested changes. Here, all countries are added separately to individual search strings. The publications are reduced to the last 5 years and filtered to only show English publications in the chosen countries: USA, UK, Germany, France, Spain, Italy, Sweden, Australia, Canada, and Japan. Before, we used the MeshTerm Europe to only show publications regarding Europe. This MeshTerm has now been removed from the search string and exchanged by the countries mentioned before. The filters are added as the last step to show how many results were given before.

Research Questions:

1. What are the most common types of RWE used in HTA submissions, and how effective are they in supporting positive reimbursement decisions?
2. How do different methodological approaches in RWE affect the robustness and credibility of HTA outcomes?
3. What global guidelines exist for using RWE in HTAs?
4. What successful case studies show the use of RWE in HTAs?

Concept 1: Real-World Evidence (RWE)

Keywords: Real-World Evidence, RWE

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR “Real-World Evidence”[tw] OR “RWE”[tw]

Concept 2: Health Technology Assessment (HTA)

Keywords: Health Technology Assessment, HTA

Mesh: "Technology Assessment, Biomedical"[Mesh]

Complete: "Technology Assessment, Biomedical"[Mesh] OR “Health Technology Assessment”[tw] OR “HTA”[tw]

Concept 3: Global Guidelines

Keywords: Global guidelines, international standards, best practices

Mesh: “Reference Standards”[Mesh], "Guidelines as Topic"[Mesh]

Complete: "Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh]

OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]

Concept 4: Case Studies

Keywords: case stud*, case example*, best practice*

Mesh: "Single-Case Studies as Topic"[Mesh]

Complete: "Single-Case Studies as Topic"[Mesh] OR “case stud*”[tw] OR “case example*”[tw] OR “best practice*”[tw]

Concept 5: each country, individually

Keywords: USA, UK, Germany, France, Spain, Italy, Sweden, Australia, Canada, Japan

Mesh: "United States"[Mesh] OR "United Kingdom"[Mesh] OR "Germany"[Mesh] OR "France"[Mesh] OR "Spain"[Mesh] OR "Italy"[Mesh] OR "Sweden"[Mesh] OR "Australia"[Mesh] OR "Canada"[Mesh] OR "Japan"[Mesh]

Complete: "United States"[Mesh] OR "United Kingdom"[Mesh] OR "Germany"[Mesh] OR "France"[Mesh] OR "Spain"[Mesh] OR "Italy"[Mesh] OR "Sweden"[Mesh] OR "Australia"[Mesh] OR "Canada"[Mesh] OR "Japan"[Mesh]

United States	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR**	3,120

	"case example*"[tw] OR "best practice*"[tw])) AND ("United States"[Mesh]) Filters: **in the last 5 years, English**	
United Kingdom	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("United Kingdom"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	891
Germany	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Germany"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) Filters: in the last 5 years, English**	179
France	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("France"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	126
Spain	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Spain"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	235
Italy	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR**	335

	"international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Italy"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) Filters: **in the last 5 years, English**	
Sweden	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Sweden"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	141
Australia	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Australia"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	1,048
Canada	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Canada"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	1,014
Japan	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Japan"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	171
All countries		**7,251**

3. Search String Documentation (Europe)

Final Version: This version contains all the suggested changes. If publications are reduced to the last 5 years and filtered to only show English publications, 3,233 results can be seen.

Research Questions:

5. What are the most common types of RWE used in HTA submissions, and how effective are they in supporting positive reimbursement decisions?
6. How do different methodological approaches in RWE affect the robustness and credibility of HTA outcomes?
7. What global guidelines exist for using RWE in HTAs?
8. What successful case studies show the use of RWE in HTAs?

Concept 1: Real-World Evidence (RWE)

Keywords: Real-World Evidence, RWE

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR “Real-World Evidence”[tw] OR “RWE”[tw]

Concept 2: Health Technology Assessment (HTA)

Keywords: Health Technology Assessment, HTA

Mesh: "Technology Assessment, Biomedical"[Mesh]

Complete: "Technology Assessment, Biomedical"[Mesh] OR “Health Technology Assessment”[tw] OR “HTA”[tw]

Concept 3: Global Guidelines

Keywords: Global guidelines, international standards, best practices

Mesh: “Reference Standards”[Mesh], "Guidelines as Topic"[Mesh]

Complete: "Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh]

OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]

Concept 4: Case Studies

Keywords: case stud*, case example*, best practice*

Mesh: "Single-Case Studies as Topic"[Mesh]

Complete: "Single-Case Studies as Topic"[Mesh] OR “case stud*”[tw] OR “case example*”[tw] OR “best practice*”[tw]

Concept 5: Europe

Keywords: Europe

Mesh: "Europe"[Mesh]

Complete: "Europe"[Mesh]

Final Version		
Number	**Search String**	**Results**
#8	Search: **((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Europe"[Mesh])**Filters: **in the last 5 years, English**	3,233
#7	Search: **((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Europe"[Mesh])**	14,430
#6	Search: **"Europe"[Mesh]**	1,581,992
#5	Search: **((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])**	197,004
#4	Search: **"Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw]**	196,450
#3	Search: **"Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]**	739,449
#2	Search: **"Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]**	18,421
#1	Search: **"Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]**	1,333,439

1. Initial Drafts: Search String Documentation

Search String Composition

Our search string analysis explores four options, each incorporating different concepts. All options include the core concepts of "Healthcare Systems," "Real-World Evidence (RWE)," "Health Technology Assessment (HTA)," and "Global Guidelines."

Option 1, which includes only these core concepts, resulted in 86 hits. Option 2 adds the "Robustness and Credibility" concept, narrowing the results to 8. Option 3 includes "Case Studies," generating 62 results, and Option 4 adds "Impact on Reimbursement Decisions," with 23 results.

Options 2 and 4 might be too restricting, showing too few results, while Options 1 and 3 offer a broader and more informative search.

Option 1:

Research Questions:

1. What are the most common types of RWE used in HTA submissions, and how effective are they in supporting positive reimbursement decisions?
2. How do different methodological approaches in RWE affect the robustness and credibility of HTA outcomes?
3. What global guidelines exist for using RWE in HTAs?
4. What successful case studies show the use of RWE in HTAs?

Concept 1: Healthcare Systems

Keywords: Healthcare system

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]

Concept 2: Real-World Evidence (RWE)

Keywords: Real-World Evidence, RWE

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]

Concept 3: Health Technology Assessment (HTA)

Keywords: Health Technology Assessment, HTA

Mesh: "Technology Assessment, Biomedical"[Mesh]

Complete: "Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]

Concept 4: Global Guidelines

Keywords: Global guidelines, international standards, best practices

Mesh: "Reference Standards"[Mesh]

Complete: "Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]

Option 1		
Number	**Search String**	**Results**
#5	Search: **((("Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]) AND ("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw])) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])**	86
#4	Search: **"Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]**	102,126
#3	Search: **"Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]**	18,394
#2	Search: **"Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]**	1,331,676
#1	Search: **"Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]**	1,359,931

Option 2:

Research Questions:

1. What are the most common types of RWE used in HTA submissions, and how effective are they in supporting positive reimbursement decisions?
2. How do different methodological approaches in RWE affect the robustness and credibility of HTA outcomes?
3. What global guidelines exist for using RWE in HTAs?
4. What successful case studies show the use of RWE in HTAs?

Concept 1: Healthcare Systems

Keywords: Healthcare system

Mesh: "Delivery of Health Care"[Mesh]

Complete: “Delivery of Health Care"[Mesh] OR **“**Healthcare system*”[tw]

Concept 2: Real-World Evidence (RWE)

Keywords: Real-World Evidence, RWE

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR “Real-World Evidence”[tw] OR “RWE”[tw]

Concept 3: Health Technology Assessment (HTA)

Keywords: Health Technology Assessment, HTA

Mesh: "Technology Assessment, Biomedical"[Mesh]

Complete: "Technology Assessment, Biomedical"[Mesh] OR “Health Technology Assessment”[tw] OR “HTA”[tw]

Concept 4: Robustness and Credibility

Keywords: robustness, credibility, validity, reliability

Mesh: "Task Performance and Analysis"[Mesh]

Complete: "Task Performance and Analysis"[Mesh] OR “robustness”[tw] OR “credibility”[tw] OR “validity”[tw] OR “reliability”[tw]

Concept 5: Global Guidelines

Keywords: Global guidelines, international standards, best practices

Mesh: “Reference Standards”[Mesh]

Complete: "Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]

Option 2		
Number	**Search String**	**Results**
#6	Search: **((("Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]) AND ("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw])) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Task Performance and Analysis"[Mesh] OR**	8

	"robustness"[tw] OR "credibility"[tw] OR "validity"[tw] OR "reliability"[tw])) AND ("Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])	
#5	Search: **"Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]**	102,126
#4	Search: **"Task Performance and Analysis"[Mesh] OR "robustness"[tw] OR "credibility"[tw] OR "validity"[tw] OR "reliability"[tw]**	500,974
#3	Search: **"Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]**	18,394
#2	Search: **"Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]**	1,331,676
#1	Search: **"Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]**	1,359,931

Option 3:

Research Questions:

9. What are the most common types of RWE used in HTA submissions, and how effective are they in supporting positive reimbursement decisions?
10. How do different methodological approaches in RWE affect the robustness and credibility of HTA outcomes?
11. What global guidelines exist for using RWE in HTAs?
12. What successful case studies show the use of RWE in HTAs?

Concept 1: Healthcare Systems

Keywords: Healthcare system

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]

Concept 2: Real-World Evidence (RWE)

Keywords: Real-World Evidence, RWE

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]

Concept 3: Health Technology Assessment (HTA)

Keywords: Health Technology Assessment, HTA

Mesh: "Technology Assessment, Biomedical"[Mesh]

Complete: "Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]

Concept 4: Global Guidelines

Keywords: Global guidelines, international standards, best practices

Mesh: "Reference Standards"[Mesh]

Complete: "Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]

Concept 5: Case Studies

Keywords: case stud*, case example*, best practice*

Mesh: "Organizational Case Studies"[Mesh], "Single-Case Studies as Topic"[Mesh]

Complete: "Organizational Case Studies"[Mesh] OR "Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case. Example*"[tw] OR "best practice*"[tw]

Option 3		
Number	**Search String**	**Results**
#6	Search: **((("Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]) AND ("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw])) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) AND ("Organizational Case Studies"[Mesh] OR "Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case. Example*"[tw] OR "best practice*"[tw])**	62
#5	Search: **"Organizational Case Studies"[Mesh] OR "Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case. Example*"[tw] OR "best practice*"[tw]**	196,052
#4	Search: **"Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]**	102,126

#3	Search: **"Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]**	18,394
#2	Search: **"Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]**	1,331,676
#1	Search: **"Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]**	1,359,931

Option 4:

Research Questions:

1. What are the most common types of RWE used in HTA submissions, and how effective are they in supporting positive reimbursement decisions?
2. How do different methodological approaches in RWE affect the robustness and credibility of HTA outcomes?
3. What global guidelines exist for using RWE in HTAs?
4. What successful case studies show the use of RWE in HTAs?

Concept 1: Healthcare Systems

Keywords: Healthcare system

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]

Concept 2: Real-World Evidence (RWE)

Keywords: Real-World Evidence, RWE

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]

Concept 3: Health Technology Assessment (HTA)

Keywords: Health Technology Assessment, HTA

Mesh: "Technology Assessment, Biomedical"[Mesh]

Complete: "Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]

Concept 4: Global Guidelines

Keywords: Global guidelines, international standards, best practices

Mesh: "Reference Standards"[Mesh]

Complete: "Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]

Concept 5: Impact on Reimbursement Decisions

Keywords: Reimbursement decision, cost-effectiveness, budget impact

Mesh: "Cost-Effectiveness Analysis"[Mesh], "Insurance, Health, Reimbursement"[Mesh]

Complete: "Cost-Effectiveness Analysis"[Mesh] OR "Insurance, Health, Reimbursement"[Mesh] OR "reimbursement decision*"[tw] OR "cost-effectiveness"[tw] OR "budget impact*"[tw]

Option 4		
Number	**Search String**	**Results**
#6	Search: **((("Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]) AND ("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw])) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) AND ("Cost-Effectiveness Analysis"[Mesh] OR "Insurance, Health, Reimbursement"[Mesh] OR "reimbursement decision*"[tw] OR "cost-effectiveness"[tw] OR "budget impact*"[tw])**	23
#5	Search: **"Cost-Effectiveness Analysis"[Mesh] OR "Insurance, Health, Reimbursement"[Mesh] OR "reimbursement decision*"[tw] OR "cost-effectiveness"[tw] OR "budget impact*"[tw]**	131,045
#4	Search: **"Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]**	102,126
#3	Search: **"Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]**	18,394
#2	Search: **"Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]**	1,331,676
#1	Search: **"Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]**	1,359,931

First Draft

Research Question 1: How do healthcare systems (like NICE in the UK and IQWiG in Germany) incorporate Real-World Evidence (RWE) into their Health Technology Assessment (HTA) processes, and how do they impact reimbursement decisions and patient access to innovative therapies?

Concept 1: Healthcare Systems

Keywords: Healthcare system

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]

Concept 2: Real-World Evidence (RWE)

Keywords: Real-World Evidence, RWE

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]

Concept 3: Health Technology Assessment (HTA)

Keywords: Health Technology Assessment, HTA

Mesh: "Technology Assessment, Biomedical"[Mesh]

Complete: "Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]

Concept 4: Impact on Reimbursement Decisions

Keywords: Reimbursement decision, cost-effectiveness, budget impact

Mesh: "Cost-Effectiveness Analysis"[Mesh], "Insurance, Health, Reimbursement"[Mesh]

Complete: "Cost-Effectiveness Analysis"[Mesh] OR "Insurance, Health, Reimbursement"[Mesh] OR "reimbursement decision*"[tw] OR "cost-effectiveness"[tw] OR "budget impact*"[tw]

Concept 5: Patient Access to Innovative Therapies

Keywords: Patient access, innovative therapies, healthcare accessibility

Mesh: "Health Services Accessibility"[Mesh]

Complete: "Health Services Accessibility"[Mesh] OR "patient access"[tw] OR "innovative therap*"[tw] OR "healthcare accessibility"[tw

Number	Search String	Results
#6	Search: **((((("Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]) AND ("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw])) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Cost-Effectiveness Analysis"[Mesh] OR "Insurance, Health, Reimbursement"[Mesh] OR "reimbursement decision*"[tw] OR "cost-effectiveness"[tw] OR "budget impact*"[tw])) AND ("Health Services Accessibility"[Mesh] OR "patient access"[tw] OR "innovative therap*"[tw] OR "healthcare accessibility"[tw])**	174
#5	Search: **"Health Services Accessibility"[Mesh] OR "patient access"[tw] OR "innovative therap*"[tw] OR "healthcare accessibility"[tw]**	149,616
#4	Search: **"Cost-Effectiveness Analysis"[Mesh] OR "Insurance, Health, Reimbursement"[Mesh] OR "reimbursement decision*"[tw] OR "cost-effectiveness"[tw] OR "budget impact*"[tw]**	130,988
#3	Search: **"Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]**	18,393
#2	Search: **"Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]**	1,331,242
#1	Search: **"Delivery of Health Care"[Mesh] OR "Healthcare system*"[tw]**	1,359,463

Research Question 2: What global guidelines exist for using RWE in HTAs?

Concept 1: Global Guidelines

Keywords: Global guidelines, international standards, best practices

Mesh: "Reference Standards"[Mesh]

Complete: "Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]

Concept 2: Real-World Evidence (RWE)

Keywords: Real-World Evidence, RWE

Mesh: "Delivery of Health Care"[Mesh]

Complete: "Delivery of Health Care"[Mesh] OR “Real-World Evidence”[tw] OR “RWE”[tw]

Concept 3: Health Technology Assessment (HTA)

Keywords: Health Technology Assessment, HTA

Mesh: "Technology Assessment, Biomedical"[Mesh]

Complete: "Technology Assessment, Biomedical"[Mesh] OR “Health Technology Assessment”[tw] OR “HTA”[tw]

Number	Search String	Results
#4	Search: **(("Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]) AND ("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw])) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])**	96
#3	Search: **"Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw]**	18,393
#2	Search: **"Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]**	1,331,242
#1	Search: **"Reference Standards"[Mesh] OR "global guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw]**	102,094

Appendix F: SLR Protocol

IQVIA PAP – SLR Protocol

NOVA SBE

The Role of Real-World Evidence in Health Technology Assessment: Challenges, Opportunities, and International Perspectives

Elena Lialina

2024

Tables and Figures

List of Tables

List of Figures

1. Title and Background

The Title of this SLR is “The Role of Real-World Evidence in Health Technology Assessment: Challenges, Opportunities, and International Perspectives”

The integration of Real-World Evidence (RWE) into Health Technology Assessment (HTA) processes has become increasingly significant in shaping the decision-making of healthcare systems regarding the reimbursement and accessibility of innovative therapies. Traditional methods of generating evidence from clinical trials face challenges as more drugs are authorized for use in specific patient populations and early stages of disease, limiting the availability of suitable participants and increasing the time required to generate mature results (Graili et al., 2023). This shift has led to an increasing focus on RWE that complements clinical trial data and addresses uncertainties in HTA processes (Curtis et al., 2023). Therefore, it is crucial for stakeholders, including policymakers, payers, and patients, to understand how various healthcare systems incorporate RWE into their HTA frameworks and the subsequent effects on reimbursement decisions and patient access to new treatments (Claire et al., 2023).

HTA is a comprehensive process used to evaluate new medical technologies' clinical, economic, and societal implications (Sullivan et al., 2009). It systematically analyzes various evidence types, including data from randomized controlled trials (RCTs), economic evaluations, and RWE. The primary goal of HTA is to inform decision-making in healthcare, particularly regarding the allocation of resources and the approval and reimbursement of new therapies (Thokagevistk et al., 2024). Prominent HTA bodies, such as the National Institute for Health and Care Excellence (NICE) in the UK, the Haute Autorité de Santé (HAS) in France, and the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany, play a crucial instead of processes.

RWE refers to clinical evidence gathered from real-world settings, as opposed to controlled clinical trials. This evidence can include data from electronic health records (EHRs), patient registries, insurance claims, and observational studies (Sherman et al., 2016). RWE is increasingly utilized in HTA to complement traditional clinical trial data, offering insights into medical interventions’ effectiveness, safety, and economic impact on broader, more diverse patient populations. It provides a more comprehensive view of a therapy's performance under everyday clinical practice conditions, which can differ significantly from controlled trial environments (Oortwijn, 2018; Yang & Nguyen, 2022).

In this context, incorporating RWE into HTA processes carries significant implications. RWE can help alleviate the limitations of RCTs, such as their restricted generalizability due to rigorous eligibility criteria and controlled conditions. Furthermore, RWE can furnish valuable information on long-term outcomes, adverse effects, and patient-reported outcomes, often not fully captured in clinical trials. By integrating RWE, HTA can offer a more comprehensive evaluation of a technology's value, guiding more nuanced reimbursement decisions and potentially accelerating patient access to innovative therapies.

The outcomes of HTA, shaped by both RCT and RWE data, play a pivotal role in determining whether a new therapy will be reimbursed and accessible to patients (IQVIA 2022). A favorable HTA outcome can lead to full reimbursement and broad market access, while a negative outcome may restrict access or limit it to specific patient groups. The consideration of RWE in these assessments can significantly impact the final decision, especially in cases where traditional trial data is lacking or insufficient (Thokagevistk et al., 2024). This insufficiency often arises due to the limitations of RCTs, which may not fully capture the intricacies of real-world clinical scenarios despite being the gold standard for clinical evidence.

However, the extent of RWE integration into HTA processes varies across countries, with some HTA bodies demonstrating greater acceptance and reliance on RWE. This disparity underscores the importance of developing robust methodological guidelines and clear acceptance criteria to ensure the effective utilization of RWE in decision-making.

Consequently, this paper will conduct a systematic literature review (SLR) following a structured and methodical approach. By systematically synthesizing the evidence, this SLR will provide stakeholders with a comprehensive understanding of RWE’s role in HTA.

2. Objectives

The objective of this SLR is to identify, evaluate, and synthesize evidence on:

- What factors influence the integration of RWE into HTA processes across different countries and healthcare systems, and what are the implications for decision-making outcomes such as reimbursement approvals and clinical guideline development?

- What recommendations can be derived from successful case studies of RWE implementation in HTA to inform the development of robust methodologies and global health policy frameworks?
- What are the key methodological challenges in developing robust RWE for HTA decision-making, and how do different health systems address these challenges?
- What differences between RWE and RCTs are highlighted in HTA guidelines, and how do these differences impact the assessment of effectiveness and safety?
- How do international HTA bodies harmonize evidence requirements for RWE, and what are the most effective methodologies and frameworks for supporting reimbursement decisions?

3. Methods

For this systematic literature review, we will adhere to the guidelines from the Cochrane Handbook for Systematic Reviews of Interventions (Chandler J. et al., 2019). By applying these methods, our goal is to ensure the minimization of bias, a transparent methodology, and the reproducibility of our findings. The steps outlined below detail our approach.

4. Eligibility Criteria

We will use the PICOS framework to define the inclusion and exclusion criteria for studies to be considered in this review:

- Population (P): This review will include studies on any patient population. There are no specific exclusions for the population, provided the studies address the integration of Real-World Evidence (RWE) within the Health Technology Assessment (HTA) process.
- Intervention (I): Studies involving any intervention that incorporates or evaluates the use of RWE within the HTA process will be included. There are no specific exclusions based on the type of intervention.
- Comparator (C): No specific comparator is required for inclusion, as the focus of the review is on the use of RWE in HTA. There are also no exclusions based on comparators.

- Outcomes (O): Only studies reporting outcomes related to positive reimbursement decisions, negative reimbursement decisions, or recommendations on the use of RWE in HTA will be included. Studies reporting other types of outcomes will be excluded.
- Study Design (S): The review will include case studies and guidelines. Studies with other designs, such as RCTs, cohort studies, and observational studies, will be excluded, unless they directly integrate RWE into HTA decision-making.
- Restrictions: The review will consider only studies published in English within the last five years from the following countries: the UK, Germany, France, Spain, Italy, Sweden, Australia, Canada, and Japan. Studies published in any other language, older studies, or those from countries not listed will be exclude

PICOS Criteria

PICOS	Inclusion	Exclusion
Population	Any	Not applicable
Intervention	Any	Not applicable
Comparator	Not applicable	Not applicable
Outcomes	Positive reimbursement decision Negative reimbursement decision Recommendations on RWE	Other outcomes
Study Design	Case studies Guidelines	E.g., RCTs, cohort studies, observational studies
Restrictions	Studies published in English within the last 5 years for the following countries: UK, Germany, France, Spain, Italy, Sweden, Australia, Canada, Japan	Any other language, any older study, any other country

Table 1 - PICOS criteria

4.2 Information Sources

The primary data sources to be used are listed below. These mainly include PubMed, HTA websites, and other sources relevant to HTA and RWE. The search will be limited to studies published in English within the last five years. A further hand search will be conducted to identify Guidelines on the use of RWE in HTA from the following HTA Agencies:

Country	HTA Agency
Spain	Provincial HTA Committees
Italy	AIFA – Italian Medicines Agency
Germany	IQWiG – Institute for Quality and Efficiency in Health Care G-BA – Federal Joint Committee
France	HAS – French National Authority for Health
Sweden	TLV – Swedish Dental and Pharmaceutical Benefits Agency
United Kingdom	NICE - National Institute for Health and Care Excellence
Canada	Canadas Drug and Health Technology Agency
Australia	TGA – Therapeutic Goods Administration
Japan	PMDA – Pharmaceuticals and Medical Devices Agency

4.3 Search Strategy

A comprehensive search strategy will be developed using a structured approach integrating Medical Subject Headings (MeSH) and relevant keywords for each key concept, including RWE, HTA, guidelines, and case studies. This strategy will be crafted iteratively, ensuring that the search string captures only the most pertinent studies. The development process for the search strings will be thoroughly documented, including each iteration and the rationale for refinements, in a dedicated Word document. The final search strings, which will form the foundation for the subsequent phases of this review, will also be recorded in this document.

When a database or source does not support complex search strings, we will conduct manual searches using relevant keywords. These keywords and the results will be documented in the same Word file, maintaining transparency and consistency across our search methodology. The final search strings are listed below:

Search strings (PubMed):

Country	Search string	Hits
United Kingdom	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("United Kingdom"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: in the last 5 years, English	891
Germany	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Germany"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) Filters: in the last 5 years, English**	179
France	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("France"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	126
Spain	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology**	235

	Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Spain"[Mesh]) AND ((y_5[Filter]) AND (english[Filter])) Filters: **in the last 5 years, English**	
Italy	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Italy"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	335
Sweden	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Sweden"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	141
Australia	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Australia"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	1,048
Canada	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Canada"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	1,014

Japan	Search: **((((("Delivery of Health Care"[Mesh] OR "Real-World Evidence"[tw] OR "RWE"[tw]) AND ("Technology Assessment, Biomedical"[Mesh] OR "Health Technology Assessment"[tw] OR "HTA"[tw])) AND ("Reference Standards"[Mesh] OR "Guidelines as Topic"[Mesh] OR "guideline*"[tw] OR "international standard*"[tw] OR "best practice*"[tw])) OR ("Single-Case Studies as Topic"[Mesh] OR "case stud*"[tw] OR "case example*"[tw] OR "best practice*"[tw])) AND ("Japan"[Mesh]) AND ((y_5[Filter]) AND (english[Filter]))** Filters: **in the last 5 years, English**	171
All countries		**4.140**

Table 2 - Search strings

4.4 Study Selection

The study selection process will be carried out in two stages: abstract screening and full-text review. Both will involve two independent reviewers to minimize bias and ensure robustness in the selection of studies. All steps in the study selection process will be meticulously documented, including reasons for exclusions at both the abstract and full-text stages. This documentation will be essential for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, which will visually depict the process of study selection, including the number flow diagram, which will visually depict the process of study selection, including the number of records identified, included, and excluded, along with reasons for exclusions.

- Abstracts

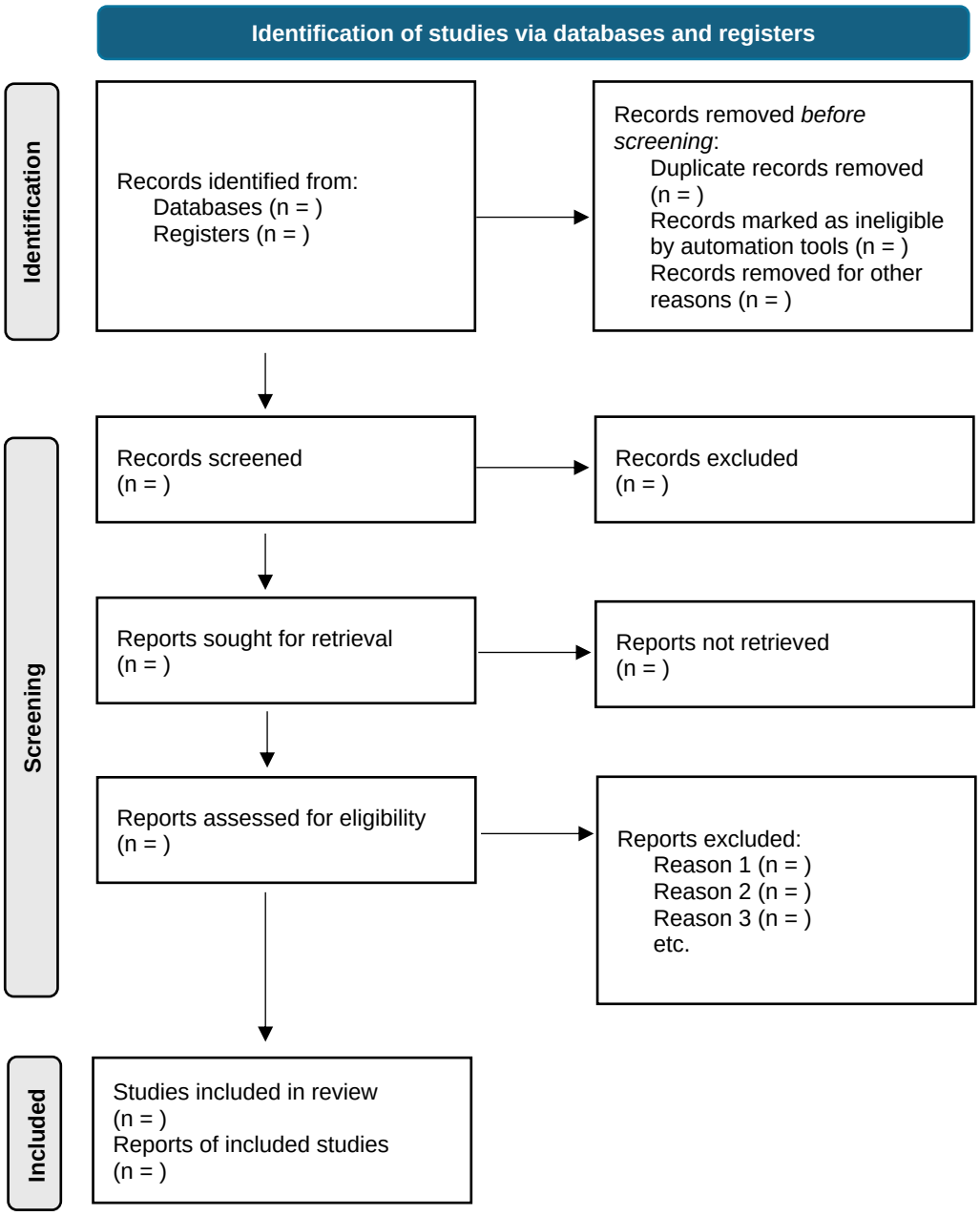
The abstracts of all identified studies will be screened independently by two reviewers. They will apply the inclusion and exclusion criteria defined by the PICOS framework. In cases where there is a discrepancy between the two reviewers, a third reviewer will resolve the conflict.

- Full Text

The full texts of selected studies will be independently reviewed in the same manner by two reviewers. Each reviewer will thoroughly assess the studies' compliance with the predefined PICOS criteria. As with the abstract screening, any conflicts in the assessment of a source will be resolved through a third opinion. The inclusion and exclusion criteria based on the PICOS framework will be strictly applied throughout this process to ensure consistency and focus.

- PRISMA

Documenting numbers screened, excluded, and reason for exclusion (Moher D. et al., 2010). – to be filled out.



4.6 Data Extraction

Data extraction will be conducted systematically using a pre-defined Excel sheet designed to capture key variables relevant to the research questions. The extraction process will focus on gathering essential information to maintain the scope of the SLR within a manageable and analytically feasible framework.

To ensure the scope of the review remains focused and manageable, the total number of variables extracted will be at most 10. This limit is set to ensure that the review remains comprehensive yet concise, avoiding unnecessary complexity and facilitating a more straightforward analysis and synthesis of the data.

All extracted data will be independently verified by a second reviewer to ensure accuracy and consistency. The data extracted will be directly relevant to the research questions posed in this review, ensuring that the analysis remains aligned with the study's objectives.

The specific data points to be extracted will be decided at a later date.

Quality Assessment

The quality of the evidence will be rigorously assessed and considered a critical factor in interpreting the results of the SLR. This assessment will help ensure that the conclusions drawn are based most reliable and valid data on the most reliable and valid data available.

5. Data Synthesis and Reporting

The data synthesis will be conducted in a structured manner to ensure that the findings are presented comprehensively and coherently. The synthesis process will involve both qualitative and, where appropriate, quantitative methods, although the primary focus will be on qualitative synthesis due to the diverse nature of the included studies.

5.1 Qualitative Synthesis

A detailed narrative synthesis will be provided, summarizing the findings across all included studies. This synthesis will aim to identify patterns, themes, and trends in the data, with a particular focus on how RWE is integrated into HTA processes. The synthesis will be organized by key topics such as the types of RWE used, the HTA bodies involved, and the outcomes of the reimbursement processes.

The synthesis will highlight findings related to global guidelines on using RWE in HTA. We will examine how different HTA agencies, such as NICE (UK), IQWiG (Germany), and HAS (France), incorporate RWE into their assessment processes. Any commonalities or significant differences in the guidelines across these organizations will be identified and discussed. This analysis will provide valuable insights into the global landscape of RWE utilization in HTA.

Successful case studies where RWE has led to favourable HTA outcomes, such as the approval or reimbursement of new therapies, will be particularly emphasized. These case studies will be presented in detail, showcasing best practices and strategies that have proven effective in real-world settings. The key factors contributing to the success of these case studies will be extracted and discussed, providing practical insights for future applications of RWE in HTA.

The qualitative synthesis will also compare the approaches and outcomes across different studies. This comparison will help identify factors that influence the effectiveness of RWE in HTA, such as the quality of the data, the methodological rigor of the studies, and the specific criteria used by HTA bodies.

5.2 Quantitative Synthesis (If Applicable)

Although the primary focus will be on qualitative synthesis, a quantitative synthesis may be conducted if sufficient homogeneity is found among the studies. This could involve pooling data using meta-analytic techniques to provide a more precise estimate of the effects of RWE on HTA outcomes. However, this will only be done if the data across studies are sufficiently comparable and if conducting a meta-analysis would add value to the review.

5.3 Data Visualization

Data visualization techniques such as thematic maps, charts, and tables will complement the qualitative synthesis. These visual aids will help to present the key findings, making it easier to understand the relationships and trends identified in the data.

5.4 Reporting of Synthesis

The findings of the data synthesis will be reported in a clear and structured format, ensuring that the key takeaways are easily accessible to readers. The synthesis will be integrated into the overall discussion of the review, linking the findings back to the original research questions and the objectives of the systematic review. The final report will be written as a collaborative effort in Microsoft Word (TM), including recommendations for future research and implications for HTA bodies. The reporting will adhere to the norm required by Nova SBE. This approach will ensure that the synthesis is both informative and directly applicable to the ongoing development and implementation of RWE in HTA processes worldwide.

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