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The Role of Real-World Evidence in Health Technology Assessment Decision-Making: Best Practices and Lessons from Successful RWE Implementation

A Systematic Literature Review

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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*

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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

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.

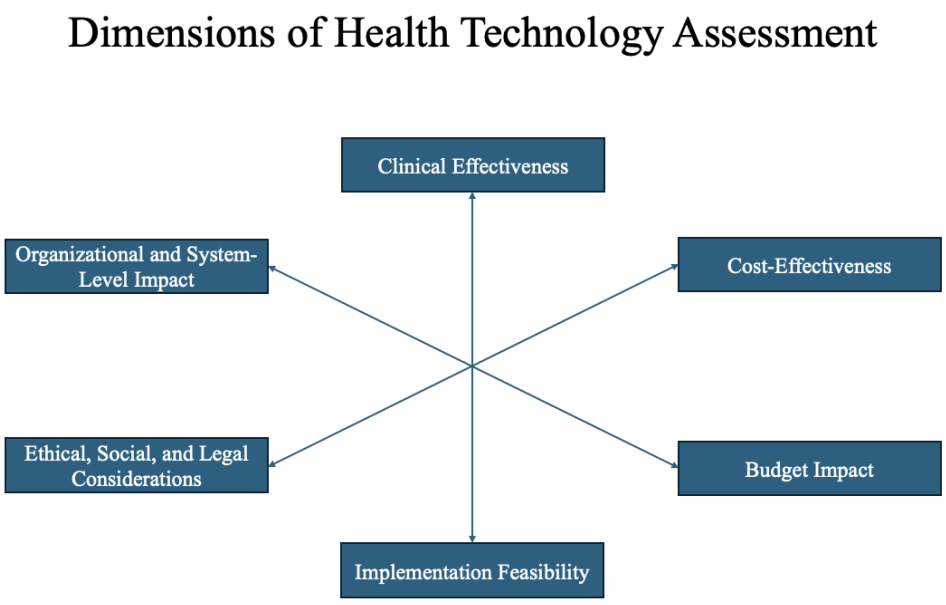

Figure 2 – Dimensions of Health Technology Assessment
Source: Constructed by author

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

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

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

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.

4.2 Research Question 2 – Tizian Müller (60559)

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?

Healthcare decision-making has traditionally relied on RCTs as the "gold standard" for evaluating the efficacy of medical interventions. Their advantage is that they achieve high internal validity through controlled conditions and randomisation, therefore ensuring minimal bias. However, their external validity is at times limited, as idealised settings and exclusion criteria often don't reflect real-world settings and limit their applicability to real-world populations (Graili et al., 2023). This shortcoming is where RWE can be implemented to great benefit. While RCTs with shorter durations are well-suited for establishing causality, particularly in early efficacy testing, RWE addresses the gaps left by RCTs, such as evaluating long-term safety and effectiveness (Graili et al., 2023). Especially in recent years, RWE has emerged as a valuable complement to RCTs in HTA. Due to its multifaceted nature, it allows data collection from various sources at relatively low costs, therefore enabling insights into the performance of interventions across diverse populations (IQVIA, 2024). This can be particularly relevant in HTAs for rare diseases or complex therapies, where traditional RCTs may be infeasible or impractical (Zisis et al., 2024).

Despite these practical benefits, RWE faces inherent challenges, including biases such as confounding and selection bias due to its observational nature. Addressing them requires robust statistical techniques, such as propensity score matching and/or target trial emulation, to enhance reliability and comparability (Graili et al., 2023). Acknowledging and addressing these challenges is critical for the successful implementation of RWE in HTA and will be closely discussed in Chapter 4.3.1.

4.2.1 Methodological Challenges in RWE for HTA

Chapter 4.3 introduced some of the challenges regarding the integration of RWE into HTA processes. This chapter will elaborate on three of the problems which the literature most often identified as major hurdles when it comes to the integration of RWE into HTA.

Data quality and consistency

The literature gathered for this review indicates that RWE in submissions to HTA bodies such as NICE and PBAC have critical issues. One recurringly mentioned challenge involves heterogeneity between populations. In their study, Appiah et al. (2024) found that among 19 NICE submissions utilising external control (EC) arms, only six provided sufficient justification for the comparability between the EC population and the SAT population (Appiah et al. 2024a). This lack of comparability undermines the robustness of treatment effect estimates (Moler-Zapata et al. 2023a). Another common issue is small sample sizes and missing prognostic variables, which are particularly problematic in rare disease contexts. Appiah et al. (2024) state that NICE observed that in 10 submissions, EC datasets lacked adequate sample sizes and excluded key prognostic factors, such as prior treatment history and baseline health status. These deficiencies increased the uncertainty of indirect treatment comparisons (Appiah et al. 2024a).

The variability in data quality and inconsistent standards for RWE submissions have profound implications for HTA decision-making. Gao et al. (2023) assessed the quality of clinical evidence submitted for government subsidy decisions on cancer medicines in Australia over 15 years. Their key findings indicated a high proportion of evidence with poor internal validity and increasing concerns about bias, particularly in indirect comparisons. This shows that poor data quality exacerbates uncertainty in assessing the comparative effectiveness of interventions, especially for

complex conditions such as cancer (Gao, Laka, and Merlin 2023). Such inconsistencies undermine the trustworthiness of RWE and reduce its utility in HTA.

Bias and confounding in non-randomized studies

In addition to data quality and consistency, the investigated literature broadly identifies bias and confounding as other substantial challenges in the effective use of RWE in HTA. As described in Chapter 4.3, RWE-based studies, unlike RCTs, inherently lack the randomisation mechanism that minimises confounding. This makes them more susceptible to systematic biases. For example, Moler-Zapata et al. (2023) identified confounding by indication. Confounding by indication arises when the choice of treatment is influenced by patient characteristics, leading to biased treatment effect estimates. In their study, Moler-Zapata et al. (2023) conducted a study on emergency surgery in which they highlighted those differences in baseline health characteristics, such as comorbidities and severity of illness, significantly influenced treatment outcomes. This confounding complicated the estimation of causal effects. As a way to address this, they employed a local instrumental variable approach, using the hospital's tendency to operate as an instrumental variable, which helped balance observed covariates while accounting for unmeasured confounders. However, the generalizability of this approach still remains limited to datasets with similar characteristics (Moler-Zapata et al. 2023a).

Similarly, to the confounding by indication highlighted by Moler-Zapata et al. (2023) other confounding issues also arise when using RWE in HTA. In their study, Appiah et al. (2024) observe that in SAT submissions to NICE, manufacturers frequently provided limited justification for the choice of EC data sources, increasing the risk of selection bias (Appiah et al. 2024a). Similarly, Buyukkaramikli et al. (2021) reported that the limited representativeness of RWE-derived control arms in MEAs often reduced their applicability across diverse healthcare settings (Buyukkaramikli,

Wigfield, and Hoang 2021b). Another example for biases in RWE was given by Thokala et al. (2020). They identified immortal time bias, where one treatment group has a guaranteed survival period before treatment initiation for heart failure. This bias skewed treatment effect estimates and serves as a good illustration of how biases can negatively influence the quality of RWE used in HTA.

Generalisability and representativeness

A significant issue with RWE lies in ensuring that the study population accurately reflects the broader patient population. Badaiki et al. (2022) highlight this challenge in their study, which used healthcare data from Newfoundland and Labrador. While it was comprehensive for its region, the dataset reflects the unique demographic and geographic characteristics of Newfoundland and Labrador, making it less representative of any broader Canadian or global populations. This limitation restricts the generalizability of findings to other contexts (Badaiki et al. 2022).

Data source heterogeneity further exacerbates these issues. RWE frequently relies on diverse datasets, including EHR, registries, and administrative claims, which are often not harmonised. This lack of standardization in data collection and reporting leads to inconsistencies in how patient characteristics, treatments, and outcomes are measured. The literature provides clear evidence that inconsistent data quality reduces the utility of findings in informing HTA (Buyukkaramikli, Wigfield, and Hoang 2021b).

4.2.2 Existing Frameworks and Standards for RWE

The review of all existing guidelines in accordance with the set PICOS criteria reveals that there has been notable progress in integrating RWE into HTA processes. However, significant differences remain between countries.

A key shared value is data quality and transparency. All investigated agencies underline the importance of high-quality, well-documented data sources to ensure reliability and reproducibility. Especially NICE, CADTH, and HAS underline the importance of high-quality, well-documented data sources to ensure reliability and reproducibility. These agencies require standardized reporting practices and detailed descriptions of data provenance to establish confidence in the validity of the evidence. Another common principle is the recognition of RWE as valuable complementary evidence to RCTs. This is particularly crucial in areas such as rare diseases, post-market surveillance, and managed access agreements. Especially HAS and IQWiG focus on the role of RWE in validating assumptions derived from clinical trials in the long term and providing evidence that reflects broader patient populations and real-world settings (IQWIG 2023),(HAS 2021b). However, as mentioned in Chapter 4.3.1, RWE is inherently prone to bias and confounding. Most guidelines, therefore, stress the importance of robust statistical techniques, such as propensity score matching and sensitivity analyses, to mitigate these issues as best as possible.

When it comes to the use of RWE in HTA, the investigated guidelines clearly demonstrate differences in their approaches. NICE introduced its RWE Framework in 2022 and provides detailed guidance on the collection, analysis, and application of RWE in decision-making. The guidelines include the use of RWE in economic modelling and managed access programs, highlighting its potential to complement traditional evidence. NICE also offers specific guidance on blending data from multiple sources, such as registries and EHRs, to construct robust external control arms and prevent biases (NICE 2022a). CADTH focuses on cross-agency harmonisation, aiming to optimise the integration of RWE into HTA and regulatory decisions. In contrast to NICE, CADTH acknowledges the challenges of harmonizing disparate data sources, its guidelines however, emphasise more practical approaches to overcoming these obstacles (CADTH 2023a).

IQWiG in Germany takes a more cautious stance. While integrating RWE into routine evaluations, it primarily uses RWE for supplementary analyses rather than as standalone evidence. IQWiG follows this rather cautious approach because, as outlined in Chapter 4.2, “Health economic evaluation of drugs according to §35b SGB V” of the IQWIG guidelines, they focus on comparative clinical effectiveness. The explanation for this is that Germany does not require cost-effectiveness analysis in its HTA processes. Consequently, clinical evidence, including RWE, plays a more significant role in decision-making. This makes the harmonisation of methodologies and the mitigation of biases even more critical in the German context (IQWIG 2023).

HAS strikes a balance between the two approaches. Its guidelines contain criteria for using RWE to reassess technologies that were already initially approved based on RCT data. Unlike the previously mentioned agencies, HAS actively incorporates RWE not only for initial evaluations but also for ongoing reassessments, ensuring the continued effectiveness of technologies in real-world contexts (HAS 2021b).

Australia’s TGA takes an approach similar to IQWiG in that TGA places a strong emphasis on post-market surveillance, using RWE mainly, to evaluate the long-term safety and performance of medical devices. This focus reflects the prioritization of monitoring ongoing outcomes rather than solely relying on pre-market evidence (TGA 2024). Ultimately, the guidelines often diverge on the topic of PROs, with some prioritising their inclusion (HAS, NICE) while others places less emphasis (IQWIG, PMDA).

Despite these advancements, there is no binding international regulation governing the use of RWE in HTA. The EMA has taken steps towards addressing this gap with its 2024 "Real-World Evidence Framework to Support EU Regulatory Decision-Making,". However, this framework is non-

binding and serves more as a reference for EU member states rather than a standardized directive. The EMA framework will be closer described in chapter 5.2.2.

4.2.3 Findings: Examples of Successful RWE Implementation in HTA

Building on the analysis in chapter 4.3.2, this chapter examines successful case studies of RWE integration into HTA, highlighting variations in methodologies and regulatory frameworks across jurisdictions. The focus will lie on Germany (IQWiG), France (HAS), and the United Kingdom (NICE), as they represent the biggest European health systems and pursue distinct approaches in their use of RWE in HTA.

Case Study: NICE (UK)

Chapter 4.3.2 highlighted how NICE underscores the importance of RWE in complementing RCTs, particularly when addressing gaps in real-world applicability and evidence generation. The case study by Thokala et al. (2020) on telemonitoring for heart failure well exemplifies this principle. The study assessed the cost-effectiveness of telemonitoring compared to standard care for heart failure patients in England, using RWD from a dataset, that provided comprehensive patient-level information on hospital admissions, lengths of stay, and discharge outcomes. The data was then used to build a Markov model.

The findings revealed that telemonitoring effectively reduced hospital admissions and mortality among heart failure patients. However, the incremental cost-effectiveness ratio of £48.172 per quality-adjusted life year exceeded NICE's conventional threshold of £20.000 , leading to a more unfavourable conclusion regarding its cost-effectiveness, since it questions the economic viability of telemonitoring (Thokala et al. 2020). The study demonstrated that using RWE, specifically administrative data, provided a locally tailored and data-driven approach to model transitions

between health states and assess the cost-effectiveness of telemonitoring. The authors specifically pointed out the advantage of using RWE for the customisation of models to reflect regional variations in hospitalisation rates and clinical practices, which would not have been feasible with RCT-derived data. RWE, in this case, clearly filled gaps that RCTs could not initially address. The case study also aligns closely with Chapter 4 of the NICE guidelines, which outlines the necessity of high-quality data and relevance to healthcare systems (NICE 2022a). The study adhered to this standard by relying on a robust administrative dataset and employing advanced analytical methods to ensure the reliability of the evidence. The case study serves as a clear example of how RWE can be successfully integrated into HTA processes.

Case Study: IQWIG/G-BA (Germany)

The second case study was conducted by Brönneke et al. (2023) and revolves around digital health applications in the German healthcare system. The German Federal Institute for Drugs and Medical Devices oversees the 'DiGA' fast-track program, which allows digital health applications to receive preliminary reimbursement even before robust evidence of their positive-care effects is fully established. Unlike traditional pharmaceuticals or hardware-based medical devices, digital health tools often evolve post-implementation, requiring a dynamic HTA approach that incorporates ongoing updates in RWE. This special procedure enables healthcare providers and insurers to iteratively refine their evaluations based on patient-centred data, aligning with the need for more flexible research designs (Brönneke et al. 2023a). Because RCTs are not feasible for each iteration of software updates and improvements in digital health applications, RWE played a critical role in addressing the evidence gaps left by RCTs. RWE is better suited for this assessment since it allows for a real-time continuous evaluation of evolving technologies without the delays

and limitations of RCTs. This way, DiGA could integrate data from diverse sources to provide a broader spectrum of insights into patient care and system-level impacts.

This approach also aligns with IQWiG's general methodological principles, as outlined in chapter 3.3.4 of the IQWIG guidelines. This case study shows how RWE is used to create a successful and dynamic HTA process that meets the challenges of evaluating digital health innovations.

Case Study: HAS (France)

As mentioned in Chapter 4.3.2, HAS emphasises the role of RWE in complementing traditional RCTs, particularly for re-evaluations of health technologies post-market. The study conducted by de Pourvourville et al. (2020) is a good illustration of this principle. The case study revolves around Dabigatran Etexilate, a direct oral anticoagulant used to prevent thromboembolic events in patients with non-valvular atrial fibrillation. It compares an ex-ante CEA based on clinical trial data (RE-LY trial) to an ex-post CEA using RWE from two post-launch studies (ENGEL-2 and SPA). The ex-post analysis relied on data from the French National Health Data System and hospital discharge databases to provide insights into real-world usage, costs, and outcomes of Dabigatran compared to vitamin k antagonists (VKAs).

The analysis revealed that Dabigatran was more effective in reducing ischemic strokes, intracranial haemorrhages, and major extracranial haemorrhages compared to VKAs. Furthermore, the RWE scenarios were cost-saving and demonstrated better effectiveness for both dosages of Dabigatran than the estimates derived from the RE-LY trial (de Pouvourville, Blin, and Karam 2020). This underscores the value of RWE in capturing real-world complexities and variabilities that RCTs might not fully address.

The Case study also aligns well with several principles outlined in the HAS methodological guide. At first, it used comprehensive and good quality data sources, as is especially outlined in chapters 2.3 and 2.4 of the HAS guidelines (HAS 2021b). Secondly, it reevaluates already marketed products post launch, which is required after five years by HAS policies and was a driving factor behind the Dabigatran ex-post analysis (de Pouvourville, Blin, and Karam 2020). Ultimately, the case study provides a relevant and context-specific outcome, because French-specific cost and utility data was used.

4.2.4 Recommendations for Methodological Improvement

Building on the synthesis of findings which can be found in chapter 5.1.2, this chapter outlines key recommendations for improving the integration and application of RWE in HTA. These recommendations are derived from the analysis of successful case studies of RWE integration.

The investigated HTA agencies emphasize the need for high-quality, transparent data, yet their approaches remain fragmented. To address this, efforts should focus on developing universal data standards and encouraging data interoperability among health systems to facilitates data sharing across platforms and countries, ensuring that RWE can be aggregated and analysed at scale. It would be advisable that a supranational agency, such as the EMA, lead such efforts, since, as discussed in chapter 4.7, it has already published a first document towards a similar end.

Chapter 4.3.1 explains how RWE is inherently prone to biases. To mitigate these challenges, all HTA bodies should adopt advanced analytical techniques and promote best practices.

Chapter 4.3.2 has illustrated, that traditional HTA models at times fail to accommodate the evolving nature of healthcare technologies, particularly digital health innovations. Therefore, all HTA bodies should require ongoing data collection post-market approval to continuously validate

and refine evidence on safety, effectiveness, and cost-efficiency. Also, regular reassessments, as practiced by HAS in France, should be mandated to ensure that RWE reflects current clinical practices and healthcare environments.

Ultimately, the literature review shows that RWE offers unique opportunities to capture patient-reported data and real-world quality-of-life metrics, which are often underrepresented in RCTs. To maximize the value of RWE to healthcare recipients, HTA bodies should standardize PRO data collection and establish clear guidelines for incorporating patient-reported outcomes into RWE studies, ensuring their validity and comparability. Efforts should also be made to include underrepresented populations in RWE studies to enhance generalizability and equity in healthcare decisions.

5. Discussion

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 Key Findings & Implications for HTA Decision-making

5.1.1 Key Findings – Research Question 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?

The synthesis of findings presented in this chapter accounts for all sources from the comprehensive review of guidelines, literature, and case studies, which are discussed in previous chapters. While

Chapter 4.6 focused on analysing individual guidelines and cases, this synthesis consolidates the evidence to answer the central research question stated in Chapter 4.3.

The literature clearly reveals a shared recognition of the value of RWE as a complementary source of evidence to RCTs. All HTA bodies agree on the critical importance of data quality, transparency in methodologies, and robust measures to mitigate biases and confounding factors. These shared principles indicate a universal commitment to integrating RWE into HTA to enhance decision-making. However, despite these commonalities, the guidelines diverge in several key areas, often reflecting differences in healthcare systems, regulatory priorities, and HTA objectives. One major difference is the scope of RWE application: Some agencies emphasise the use of RWE for post-market reassessments of already approved technologies (HAS), while others focus on its role during initial evaluations (NICE). For instance, guidelines differ on whether RWE should primarily supplement RCTs or serve as standalone evidence in specific contexts such as rare diseases or digital health technologies. Agencies also vary in their expectations for the types of data sources considered acceptable, with some requiring comprehensive administrative datasets and registries (NICE), while others accept broader data inputs such as patient-reported outcomes (TGA). Additionally, the level of methodological rigour demanded differs between jurisdictions. Ultimately, certain agencies integrate RWE directly into cost-effectiveness and budget impact analyses (CADTH), while others restrict its use to clinical effectiveness assessments, excluding economic considerations altogether (IQWIG/G-BA).

The analysis of case studies demonstrates how RWE has been effectively and successfully integrated into HTA, providing valuable insights and improving decision-making. However, the literature also reveals reoccurring challenges such as data heterogeneity, bias and lack of standardisation, which are described in Chapter 4.3.1.

These divergences and challenges reflect the broader challenge of harmonising RWE integration globally as agencies tailor their approaches to fit national contexts and priorities. While the absence of a unified standard allows for flexibility, it also creates barriers to international collaboration and comparability of findings. The EMA published a framework, though non-binding, which offers a potential pathway for harmonising practices across jurisdictions. However, the literature clearly shows that variability in data sources, methodologies, and objectives among HTA agencies often calls for tailored frameworks that respect local healthcare contexts while adhering to universal standards of evidence quality (EMA 2024b).

5.2 Collaborative Discussion

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

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 7 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 8 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*

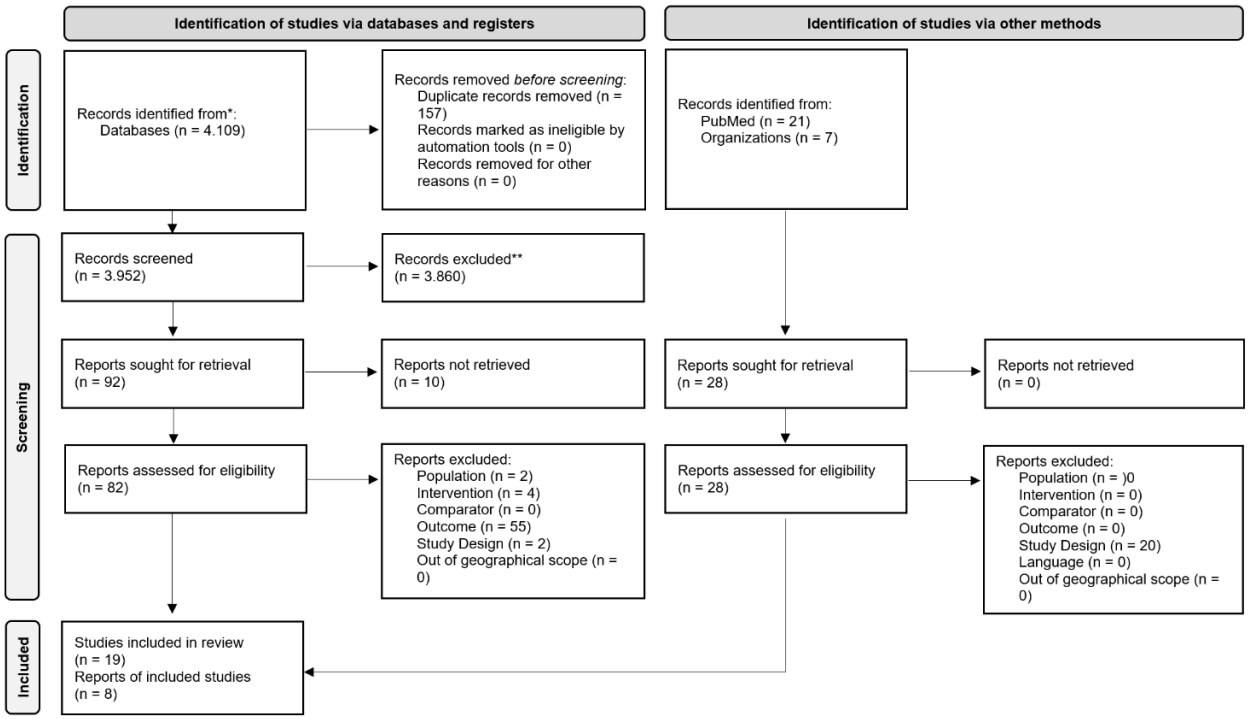
6	*UULVHFL9*	*Nabarette, Hervé; Chastenay, Marie-Hélène; Dupont, Jean-Claude K.; Ganache, Isabelle; Single, Ann N. V.*	*Patient and citizen participation at the organizational level in health technology assessment: an exploratory study in five jurisdictions.*	*2023*
7	*XRBV3H64*	*Buyukkaramikli, Nasuh 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

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2024

Tables and Figures

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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

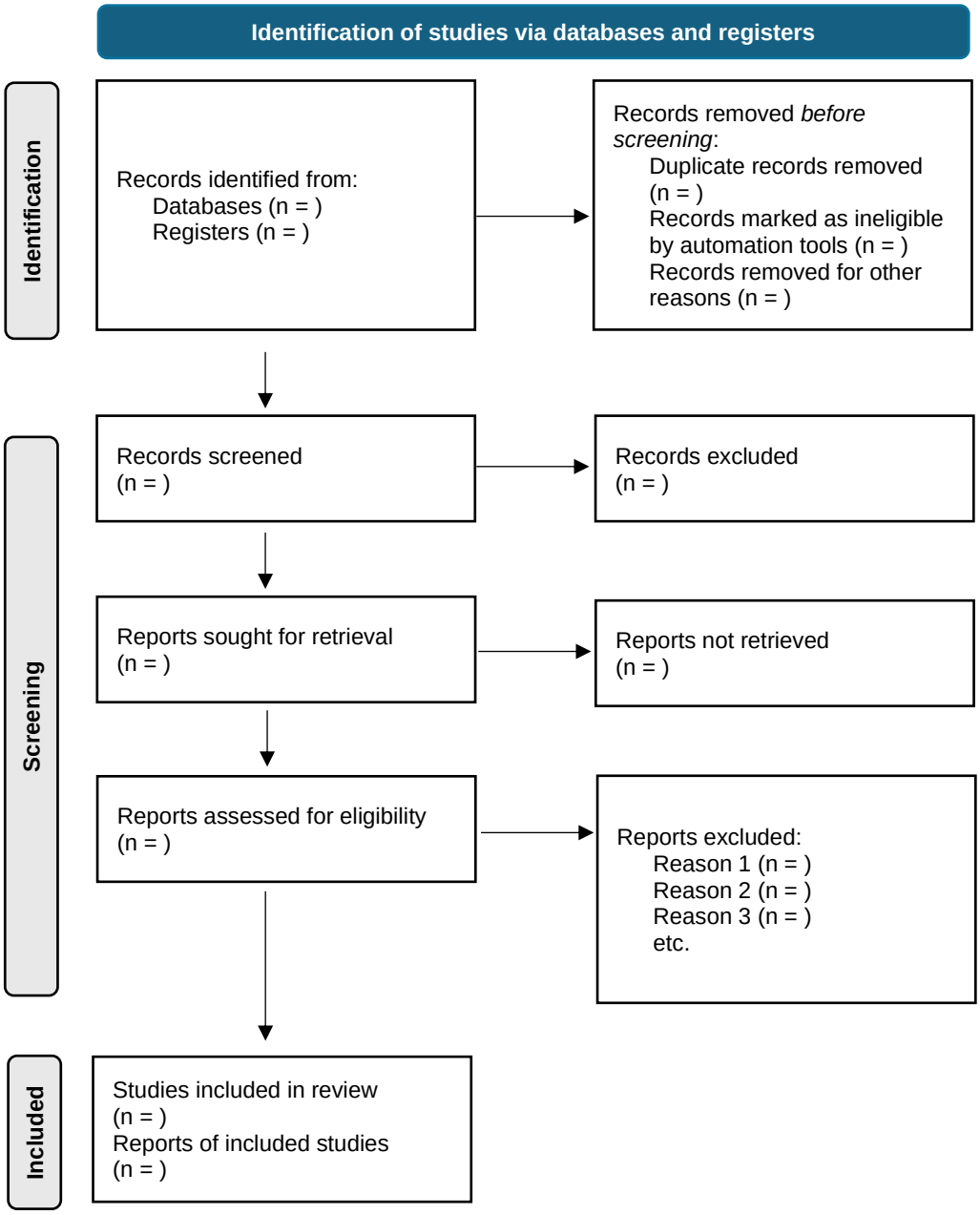
The abstracts of all identified studies will be screened independently by two reviewers. They will apply the inclusion and exclusion criteria defined by the PICOS framework. In cases where there is a discrepancy between the two reviewers, a third reviewer will resolve the conflict.

- 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.

Appendix G: Group Members Individual Parts

Research Question 1 – Sophie Spilles (59521)

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?

Incorporating RWE into HTA processes is crucial in influencing healthcare and reimbursement decisions across various healthcare systems. This study examines the factors influencing the integration of RWE into HTA processes across different countries and healthcare systems, as well as the implications for decision-making outcomes such as reimbursement approvals. Comprehending these characteristics is crucial to advancing the use of RWE to connect clinical trials with real-world clinical practice, improving the inclusivity and dependability of HTA frameworks (Higgins et al. 2021; Grimm et al. 2020a).

Globally, RWE is increasingly recognised as an essential complement to traditional evidence sources such as RCTs. The use of RWE in HTA varies significantly and is influenced by factors such as legal frameworks, methodological challenges, data quality, and stakeholder trust. While organisations like NICE in the UK promote the utilisation of RWE through organised frameworks, other HTA organisations, such as IQWiG in Germany, are hesitant due to concerns regarding potential biases in observational data (Norburn and Thomas 2020; Ciminata et al. 2022). These variations not only highlight the importance of analysing methodologies used by different healthcare systems in incorporating RWE but also display insights that can be gained to standardise evidence standards and improve decision-making (Mitchell 2020b).

This section analyses the main elements affecting RWE integration, emphasising stakeholder trust and acceptability, data quality, economic and ethical issues, and the significance of regulatory frameworks. These elements offer an extensive perspective on the global challenges and prospects of incorporating RWE into HTA processes.

Stakeholder Trust and Acceptance

As mentioned above, incorporating RWE into HTA processes significantly depends upon stakeholder trust and acceptance. This trust differs among countries and healthcare systems and is influenced by opinions of the utility and reliability of RWE and the methodological frameworks employed for its assessment. Key stakeholders, such as regulatory agencies, healthcare providers, and patients, play a decisive role in determining whether RWE is used in HTA decision-making processes (Grimm et al. 2020a).

Uncertainty in HTA complicates decision-making processes. These uncertainties must be acknowledged to avoid biased evaluations, resulting in suboptimal decisions. These decisions may cause missed opportunities or potential health benefits that could be realised through additional evidence. The TRUST tool was developed as part of a joint initiative to improve transparency in health economic modelling. It facilitates the systematic identification, assessment, and reporting of uncertainties in these models and promotes more informed and transparent decision-making when faced with uncertainty. The TRUST framework is designed to enhance transparency and address uncertainties, which is crucial for building trust in RWE methodologies (Grimm et al. 2020a).

NICE has developed an RWE Framework that provides structured guidelines for integrating RWE. The framework fosters trust among regulatory bodies and stakeholders. Additionally, the shift to computable biomedical knowledge represents a significant innovation in standardising evidence

use. The guidelines NICE highlights that structured data and knowledge are crucial to enabling the concepts of a continually learning healthcare system (Mitchell 2020b).

Additionally, NICE guidelines stress the value of patient involvement in HTA and highlight patients' unique perspectives and experiences to the HTA committee. Through continual development, expansion, and evaluation of our patient involvement methods in HTA, NICE has ensured that patient involvement in HTA is complete and adequate and that the views and experiences of those most affected by the technologies and conditions we are considering are strongly heard (Norburn and Thomas 2020).

Although RWD presents prospects to enhance RCTs in HTA, scepticism persists among stakeholders. IQWiG emphasises that observational data frequently fails confounders, making it inappropriate for evaluating treatment effects. An observed difference in health outcomes between two groups of patients could be causally related to treatment but could also be unknown differences in patient characteristics. This doubt illustrates the difficulties in establishing faith in RWD when the evidence lacks transparency and rigour. To mitigate these problems, IQWiG promotes the incorporation of RWE into RCTs, their "gold standard." This methodology integrates the systematic precision of trials with the practical relevance of RWD, alleviating stakeholder concerns over evidence reliability while upholding stringent criteria for decision-making. These innovations are crucial for cultivating trust and guaranteeing confidence in HTA processes (IQWiG 2023a).

In contrast, NICE addresses these concerns by emphasising RWE's complementary role, particularly for long-term outcomes and rare diseases. Its RWE Framework promotes advanced statistical methods and transparency, offering a scalable solution without fully integrating RWE into RCTs (NICE 2022).

Data Availability and Quality

The availability and quality of healthcare data are fundamental to generating reliable RWE for HTA. Countries with centralised and well-structured data systems, such as the UK, exemplify the potential for consistent RWE generation, while nations like Germany face challenges due to fragmented systems. Additionally, ensuring methodological rigour in observational studies is critical to addressing biases and maintaining data reliability.

The United Kingdom's healthcare system demonstrates the potential of centralised data infrastructures for generating high-quality RWE. Centralised health services facilitate the integration of data from various sources, such as primary care, hospitals, and pharmacies, enabling robust analyses that inform HTA processes. This structure supports comprehensive evaluations that enhance decision-making and cost-effectiveness assessments, as evidenced by frameworks like NICE's RWE Framework (NICE 2023).

In Germany, data fragmentation presents significant challenges for generating consistent and reliable RWE. The decentralized nature of its healthcare data systems restricts the ability to conduct longitudinal analyses, limiting the robustness of RWE in HTA. IQWiG highlights these limitations, noting that data fragmentation makes it difficult to establish causality and incorporate RWD into evidence frameworks. While RCTs remain the gold standard for IQWiG, the organization acknowledges that RWE can complement these trials under stringent conditions (IQWiG 2022).

In addition to systemic challenges, observational data often face methodological issues such as biases and confounding factors that can undermine reliability. Techniques like propensity score methods are essential for addressing these challenges. Propensity score matching and inverse

probability weighting help to ensure comparability between treatment groups, improving the validity of observational data for HTA (Ciminata et al. 2022).

As mentioned above, frameworks like the TRUST tool also address uncertainties in health economic models by promoting transparency and rigor. By systematically quantifying and managing uncertainties, the TRUST tool ensures that RWE meets the high standards required for HTA decision-making (Grimm et al. 2020a).

Efforts to harmonise healthcare data systems, such as the European Health Data Space (EHDS), provide a promising pathway to reduce fragmentation and enhance RWE consistency across member states. The EHDS initiative aims to improve data availability and reliability for HTA applications by fostering interoperability and creating standardized frameworks for data sharing (European Commission 2024).

In conclusion, robust data systems like those in the United Kingdom demonstrate the value of centralised infrastructures for generating high-quality RWE. In contrast, Germany's fragmented systems underscore the importance of harmonization efforts. Addressing systemic and methodological challenges is essential for advancing the integration of RWE into global HTA frameworks.

Economic, Ethical, and Equity Considerations

Integrating RWE into HTA processes presents key economic, ethical, and equity considerations.

First, economic considerations are integral to integrating RWE into HTA frameworks. Managed Entry Agreements (MEAs), including performance-based and financial arrangements, address uncertainties surrounding the cost-effectiveness of new therapies. Therefore, MEAs reduce risks

for healthcare systems, particularly in high-cost interventions, by linking reimbursement to clinical or economic performance evidence. NICE focuses on financial arrangements in the UK, such as discount schemes. These are essential tools for improving patient access to innovative therapies while keeping budgetary control in mind. This approach emphasises the importance of RWE in minimising decision-making uncertainty during the early adoption of new treatments (Buyukkaramikli, Wigfield, and Hoang 2021a).

Second, ethical problems often arise when ensuring that RWE facilitates inclusive evaluations of diverse patient populations. In contrast to RCTs, which may overlook underrepresented populations, RWE enables assessments across a broader range of demographic and clinical contexts. The TRUST tool offers a framework for managing ambiguity, enhancing honest reporting, and assuring equitable evaluations of treatment benefits across diverse groups (Grimm et al. 2020a).

Finally, from an equity standpoint, RWE significantly supplements RCTs in HTA processes by facilitating assessments of real-world healthcare provision across diverse socio-economic environments. For example, patient involvement frameworks, like those utilised by NICE, guarantee that the viewpoints of individuals most impacted by health technologies are considered in decision-making. NICE improves the inclusion and equity of HTA processes, linking them with overarching public health goals (Norburn and Thomas 2020). Incorporating equity problems corresponds with global trends aimed at standardising HTA processes. Initiatives such as the EHDS seek to provide uniform frameworks for data exchange, minimising diversity in evidence collection and implementation across governments. These initiatives are essential for tackling healthcare access and outcomes disparities while facilitating comprehensive HTA evaluations worldwide (European Commission 2024).

In summary, economic strategies such as MEAs, ethical frameworks for inclusive evaluations, and equity-centered initiatives illustrate the multifaceted influence of RWE on HTA processes. By focusing on cost-effectiveness, openness, and inclusivity, RWE improves HTAs' ability to guide sustainable and equitable healthcare decision-making worldwide.

Regulatory and Guideline Frameworks

Various regulatory regimes and international harmonization efforts influence the incorporation of RWE into HTAs. These frameworks offer methodological advice while tackling issues with data quality, stakeholder acceptance, and cross-border discrepancies in evidence standards.

In Europe, EUnetHTA is a crucial entity in harmonisation initiatives, advocating for unified methodologies via its HTA Core Model. This framework prioritises transparency and uniformity in data usage to minimise duplication and variability in HTA processes among member states (EUnetHTA 2016). The EHDS enhances existing initiatives by promoting interoperability and standardising data sharing across jurisdictions (European Commission 2024a). Germany adopts a sensible approach to RWE integration. The G-BA and IQWiG highlight the significance of RCTs as the "gold standard" while recognising the potential of RWE under rigorous methodological criteria. IQWiG's General Methods Version 7.0 defines specific criteria for integrating RWE into HTA processes, facilitating reliable decision-making (IQWiG 2023c). HAS integrates RWE into its assessments via registry-based studies and pragmatic trials in France. The HAS recommendations emphasise the importance of RWE in fulfilling unmet clinical requirements, particularly for rare illnesses, and underscore methodological issues for real-world studies in HTA (HAS 2021a). Sweden's TLV adopts a balanced strategy, utilising RWE to enhance RCTs, especially in assessing breakthrough medicines and medical technologies. TLV underscores transparency in its procedures, as detailed in its 2021 report on innovative treatments (TLV 2021).

NICE has excelled in incorporating RWE into HTA processes in the UK. NICE's RWE Framework, underpinned by centralised data systems such as the NHS, emphasizes stakeholder engagement and rigorous methodological criteria to guarantee the dependability of RWE in decision-making (NICE 2022c).

Canada's CADTH underscores the significance of RWE in post-market assessments. The 2023 guidance emphasises the significance of patient-reported outcomes and real-world clinical data in mitigating uncertainties and facilitating payment choices (CADTH 2023b).

The Department of Health and Aged Care incorporates RWE into its HTA processes to improve equity and transparency in Australia. Recent guidance emphasises the necessity of addressing the requirements of underrepresented populations and implementing comprehensive reporting processes for RWE (Department of Health 2024).

Finally, Japan's PMDA implements RWE for early access routes and post-market monitoring. The agency utilises EHR and insurance data to reconcile prompt therapy access with rigorous safety oversight (PMDA 2014).

Despite progress, cross-border discrepancies in the use of RWE still need to be addressed. Initiatives such as the EHDS seek to unify data frameworks, diminish inequalities in evidence collection, and foster uniform HTA evaluations worldwide (European Commission 2024a). In conclusion, frameworks such as EUnetHTA, in conjunction with national organizations like NICE, HAS, and IQWiG, illustrate the capacity for unifying the inclusion of RWE into HTA. These frameworks strengthen the legitimacy and inclusivity of HTA conclusions by mitigating uncertainty and assuring methodological rigour.

Agency	Framework / Approach
Europe (EUnetHTA)	Unified methodologies via the HTA Core Model, focusing on transparency and standardization
Germany (G-BA/IQWiG)	RCTs as the "gold standard"; RWE included under strict criteria
France (HAS)	Registry-based studies and pragmatic trials, particularly for rare diseases.
Sweden (TLV)	RWE complements RCTs for breakthrough medicines; emphasizes transparency.
UK (NICE)	RWE Framework supported by NHS data; promotes rigorous methods and stakeholder engagement.
Canada (CADTH)	Patient-reported outcomes emphasized in post-market assessments to reduce uncertainties.
Australia (Dept. of Health)	Equity-focused integration of RWE, addressing underrepresented populations.
Japan (PMDA)	EHRs and insurance data used for early access and post-market safety monitoring.

Figure 7 9 - Integration of RWE into HTA Frameworks by Country

Source: Constructed by author

Implications for Decision-Making Outcomes

RWE substantially impacts reimbursement decisions, especially when RCTs yield insufficient data. MEAs have emerged as a crucial tool in resolving issues related to the cost-effectiveness of novel medicines. MEAs, encompassing financial and performance-based agreements, seek to guarantee prompt access to new therapies while mitigating economic risks for healthcare systems. The European Journal of Health Economics emphasises that MEAs frequently mitigate financial uncertainty, especially in oncology, and are crucial for enhancing patient access to expensive medicines (Buyukkaramikli, Wigfield, and Hoang 2021a). Likewise, the General Methods Version

7.0 from IQWiG underscores rigorous methodological standards for the inclusion of RWE, so ensuring its dependability in augmenting RCTs during reimbursement evaluations (IQWiG 2023c).

The HAS of France utilises RWE via registry-based studies to improve the assessment of therapy efficacy for rare diseases and high-priority ailments. The agency emphasises the significance of RWE in fulfilling unmet clinical requirements, especially when clinical trials do not accurately reflect real-world conditions (HAS 2021a). In Sweden, TLV employs RWE to enhance reimbursement determinations for new medicines, reconciling innovation with economic viability (TLV 2021). NICE in the UK emphasises the significance of RWE in addressing uncertainties in assessments, especially via its Cancer Drugs Fund, which employs RWD to reassess medications after their debut (NICE 2023).

Furthermore, RWE promotes fairness in healthcare by catering to the needs of diverse populations sometimes marginalised in conventional clinical trials. It facilitates the evaluation of interventions among diverse demographic and socio-economic groups, promoting equitable decision-making. Frameworks such as NICE prioritise patient engagement, ensuring the incorporation of viewpoints from marginalised populations into HTA processes, thus fostering inclusivity (Norburn and Thomas 2020). Australia's Department of Health utilises RWE to tackle disparities in Indigenous healthcare, emphasising its capacity to close gaps in healthcare access (Department of Health 2024).

Ethical considerations are paramount, especially in evaluating treatments for uncommon diseases or marginalised populations. The TRUST tool offers a framework for transparent decision-making, methodically addressing uncertainties in real-world studies to maintain equity in HTA evaluations (Grimm et al. 2020a). The EHDS aims to standardize data exchange among member states,

mitigating disparities in evidence generation and guaranteeing uniform access to breakthrough therapies (European Commission 2024).

In summary, RWE significantly influences HTA decision-making by resolving reimbursement ambiguities, promoting equity, and maintaining ethical standards. By combining many data sources and rigorous analytical frameworks, RWE enhances HTA processes, facilitating more inclusive and sustainable healthcare policy worldwide.

Summary and Transition

Multiple factors shape the incorporation of RWE into HTA processes, including stakeholder trust, data quality, economic and ethical considerations, and country-specific regulatory frameworks. These factors influence how RWE complements traditional RCT-based evidence. For instance, the UK and Sweden integrate RWE systematically, while Germany emphasises RCTs as the gold standard, reflecting trust and data infrastructure differences.

Economic and ethical considerations are critical, as RWE fills gaps in RCTs by providing real-world insights and promoting inclusivity. Data fragmentation, methodological inconsistencies, and scepticism persist, highlighting the need for harmonised frameworks like the EHDS to standardize evidence, promote equity, and improve HTA reliability.

In conclusion, integrating RWE into HTA requires balancing rigour, stakeholder engagement, and collaboration. Addressing these factors will maximise RWE's impact on decision-making, such as reimbursement approvals, and drive the evolution of global HTA frameworks.

Research Question 3 – Nina Ströhmer (60541)

What are the key methodological challenges in developing robust RWE for HTA decision-making, and how do different health systems address these challenges?

Robust data forms the foundation of every study, and RCTs remain one of the most reliable methods for generating high-quality evidence in controlled environments. While RCTs provide valuable insights, they are often limited to short-term outcomes. In contrast, RWE offers the potential to uncover insights about long-term effects and real-world applicability, which has led to its increasing integration into HTA processes. However, incorporating RWE into HTA requires the use of robust methodologies to ensure its relevance and reliability over time. As highlighted by the reviewed literature and existing guidelines, achieving this robustness in real-world settings is not always straightforward. Given the growing reliance on RWE in HTA decision-making, it is crucial to address the methodological challenges associated with its development and application.

The following sections examine four key methodological challenges involved in building robust RWE for HTA. Additionally, the responses of international health systems to these challenges will be evaluated. The theoretical background concerning definitions and characterizations is outlined in Chapter 2. Furthermore, to address the research question, only studies and guidelines meeting the predefined PICOS criteria have been included.

Identification & analysis of key methodological challenges in developing robust RWE for HTA

The following section identifies and analyses four key methodological challenges frequently discussed in the literature. It is important to highlight that other challenges also exist, such as

variability in evidence requirements across systems, context-specific challenges, regulatory and ethical considerations, and stakeholder engagement.

First Key Methodological Challenge: Data Quality and Validity

A significant key methodological challenge identified in the literature regarding the development of robust RWE for HTA decision-making is the necessity to ensure that the RWD used possesses high quality and validity transparency. Given that RWE is fundamentally dependent on RWD, it often suffers from inconsistencies, incompleteness, and susceptibility to errors, as this data is typically gathered in non-research settings, including EHRs, claims data, or patient registries (National Institute for Health and Care Excellence 2022; Haute Autorité de santé 2021; Therapeutic Goods Administration 2024). For instance, the case study conducted by Brönneke et al., published in 2023 and focusing on the context of Germany, highlights that data for digital health applications (DiGA) frequently depends on various RWD sources, such as patient-generated data, claims data, and EHRs. However, these sources may exhibit challenges related to data completeness, consistency, and reliability. For DiGA listed in Germany's registry, the preliminary evidence may often rely on retrospective studies or incomplete datasets, posing challenges to the validity of conclusions drawn regarding their effectiveness (Brönneke et al. 2023b). A further challenge regarding data quality and validity is to ensure the accuracy and reliability of patient-reported data that have been generated using technology tools like public web-based forums that are accessible to (Kalf et al. 2021a). The case study by Moler-Zapata et al. (2023) focuses on the application of the target trial framework to RWD to enhance the quality and reliability of RWE for HTA in the United Kingdom. It underscores the importance of clearly defining eligibility criteria, treatment strategies, and outcomes in RWD studies to improve data integrity and minimise errors. By

systematically adopting the target trial framework, these challenges can be effectively addressed by emulating the rigour of RCTs (Moler-Zapata et al. 2023b).

Second Key Methodological Challenge: Data Heterogeneity

Another key methodological challenge occurs due to the fact that RWD is generated from diverse sources that have their own structure, format, and data collection practices, which leads to significant heterogeneity. Similarly to this finding, due to the dynamic nature of digital health solutions such as the previously mentioned DiGA, heterogeneous datasets can be a result of the varying patient populations, health conditions, and usage patterns. This variability poses challenges for comparing outcomes across systems and integrating data into cohesive analyses (Brönneke et al. 2023b). A further challenge is to manage diverse data formats and to channel the varying levels of detail in patient reports (Kalf et al. 2021a). The target trial framework presented in the study by Moler-Zapata et al. (2023) offers flexibility to adapt to heterogeneous data sources while maintaining methodological rigour through defined data extraction and harmonisation processes (Moler-Zapata et al. 2023b).

Furthermore, the dynamic nature of RWD collection can result in delays in evidence generation, complicating the provision of timely assessments, which can lead to data heterogeneity. Such potential delays may additionally impede the integration of RWE into policy decisions, particularly regarding innovative approaches. The findings of the study by Moler-Zapata et al. (2023) illustrate the danger of the so-called time zero. For clarification, this term refers to the time difference between the assigned treatment and the eligible assessment time, as well as the actual start of the follow-up, and demonstrates the danger of immortal time bias (Moler-Zapata et al. 2023b).

Third Key Methodological Challenge: Study Design and Methodological Rigor

A further significant key methodological challenge emerges in the literature concerning study design and methodological rigour in the context of RWE. While RWE is pivotal for dynamic HTA, observational studies, which are a primary source of such evidence, are inherently prone to selection bias and confounding variables due to the absence of the controlled environments that characterise RCTs. Moreover, the choice of a qualitative or quantitative research design critically influences the reliability and applicability of study results. As Nicod et al. (2020) argue, the established framework, as well as the relationships and interactions among factors, are also essential considerations for ensuring robust outcomes (Nicod et al. 2020). Adding to this complexity, HTA agencies often employ divergent methodological approaches, posing a challenge to the universal applicability of RWE. Nicod et al. (2020) provide an illustrative example, demonstrating how a lack of consensus on economic evaluation thresholds, such as incremental cost-effectiveness ratios (ICERs), and the fragmented integration of patient-reported outcomes lead to inconsistencies in HTA processes. This divergence is particularly evident in the differing approaches of international health systems, such as NICE and TLV, to pricing and reimbursement for similar drugs (Nicod et al. 2020).

To address these challenges, Brönneke et al. (2023) emphasise the necessity of employing robust analytical techniques to mitigate bias. For instance, the mentioned before DiGA framework in Germany provides flexibility by accommodating retrospective study designs. However, this flexibility also increases the risk of less rigorous methodologies, underscoring the need for stringent safeguards in analytical processes (Brönneke et al. 2023b).

In addition, the case study by Moler-Zapata et al. (2023) highlights the substantial impact of confounding factors when inadequately addressed, which can distort causal relationships between treatments and outcomes. Their research illustrates how the target trial framework can mitigate bias

effectively. By incorporating essential design elements, such as clearly defining the study population, intervention strategies, establishing a consistent ‘time zero’, and making appropriate adjustments for confounders, this framework provides a pathway to greater methodological rigor (Moler-Zapata et al. 2023b).

Further, Nicod et al. (2020) employed a mixed-method design, combining quantitative and qualitative approaches to provide a comprehensive overview of the HTA decision-making process. Their findings reveal that HTA bodies manage uncertainty differently, with some accepting higher degrees of uncertainty for specific medical goods, such as, for example, in this case study, orphan drugs, while others demand more robust evidence. These differences underline the context-dependent variability in HTA methodologies (Nicod et al. 2020). Resource constraints also present an additional challenge, as meaningful engagement of patients and citizens necessitates considerable time, funding, and personnel (Nabarette et al. 2023).

The Transparent Uncertainty Assessment Tool (TRUST), discussed by Grimm et al. (2020), offers a systematic framework for identifying, assessing, and communicating uncertainties in health economic decision models. Therefore, TRUST classifies uncertainties into parameter uncertainty, structural uncertainty, and methodological uncertainty, with the latter stemming from variations in analytical methods, such as discount rates or time horizons. Those parameters are particularly relevant for RWE due to its reliance on heterogeneous and often incomplete RWD. In addition, the study highlights ‘bias and indirectness’ as critical sources of uncertainty, reflecting limitations in the internal validity of non-randomized or observational data in the context of TRUST. Furthermore, TRUST also emphasises methodological uncertainties, such as deviations from best practices or assumptions in extrapolating RWD and recommends scenario analyses or expert elicitation to address their impact. By incorporating techniques like probabilistic sensitivity

analyses (PSA) and promoting transparency, TRUST helps decision-makers to understand RWE's limitations better and enhances the reliability of health economic evaluations (Grimm et al. 2020b).

Fourth Key Methodological Challenge: Integration with Traditional Evidence Frameworks

Another key methodological challenge that is highlighted in diverse literature is that aligning RWE with traditional HTA frameworks, which rely heavily on RCTs, is difficult due to differences in study design, objectives, and outcomes. This leads to limits on the acceptance and utility of RWE in HTA decision-making. The absence of universal methodologies for integrating RWE into HTA processes causes variability in evidence quality and acceptance across stakeholder jurisdictions (Nicod et al. 2020).

The article from Brönekke et al. (2023) discusses the challenges of integrating RWE into traditional HTA frameworks, which are often designed for static assessments based on RCTs. The dynamic and iterative nature of the aforementioned DiGA evaluation requires ongoing adaptation of HTA methods as products evolve, which is challenging to align with traditional, one-time HTA processes (Brönneke et al. 2023b). The same difficulty can be seen in the case study by Kalf et al. (2021), which has shown that it can be challenging to incorporate qualitative patient-reported data into conventional HTA models that prioritize quantitative data (Kalf et al. 2021a). The idea of adopting the target trial emulation methodology makes it possible for HTA bodies to establish a standardized approach to using RWD, ensuring consistency in evidence generation (Moler-Zapata et al. 2023b). Furthermore, the target trial framework bridges the gap between RWE and RCTs by incorporating RCT principles into observational study designs, making RWE more comparable to traditional evidence (Moler-Zapata et al. 2023b).

Evaluation of the responses of international health systems to address these key methodological challenges

The following section analyses the responses from international health systems in their guidelines, such as NICE, IQWiG, and HAS, regarding the above-analysed key methodological challenges. The three health institutions that have been chosen are NICE, IQWiG, and HAS, which represent some of the most well-established and influential HTA bodies globally, with robust frameworks for evaluating health technologies. Furthermore, each institution employs distinct methodologies for evidence evaluation, reflecting different healthcare systems' needs and priorities. In addition, these agencies span diverse healthcare systems across Europe, offering a balanced representation of regulatory environments, from centralised to more federalised systems. It has to be mentioned that other big global health systems, such as the Canadian CADATH or the Swedish TLV, also respond with their guidelines toward the key methodological challenges of RWE in HTA decision-making. Due to the page limitation of this work, the focus for answering this research question is on NICE, IQWiG, and HAS.

Response from the German IQWiG

IQWiG focuses more on the 'gold-standard' RCTs than on RWE in their guidelines. IQWiG, in some cases, incorporates high-quality observational data when necessary to complement RCTs (IQWiG 2023b). Furthermore, IQWiG uses systematic reviews and meta-analyses to ensure methodological rigour (IQWiG 2023b). Overall, IQWiG is rather conservative in its use of RWE, placing greater emphasis on high-quality RCTs. RWE is typically used to complement RCTs, not as primary evidence. The strengths of IQWiG lie in its high emphasis on internal validity. The internal validity in assessing and evaluating IQWiG processes relies on robust evidence-based medicine, which is essential for minimising bias and ensuring reliable results. A further tool to

emphasise internal validity, IQWiG discusses strategies to mitigate reporting bias and uses standards for selecting studies, whereby only those with high internal validity are considered to ensure the credibility of conclusions. This approach allows IQWiG to maintain the credibility and transparency of its methodologies while facilitating the cautious integration of RWE (IQWiG 2023b). In comparison to HAS and NICE, RWE is minimally used.

Response from the UK NICE

In comparison to IQWiG, NICE uses RWD and RWE in their decision-making and at all stages of HTA. The aim is thereby "to use RWD to resolve gaps in knowledge and drive forward access to innovations for patients"(National Institute for Health and Care Excellence 2022, 113). Furthermore, RWE is used to complement traditional evidence, especially in areas where RCTs are unavailable or insufficient and, therefore, face the key methodological challenge of data quality and validity. More in detail, NICE encourages the use of pragmatic trials combining RWE with RCT elements and ensures that the data is of good provenance, sufficient quality, and relevant to the research question of the decision-making. Furthermore, NICE uses the so-called Data Suitable Assessment Tool (DataSAT) to evaluate the data's relevance, quality, and representativeness (National Institute for Health and Care Excellence 2022). Due to the focus on structured quality checks, provenance verification, and data curation practices, transparency regarding the study reporting in the context of quality assessment and limitation of datasets can be encouraged. These measures ensure that RWE is robust and credible for informing HTA recommendations. In addition, NICE's RWE Framework aligns with its health technology evaluation manual, which standardises evidence requirements across programs, and different types of evidence are accepted depending on contextual factors like disease prevalence or intervention type (National Institute for Health and Care Excellence 2022). Regarding the key methodological challenge of integration with traditional

evidence frameworks, NICE developed a RWE framework to overcome those gaps and to support the decision-making process, which has been illustrated in this SLR in Chapter 2.1.3, in its steps of planning, conducting, and reporting (National Institute for Health and Care Excellence 2022). Due to this guidance, it is possible to tailor the RWE collection and to analyse the specific program needs. Furthermore, managed access agreements are used to address uncertainties through additional data collection (National Institute for Health and Care Excellence 2022). As a result, NICE addresses the challenge of the variability in evidence requirements across systems and ensures consistency while accommodating program-specific requirements.

Regarding the key methodological challenge of the handling of data heterogeneity, NICE encourages combining heterogeneous data sources, such as registries and EHRs, to enhance coverage and granularity by using methods such as statistical adjustments and pooling techniques (National Institute for Health and Care Excellence 2022). This promotes the integration of diverse data while ensuring methodological rigor. Methodological rigor is advocated by NICE due to study planning, which includes predefined protocols and data analysis plans. Furthermore, NICE formulates clear standards for non-randomised studies to minimise biases and strengthen causal inferences. Therefore, recommendations for conducting propensity score matching and other advanced techniques to adjust for confounders should be applied (National Institute for Health and Care Excellence 2022). NICE also solves other key methodologic challenges, such as context-specific challenges, regulatory and ethical considerations, and stakeholder engagement. The strengths of NICE are due to the proactive use of RWE in the early-phase and lifecycle evaluation and the establishment of detailed frameworks for RWE integration, making it a global leader in RWE-driven HTA. In contrast, the limitation of NICE is that the reliance on robust data systems like registries can be challenging for healthcare settings with underdeveloped data infrastructures.

Response from the French health institution HAS

HAS uses RWD and RWE to complement traditional clinical trial data, particularly for post-marketing surveillance, performance evaluation of medical devices, and MEAs (Haute Autorité de santé 2021). Therefore, HAS emphasises strong integration of patient-reported outcomes (PROs) and healthcare system-specific data through the National Health Data System (SNDS). The HAS report also addresses responses to methodological challenges such as data quality and validity and data heterogeneity due to the focus on the quality of real-world studies and their output (Haute Autorité de santé 2021). Therefore, HAS established methodological guidelines regarding real-world studies due to their health data being more accessible for real-world comparative studies (Haute Autorité de santé 2021). Furthermore, stakeholder engagement is high, with a focus on patient and provider input (Haute Autorité de santé 2021). More similar to NICE, HAS complements RCTs with local data, as compared to IQWiG, which supports RWD but is rarely central to decision-making.

The following table shows a comprehensive overview of the responses of NICE, IQWiG, and HAS toward the four key methodological challenges:

	IQWiG	**HAS**	**NICE**
Data Quality and Validity	· Prioritization of internal validity and applying of stringent criteria for including observational studies · RWE often supplementary of RCTs	· Leveraging of high-quality databases for robust data validation · Focus on reducing biases in post-market data	· Usage of Data Suitability Assessment Tool to assess data quality and relevance · Promotion of transparency in reporting and auditing processes
Data Heterogeneity	· Rarely usage of heterogeneous RWE datasets due to its	· Usage of national health data systems to harmonize datasets, ensuring uniformity in analysis	· Integration of heterogeneous data through linked datasets

	preference of RCT-derived data		and advanced statistical techniques
Study Design and Methodological Rigor	· Preferencing of RCT-based evidence for its methodological rigor · Observational studies are secondary and must meet stringent standards	· Advocation of pragmatical trial designs and routine data analysis for post-marketing evaluations	· Employment of hybrid evidence models combining RCT and RWE · Ensuring of rigor due to advanced methodologies like propensity score matching
Integration with traditional evidence frameworks	· Reliability primarily on RCTs and occasionally usage of RWE for post-marketing validation · No embracement of hybrid framework	· Combination of RWE and RCTs in hybrid evaluations, particularly for medical devices · Embracement of hybrid framework	· Fully integration of RWE into all stages of HTA · Embracement of hybrid framework

Figure 8 10 - Responses from International Health Systems regarding Methodological Key Challenges: Comparison of IQWiG, HAS, and NICE

Sources: Constructed by author; (IQWiG 2023b), (National Institute for Health and Care Excellence 2022), (Haute Autorité de santé 2021)

Research Question 4 – Elena Lialina (61270)

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 11 - 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).

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.

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.

Research Question 5 – Andrea Gualerzi (61628)

How do international HTA bodies harmonise evidence requirements for RWE, and what are the most effective methodologies and frameworks for supporting reimbursement decisions?

Reimbursement decisions in healthcare processes are becoming increasingly supported by the integration of RWE into HTA bodies. The use of evidence-based data can be effective when applied in addition to the capacity of RCTs to test treatments performance for reimbursement decision-making, ensuring that interventions are not only scientifically valid but also valuable for real-world use (Eichler et al. 2011; Hogervorst et al. 2022). However, HTA agencies show significant differences when it comes to the requirements and acceptance of RWE itself (Facey et al. 2020). To date, this evidence has been mostly accepted for meeting post-approval safety criteria, but there is still room for improvement in its potential in demonstrating drug effectiveness (CIOMS Working Group XIII 2024). Despite initiatives aimed at guiding decisions by following common ground, a call for harmonised evidence requirements for RWE is urgently needed. To address these challenges, one of the research questions guiding this study has been developed. In this section, the analysis will focus on studies that precisely align with the scope of the research question, along with official guidelines from the countries of interest. Our objective was to seek the most relevant results that can provide valid arguments for the discussion and, ultimately, the answer to the research question. For clarity and comprehension, the research questions were divided into two sections, beginning with the examination of the first.

Harmonisation of standards and requirements for RWE

Before analysing and commenting on the results from the included studies, it is essential to introduce a wider vision of RWE and its endorsement according to the HTA bodies and specifically on the requirements needed for acceptance. Recently, a few HTA international agencies have published guidelines and best practices on the utilisation of RWE since its increasing relevance in

clinical trials. However, some differences have emerged from the publications of the guidelines of each HTA, highlighting the need for greater harmonisation among international organisations. In practice, a hypothetical study can be accepted in one country but rejected in another. The three leading HTA agencies in Europe (NICE for the UK, HAS in France, and IQWiG for Germany) have the most comprehensive recommendations available to date. Thus, their primary requirements will serve as a benchmark for our analysis (figure 10). The table shows how organisations use similar requirements to assess the validity of RWE, but with some fundamental differences that can make its application yet reductive. The following were outlined:

Diverse data sources and methodologies

Some HTA bodies adopt more flexibility approaches, while others take a narrower focus. On the one hand, they differ in the amount of database usage and the reliability consideration that each HTA estimated. The difference stands in being more specific with the choice of the relevant data source or being more inclusive, taking a wide range of data from the real world, such as registries disease or claims data, to expand the sample population. Indeed, each data source can be more detailed for specific purposes, for instance, addressing research gaps in post-approval scenarios. On the other hand, the study designs and, therefore, methodologies are not equally accepted, or either mentioned. It must be pointed out that many agencies prioritise the comparative method to determining acceptability.

Patient involvement

To make sure that RWE represents real-world experiences, some actively use patient-reported outcome measures (PROMs) to evaluate patient-centred outcomes and quality of life, which are also a common components of RCT. By doing so, they place a strong emphasis on public

involvement in study design and evaluation. Some others prioritise clinical objectives and healthcare utilisation data over patient involvement.

Economic evaluations

RWE has not yet been accepted as a valid tool for economic evaluation purposes. Nevertheless, HTA bodies routinely integrate RWE into cost-effectiveness analyses (CEA) and budget impact models. In contrast, other HTAs recommendations suggest that it must prioritise the clinical benefit assessment rather than economic outcomes, as in the German case.

Regarding the best practices coming from the other included countries in the SLR, they showed a certain degree of variation in utilisations and purposes. For instance, the Swedish HTA agency, TLV, prioritised RWD in pricing models for reimbursement and requires that models based on RWE utilisation entail that the payment correlates with the actual clinical outcome (TLV 2021). In turn, Canada's CADTH advocates for the importance of transparent reporting of RWE, including practices like protocol registration, detailed data provenance, and open access to findings ("CADTH Methods and Guidelines Guidance for Reporting Real-World Evidence: Response to Stakeholder Feedback," n.d.). Australia, on its side, differs in a unique aspect of the acceptance requirements of RWE, which is the explicit emphasis on pre-submission meetings and tailored justifications for its use ("Real World Evidence," n.d.). For other countries, namely Italy, Spain, and Japan, insufficient data were available.

Requirement	HAS (France)	IQWiG (Germany)	NICE (UK)
Research objectives	Address clinical, economic, and organizational impacts, including safety, quality of life, and efficacy	Answer specific gaps in benefit assessments post-approval	Define clear research questions (PICO) to address gaps in evidence for NHS populations

Data sources	Preference is given to the use of pre-existing data, form sources like the National Health Data System (SNDS) or disease registries	Registries and routine practice data collection (RPDC) are central, with strict evaluation of their suitability	Includes EHRS, registries, claims data, and PROMs with good provenance, relevance, and sufficient quality
Study design	Comparative studies, pragmatic trials, causal inference models	Observational studies from registries designed to minimize bias, aligned with PICO framework	Cohort studies pragmatic trials, and other observational designs
Bias mitigation	Use causal inference methods like propensity score matching (PSM) and sensitivity analyses	Design RPDC to enable robust comparisons between treatment groups	Robust study methodology, such as using active comparators for external control (EC), and propensity score matching (PSM)
Data quality	Ensure study representativeness of centres, investigators, and patients while minimizing data loss through imputation.	Ensure high-quality data collection processes, and if not possible provide documentation	Clear documentation, ensure it reflects target population, report relevant patient outcomes
Transparency	Protocols and results must be publicly available, datasets stored for reuse (Health Data Hub)	Results must address predefined gaps in benefit assessment and focus less on open data sharing	Protocols and analysis must be registered but also open data can be used for reproducibility
Patient involvement	Use PROMs and involve patients in the design and interpretation of studies	Limited focus on patient input prioritizes clinical outcomes and healthcare utilization data	Strong focus on patient and public involvement in study design and reporting
Economic analysis	RWE informs cost-effectiveness and budget impact analyses like QALY calculations	Information requirements for assessing the drug's benefits versus the comparator therapy, excluding economic outcomes	RWE informs cost-effectiveness, budget impact models, and managed access agreements
Post-approval evidence	Supports lifecycle HTA with reassessments using post-launch RWE	RPDC required for reassessment of conditionally approved or orphan drugs.	Managed Access Agreements (MAAs) require RWE collection to address uncertainties post-approval

Figure 10 12- Requirements

Source: Constructed by author

Findings from included studies

In reviewing the included studies, a closer examination was conducted on those findings that might effectively provide an understanding for tackling the issue at hand. Particularly, a study by Zong

et al. focused on a comparison conducted between the EMA and European HTA organisations (NICE, HAS and G-BA) concerning the evaluation of RWE methods and their application in oncology drug approvals in Europe (Zong et al. 2024b). The studies were assessed based on various requirement condition factors, specifically trends, methodologies, utilisation, and acceptance. Our focus goes mainly on the acceptability aspect, where seven medicines have been analysed by both parties. Respectively, 4 case studies about different products were assessed by EMA and multiple bodies (Ayvakyt, Lumykras, Rybrevant, Tepmetko). While the remaining three are by EMA and one HTA body (Abecma, Lunsumio, Piqray). The study first examines the approach used for integrating RWE and consequently compares how these agencies evaluated and accepted it in the context of decision-making for oncology medicines (figure 11). Formal comparison was the most accepted approach, with six out of nine uses accepted as “supportive evidence” and 3 marked as “not adequate”. Indeed, supportive evidence refers to the role assigned to RWE, which does not replace primary evidence but complements it (accepted in 10 cases for the 55.5% of total). Ayvakyt and Lumykras are two examples of medications for which RWE was approved by some HTA authorities (HAS and NICE) but declared "not adequate" by others (G-BA and EMA). In the first case, EMA and G-BA agreed to reject the evidence because not adequate for decision-making due to the potential bias within the methodological findings, while HAS defined it as acceptable for supportive evidence as a formal comparator. In the second case mentioned, EMA agreed with NICE about the evaluation by justifying the usage of RWE for natural history of disease, and for picturing correctly the relevant patient population demonstrating consistency. In contrast, G-BA rejected the descriptive evaluations since they did not account for key effect modifiers or prognostic factors, and the RWE was deemed insufficient for decision-making. In conclusion, NICE adopted the most favourable approach regarding RWE, admitting 67% of cases as supporting evidence and emphasizing its importance in decision-making. HAS demonstrated mixed approval, approving

54.5% of applications while underlining the significance of benchmarking and contextualization procedures. In contrast, G-BA was the least receptive, judging 90% of RWE presentations insufficient for decision-making and with limited utility beyond efficacy and safety assessments. The findings indicate that, despite existing guidance, EMA, NICE, G-BA, and HAS all adopted their own approach to analysing RWE, in terms of acceptability and, ultimately, decision-making. Although some consistency was discovered, there was no consistent approach to evaluating RWE.

Brand product name	EMA	NICE	HAS	G-BA
Abecma	Supportive evidence as benchmark and RWE follow-up recommendations			Not adequate as formal comparator
Ayvakyt	Not adequate as formal comparator		Supportive evidence as formal comparator	Not adequate as formal comparator
Lumykras	Supportive evidence as natural history of disease	Supportive evidence as formal comparator		Not adequate as benchmarks
Lunsumio	Supportive evidence as benchmark and demonstrate unmet needs			Not adequate to understand population indication and unmet need
Piqray	Follow-up recommendation for safety	Supportive evidence as formal comparator		
Rybrevant	Supportive evidence as benchmark	Not adequate as formal comparator		Not adequate as formal comparator
Tepmetko	Follow-up recommendation for safety	Supportive evidence as formal comparator		Not adequate as benchmark

Figure 11 13 - Case studies of RWE acceptability across EMA and HTA bodies

Source: Constructed by author, adapted from (Zong et al. 2020)

The acceptability of RWE by HTA bodies in the abovementioned case studies reflects their specific requirements and methodological frameworks, as specified in the guidelines indications (figure 10), leading to inevitable disparities. What stands out from our analysis is, therefore, the need for clear criteria in acceptance of RWE.

A relevant explanatory case is also provided by the Appiah et al. work examining how EC data sources are selected and justified in single-arm trial (SAT) oncology submissions to HTA bodies like NICE (UK) and PBAC (Australia). External control data are often derived from RWE, which necessitates ensuring their reliability. A total of 48 submissions were reviewed, resulting in a consistent lack of reported justification for EC data sources. Only six out of 29 included justifications in the submissions to NICE and 2 out of 19 in those to the PBAC. Transparency and standardisation among organisations must be clarified to build trust in the application of RWE. However, the study presents some limitations. The results of the research are based on a 2021 evaluation and may not reflect developments since the 2022 NICE RWE framework. Moreover, the limited information in PBAC's documentation, as well as the lack of publicly available supplemental resources, make thorough analysis difficult. Some grounds for EC selection may have been informed by initial conversations with HTA bodies, but they were not documented (Appiah et al. 2024).

A matter for reflection is finally offered from the application of a target trials framework using RWE to inform HTA, focusing on the generalist view of decision-making. The referenced case study by Moler-Zapata et al. examines the cost-effectiveness of emergency surgery for two prevalent acute gastrointestinal conditions, recovering data from emergency hospital admissions in

England, and describes four main common challenges in the application of the framework (Moler-Zapata et al. 2023). Each challenge is then followed by a specific recommendation for its improvement.

According to the findings, by following clinical guidelines and/or expert opinion both the eligibility criteria and the treatment strategies challenges can be overcome. In the first case, the objective is to minimise selection bias as much as possible by including patient subgroups and excluding patients without balanced treatment options. In the second case, in assessing treatment strategies, it is mainly necessary to define both interventions and comparators. Then, to address the time zero barrier, the baseline must be carefully defined, preferably preceding the eligibility and reducing any delay before treatment initiation. In conclusion, statistical analysis should be supported by advanced methods that can handle unmeasured confounders more effectively since traditional practices may not always be appropriate.

The contribution from the study highlights the critical role of RWD in addressing gaps left by RCTs, particularly in conditions where RCT evidence is scarce or impractical. However, even with the broader application of these suggestions, some challenges, such as incomplete data and variability, persist. Thereby, the study also serves as a warning for harmonised global guidelines.

Most effective methodologies and frameworks for supporting reimbursement decisions

The second component of the research question focuses on the attempt to report the diverse methodologies and frameworks collected from the relevant included studies and subsequently proceed with an evaluation of their effectiveness in supporting reimbursement decisions, when possible. Three approaches can provide an area for discussion and therefore deserve to be looked at from a closer perspective: cost-effectiveness analysis (CEA) can serve as a tool for evaluating

health interventions both in terms of costs and outcomes, Managed Entry Agreements (MEA) are valuable for operationalising the reimbursement decisions, while Dynamic HTA Framework provides a model for ongoing reassessment post-introduction. Before moving to the findings, a brief description of these approaches used in the studies will precede.

Ex-ante and ex-post CEA comparison

It includes highlighting the differences between ex-ante (based on clinical trial data and initial cost estimates) and ex-post CEA (incorporating RWE) and comparing them to evaluate the effectiveness of treatments.

Managed Entry Agreement (MEA)

MEAs can be defined as tools or confidential agreements between payers and manufacturers aimed at addressing clinical and economic uncertainties for newly introduced expensive health technologies. Payers, typically either the national HTA agencies or NHS, are responsible for determining if a drug is clinically and cost-effective for reimbursement and, therefore, negotiate agreements with pharmaceutical manufacturers to secure that the specific drug can be accessible to the population. The most typical form of MEA is the price discount, but performance-based arrangements such as money-back guarantees or outcome-based reimbursement linked to clinical performance are also widely applied.

Dynamic HTA Framework

It is a method for continuously evaluating healthcare technology, namely digital and software-based solutions like apps, for example. Unlike traditional HTA, which is based on static, one-time assessments, dynamic HTA uses RWE to integrate the evaluation of the technology and its

outcomes over time. The framework aims to be essential in supporting reimbursements decisions over time, since products are expected to change and improve progressively.

Case studies examples

The first approach that deserves to be commented is the CEA. The baseline study in this case by de Pouvourville et al. aims to compare ex ante (before market launch) and ex post (after-market launch) cost-effectiveness analyses (CEAs) of Dabigatran etiolate versus vitamin K antagonists (VKAs) for preventing thromboembolic events in patients with non-valvular atrial fibrillation (De Pouvourville, Blin, and Karam 2020).

Two sets of parameters were used: ex ante data derived from the RE-LY clinical trial and initial cost estimations and ex post data based on RWE collected from post-launch studies, namely ENGEL-2 and SPA. RWE was recovered analysing claims data from the French National Sickness Fund (SNDS) in the case of ENGEL-2. A secondary purpose of this study was to use this case as a foundation for extracting insights to inform future comparisons between ex ante and ex post CEAs, driven by the fact that they were carried out separately. The findings are here reported based first on the clinical outcomes and then on the cost-analysis perspective. Clinically, the effectiveness of Dabigatran in preventing ischemic strokes compared to VKAs was found higher at both 150 mg and 110 mg dosages. There were also reductions in the potential risks of haemorrhages when using Dabigatran versus VKAs. This translated into significantly lower incremental cost-effectiveness ratios (ICERs). Therefore, scenarios where RWE was integrated demonstrated that Dabigatran not only was more effective but also cost saving. However, the study found significant disparities between the actual cost of data between clinical trials and real-word settings. Particularly, monitoring costs were differing. Even though the authors addressed the risk of bias in RWE by employing rigorous matching techniques, such as high-dimensional propensity score matching,

according to the findings “there is an obvious selection bias in the real world, with a self-selection of patients dropping out from treatment” (De Pouvourville, Blin, and Karam 2020). The study faced the three major limitations: firstly, only 1-year results were available at the time of the study, which limited the assessment of long-term outcomes; secondly, because both studies focused on rates of events during the exposure to treatment, subsequent treatment after discontinuation and switches were not analysed, and finally it lacked comprehensive long-term comparative data for all competitors, constraining robust comparisons. The study indicates that RWE can have a significant impact on the perceived cost-effectiveness of medicines following their market release, providing a deeper understanding of its value.

Subsequently, the work by Buyukkaramikli et al. to discuss the potential usefulness of MEA (Buyukkaramikli, Wigfield, and Hoang 2021c). This study delves into the role of MEA in balancing the interests of payers and manufacturers in the reimbursement of high-cost drugs. Using an economic model to examine a specific cancer medicine in the UK healthcare system, the study investigates how different MEA type, such as price reductions, cost ceilings, and performance-based schemes, affect cost-effectiveness and financial risks. Different type of RWE was used in the study. The study RWE into three primary groups. First, clinical outcomes data, which include insights from clinical trials and real-world observations on patient progression, survival rates, and treatment effectiveness. Second, economic and cost data derived from real-world settings, such as treatment costs, and financial considerations of MEAs, such as drug acquisition, administration, and monitoring expenses. Third, health utility data, calculated using QALYs based on utility scores from clinical and real-world studies. The research integrates data from various sources, including clinical trials, economic evaluations, RWD sets on patient responses and disease progression, as

well as scenario and sensitivity analyses, to provide a comprehensive understanding of MEA impacts.

Moving into the reassessment approach mentioned above, what needs to be reported is the development of a dynamic HTA framework that can broadly support the evidence for reimbursements of healthcare technologies. Following the comments of Brönneke et al. on the case of the Digital Healthcare Act (DiGA) in Germany, conclusions were drawn on how integrating RWE can reinforce this need (Brönneke et al. 2023). DiGA's introduction allowed to simplify and clarify practices for the regulation and reimbursement of medical software device (SaMD), such as mobile apps. However, as far as established by the regulation, to be reimbursed, DiGAs must demonstrate clinical or structural/process benefits. Among 55 apps evaluated, 9 claimed structural/process improvements, but only 2 succeeded, showing it is possible yet underutilised. Moreover, after being listed as successful in terms of benefits achieved, subsequent evaluations of the performance are required to set the reimbursement price. In this context, RWD and RWE can be resolutive. Firstly, RWE can provide initial evidence required for reimbursement at a significantly lower cost compared to RCTs. Secondly, it allows for ongoing evaluations of the performances and benefits over time. Lastly, a real-world setting allows for a broader data capture, including relevant patient-centred info such as quality of life, for instance. Thus, in terms of effectiveness for reimbursement decisions, RWE can be a crucial factor in the development of a dynamic HTA framework.

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