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(Good) practice organizational models using real-world evidence for public funding of high priced therapies

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(Good) practice organizational models using real-world evidence for public funding of high priced therapies

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List of abbreviations

AIFA..... Agenzia Italiana del Farmaco
AQuAS ..... Agency for Health Quality and Assessment of Catalonia
ATMP..... Advanced Therapies Medicinal Product
CADTH ..... Canadian Agency for Drugs and Technologies in Health
CanREValue..... Canadian Real-world Evidence for Value of Cancer Drugs
CAQDAS ..... Computer-aided qualitative data analysis software
CAR-T-cell ..... Chimeric antigen receptor T-cell
CatSalut ..... Catalan healthcare service
CED ..... Coverage with Evidence Development
CONITEC ..... National Commission for the Incorporation of Technologies
DARWIN..... Data Analysis Real World Interrogation Network
EC..... European Commission
EHDS..... European Health Data Space
EHR ..... Electronic health record
EMA ..... European Medicines Agency
ERP ..... External Reference Pricing
EU ..... European Union
EUnetHTA ..... European Network for Health Technology Assessment
G-BA..... Gemeinsamer Bundessausschuss
GDPR..... General Data Protection Regulation
GRADE..... Grading of Recommendations Assessment, Development, and Evaluation
HCP..... Healthcare provider
HIS ..... Health Improvement Scotland
HTA ..... Health Technology Assessment
HTAi ..... Health Technology Assessment international
IMPACT HTA ..... Improved methods and actionable tools for enhancing Health Technology Assessment
INAHTA ..... International Network of Agencies for Health Technology Assessment
INEAS ..... Instance Nationale de l'Evaluation et de l'Accréditation en Santé
INESSS ..... Institut National d'Excellence en Santé et en Services Sociaux
IQWiG..... Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRP ..... Internal Reference Pricing
ISPOR ..... International Society for Pharmacoeconomics and Outcomes Research
KCE..... Belgian Health Care Knowledge Centre
MAH ..... Marketing authorization holder
MEA ..... Managed-entry agreement
NICE..... National Institute for Health and Care Excellence
OBMEA..... Outcome-based Managed-entry agreement
OECD ..... Organisation for Economic Co-operation and Development
pCPA..... Pan-Canadian Pharmaceutical Alliance
PRISMA..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO..... Patient-reported outcome

RCT ..... Randomized controlled trial
RE ..... Respondent
REQueST ..... Registry Evaluation and Quality Standards Tool
RIZIV-INAMI- ..... Rijksinstituut voor ziekte- en invaliditeitsverzekering/ Institut national d'assurance maladie-invalidité (National Institute for Health and Disability Insurance in Belgium)
RQ ..... Research question
RWD ..... Real-world data
RWE ..... Real-world evidence
R&D ..... Research and Development
SAP ..... Statistical Analysis Plan
SMC ..... Scottish Medicines Consortium
SMDM ..... Society for Medical Decision Making
TLV ..... Tandvårds- och läkemedelsförmånsverket (The Dental and Pharmaceutical Benefits Agency)
TQF ..... Total Quality Framework
UK ..... United Kingdom
VBP ..... Value Based Pricing
WHO ..... World Health Organisation
WP ..... Work Package
ZIN ..... Zorginstituut Nederland

Executive Summary

Background

The growing market entry of high-cost medicines threatens the financial sustainability of healthcare systems. In particular, the emerging field of Advanced Therapies Medicinal Products (ATMPs), for which little data on their long-term benefits are available at the time of approval, challenges payers to assess the actual value of these medicines and forces them to make reimbursement decisions under high uncertainty.

high-cost medicines threaten financial sustainability of healthcare systems, little data on benefit at time of approval

Outcome-based Managed-entry agreements (OBMEAs) present a practical approach to share the risk of uncertainty between payers and manufacturers through funding therapies and enabling patient access on a conditional basis. During this time, new evidence on the effect of treatments in real life is collected, which allows the re-assessment of therapies. However, the lack of transparency of contractual terms and the fact that data management often lies with the Marketing Authorization Holder (MAH) increase the opacity around these agreements, limit information exchange across countries, and mutual learning.

OBMEAs: approach to share risks due to uncertainty

often lack of transparency hinders mutual learning,

Therefore, the study aimed to provide recommendations for a generic organizational model for OBMEAs for cost-intensive medicines providing conditional funding while simultaneously generating publicly accessible data on the treatment effects observed in a real-world setting.

aim of project: generic organizational model for OBMEA generating publicly accessible data

Methods

The research integrates secondary data from existing literature and primary qualitative data generated from semi-structured expert interviews.

literature review on role models for organization of OBMEAs

To identify role models for the organization of OBMEAs, a systematic literature search in one database complemented by a targeted manual search in grey literature was conducted. Besides, a request was sent to the INAHTA (International Network of Agencies for Health Technology Assessment) network inquiring about organizational frameworks in different countries.

complemented by semi-structured expert interviews (n=11)

The identification of models built the basis for selecting interview participants to gain a deeper insight into the modular structure, area of application, and experiences made with these frameworks. In total, eleven interviews with 15 experts from eight different countries (Italy, Belgium, Germany, Spain, the Netherlands, Scotland, Canada, Sweden) were carried out. The interview material was analysed by performing a structured content analysis according to Mayring (2014) utilizing a computer-aided qualitative data analysis software tool.

Results

Overall, 16 frameworks were identified, four generic and twelve country-specific models from Belgium, Canada, England, Germany, Italy, the Netherlands, Scotland, and Spain. The generic models included the OBMEA tools from the EC-project IMPACT HTA (WP10), a scheme for medical devices produced within another EC-project COMED (WP7) and further two references describing the application of Real-World Evidence (RWE) for HTA purposes and recommendations for the implementation of OBMEAs.

identification of 16 OBMEA models:

4 generic,
12 country-specific
from 8 countries

Comparing the modular structure of the models included, which was presented following the five different modules for planning OBMEAs, initiation, design and governance, evidence generation, re-assessment, and exit, showed great variation across countries in terms of the level of detail and maturity. This may be due to the different stages of development of OBMEAs, contextual factors, and classification systems used for categorizing these agreements.

modular structure of models - 5 different modules for planning OBMEAs: initiation design & governance evidence generation re-assessment exit

Therapeutic areas often targeted were oncological and rare diseases with Chimeric antigen receptor (CAR) T-cell therapies, gene therapies, and orphan drugs, the most frequently mentioned type of technology. These drugs were associated with high prices and high uncertainties on, i.e., the budget impact and clinical- and/or cost-effectiveness.

areas of application: CAR-T, gene therapies, orphan drugs

Countries reported mixed experiences with OBMEAs. Owing to operational constraints, the full potential of these schemes remains to be developed. Practical difficulties exceeded the possible benefits and hindered an effective implementation. Interview participants highlighted the significant resources required for data collection and the poor quality of data produced, leaving open questions if OBMEAs actually mitigate uncertainties.

mixed experiences: practical difficulties exceed the possible benefits of OBMEA

Following that, recommendations made were to carefully pre-specify data collection, use existing data infrastructure systems to keep the additional administrative burden to a minimum, increase stakeholder engagement, collaboration, and public transparency.

recommendations: pre-specify data collection; use existing data infrastructure, stakeholder engagement, public transparency

Compiling all information generated in this research from both the literature search and the interviews resulted in drafting a generic model for the organization of OBMEAs integrating the best practices collected.

Conclusion

Given the rapid developments and high price tags of ATMPs, the need for alternative reimbursement mechanisms mitigating the uncertainties around the value of these drugs is likely to increase.

high prices for ATMPs - likely increase of OBMEAs, imbalance between theory & practice of OBMEAs: need for standardization of data collections; transparency of outcomes and cross-country mutual exchange

In theory, OBMEAs present an alternative pricing approach by sharing risks equally between private and public entities. Yet, an imbalance is caused by the lack of transparency around these agreements, hindering the successful implementation in practice. Therefore, a higher level of standardization could lead to more comparable results, facilitate data sharing and diminish the culture of the opaqueness of these agreements. Existing collaboration initiatives provide a good starting point for exploiting the potential of real-world data to advance decision-making in healthcare.

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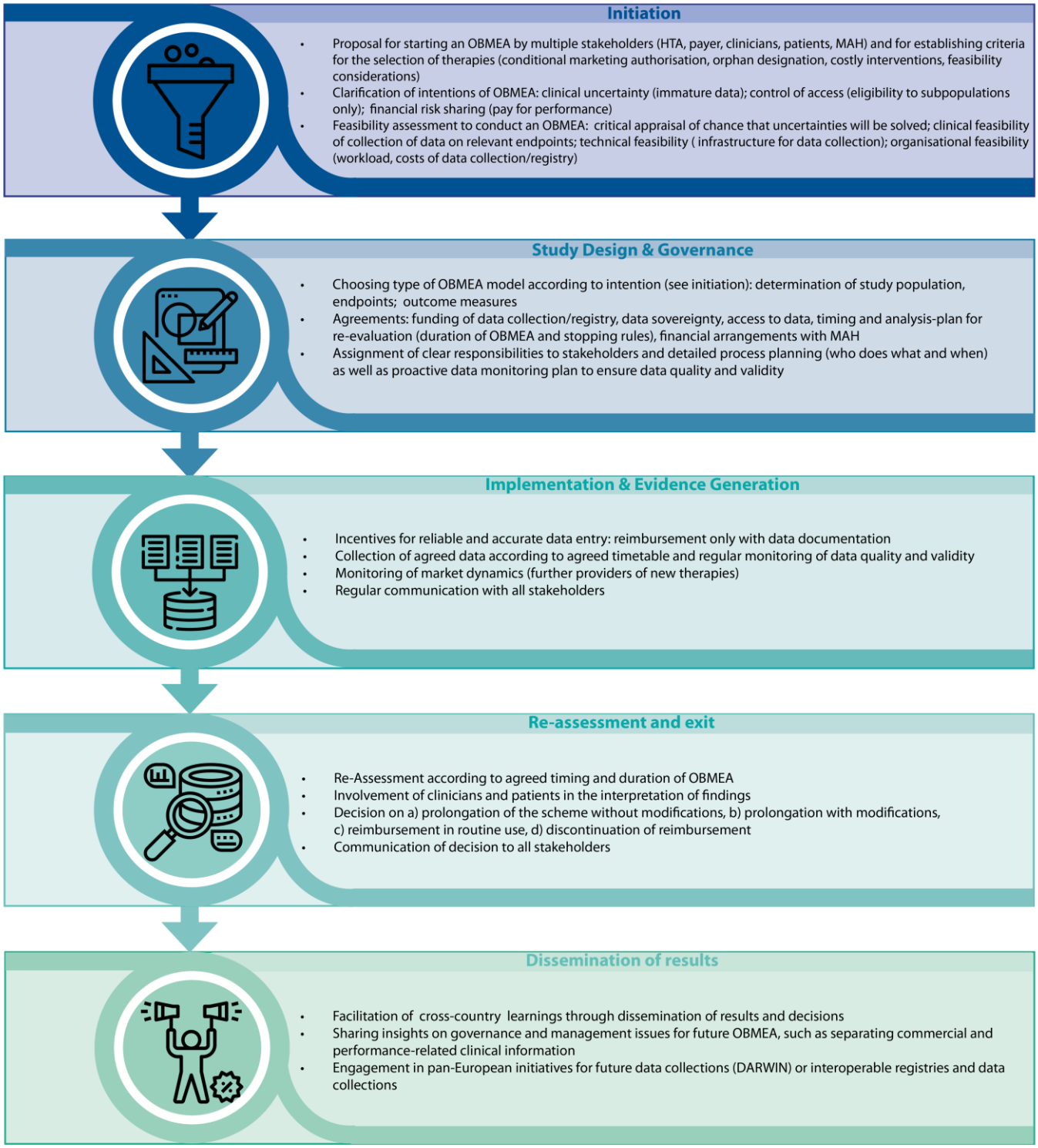

Zusammenfassung

Hintergrund

Der zunehmende Markteintritt von hochpreisigen Medikamenten bedroht die Finanzierbarkeit der Gesundheitssysteme. Insbesondere im Bereich „Advanced Therapies Medicinal Products“ (ATMPs) sowie Gentherapien liegen zum Zeitpunkt der Zulassung meist nur wenige Daten über den tatsächlichen mittel- bis langfristigen Nutzen vor. Dies stellt Kostenträger vor die große Herausforderung, den tatsächlichen Wert dieser Medikamente zu beurteilen, und zwingt sie, Erstattungsentscheidungen unter großer Unsicherheit zu treffen.

hochpreisige Medikamenten gefährden Finanzierbarkeit der Gesundheitssysteme - wenig Wissen zum tatsächlichen Nutzen bei Zulassung

Outcome-based Managed-entry agreements (OBMEAs) stellen eine praktische Option dar, bei der das Risiko wegen Unsicherheiten auf Kostenträger und Hersteller aufgeteilt wird, indem Therapien unter definierten Bedingungen finanziert werden und damit der Patient*innenzugang ermöglicht wird. Während dieser Zeit werden neue Erkenntnisse über die Wirkung von Therapien in der Praxis gesammelt, was eine Neubewertung von Therapien zu einem späteren Zeitpunkt möglich macht. Die mangelnde Transparenz der Vertragsbedingungen und die Tatsache, dass die Datenhoheit oft beim Zulassungsinhaber liegt, erhöhen jedoch die Undurchsichtigkeit dieser Vereinbarungen und schränken den Informationsaustausch zwischen den Ländern und ein gemeinsames Lernen ein.

OBMEA: Erstattungsoption unter Bedingungen zur Reduktion der Unsicherheiten

Mangel an Transparenz behindert Wert und Aussagekraft der OBMEAs

Ziel der Studie war es daher, Empfehlungen für ein generisches Organisationsmodell für OBMEAs für kostenintensive Therapien zu entwickeln, das eine bedingte Erstattung vorsieht und gleichzeitig öffentlich zugängliche Daten über die in einer realen Umgebung beobachteten Behandlungseffekte generiert.

Ziel der Studie: generisches Organisationsmodell für öffentlich zugängliche Daten aus OBMEAs

Methoden

Die Untersuchung umfasst Sekundärdaten aus der publizierten Literatur und primäre qualitative Daten, die aus teil-strukturierten Experteninterviews gewonnen wurden.

systematische Literaturanalyse & Informationen aus teil-strukturierten Interviews

Um Vorbilder für die Organisation von OBMEAs zu identifizieren, wurde eine systematische Literaturrecherche in einer Datenbank durchgeführt und um eine gezielte manuelle Suche nach grauer Literatur ergänzt. Außerdem wurde eine Anfrage an das Netzwerk INAHTA (International Network of Agencies for Health Technology Assessment) gestellt, in der nach organisatorischen Rahmenbedingungen und Leitfäden in verschiedenen Ländern gefragt wurde.

Die Identifikation der Modelle bildete die Grundlage für die Auswahl der Interviewteilnehmer*innen. Die Interviews dienten dazu, einen vertieften Einblick in den Aufbau, den Anwendungsbereich und die Erfahrungen mit diesen OBMEA-Modellen zu erhalten. Insgesamt wurden elf Interviews mit 15 Expert*innen aus acht verschiedenen Ländern (Italien, Belgien, Deutschland, Spanien, den Niederlanden, Schottland, Kanada, Schweden) durchgeführt. Die Auswertung des Interviewmaterials erfolgte mittels einer strukturierten Inhaltsanalyse nach Mayring (2014) unter Verwendung einer computergestützten Software zur qualitativen Datenanalyse.

(n=11)

Ergebnisse

Insgesamt wurden 16 OBMEA-Modelle identifiziert, vier generische und zwölf Länder-spezifische Modelle aus Belgien, Kanada, England, Deutschland, Italien, den Niederlanden, Schottland und Spanien. Zu den generischen Modellen gehörten die OBMEA-Tools aus dem EC-Projekt IMPACT HTA (WP10), ein Schema für Medizinprodukte, das im Rahmen von COMED (WP7), einem weiteren europäisch geförderten Projekt, erstellt wurde, sowie zwei weitere Referenzen, die die Anwendung von Real-World-Evidenz (RWE) für HTA-Zwecke und Empfehlungen für die Implementierung von OBMEAs beschreiben.

16 OBMEA-Modelle identifiziert
4 generische,
12 Länder-spezifische aus 8 Ländern

Ein Vergleich der einbezogenen Modelle, die nach fünf auf einander aufbauenden Modulen für die Planung von OBMEAs (Initiierung, Design und Governance, Evidenzgenerierung, Re-Evaluierung und Ausstieg) dargestellt wurden, zeigte große Unterschiede zwischen den Ländern in Bezug auf den Detaillierungsgrad und die Ausgereiftheit. Dies kann mit den unterschiedlichen Implementierungsstadien von OBMEAs, Kontextfaktoren und Klassifikationssystemen begründet werden, die zur Kategorisierung dieser Vereinbarungen verwendet werden.

modularer Aufbau von Modellen -
5 verschiedene Module zur Planung von OBMEAs:
Initiierung
Design & Governance
Evidenzgenerierung
Re-Evaluierung
Ausstieg

Die am häufigsten genannten therapeutischen Einsatzgebiete waren onkologische und seltene Erkrankungen: Chimeric Antigen Receptor (CAR) T-Zell-Therapien, Gentherapien und Orphan Drugs. Diese Therapien sind mit hohen Preisen und großen Unsicherheiten verbunden, z. B. in Bezug auf die Budget-Auswirkungen und die klinische- und/oder Kosteneffektivität.

Anwendungsgebiete: CAR-T, Gentherapien, Orphan Drugs

Die Länder berichteten über gemischte Erfahrungen mit OBMEAs. Aufgrund Ablauf-organisatorischer Einschränkungen muss das volle Potenzial dieser Modelle erst noch erschlossen werden. Praktische Schwierigkeiten behindern den möglichen Nutzen. Interviewteilnehmer*innen betonen den erheblichen Ressourcenaufwand für die Datenerhebung und die schlechte Qualität der gesammelten Daten, was die Frage offen lässt, ob OBMEAs tatsächlich klinische und ökonomische Unsicherheiten beseitigen können.

gemischte Erfahrungen: praktische Schwierigkeiten behindern den möglichen Nutzen von OBMEA

Im Anschluss daran wurde empfohlen, die Datenerfassung sorgfältig im Voraus zu spezifizieren, bestehende Dateninfrastruktursysteme zu nutzen, um den zusätzlichen Verwaltungsaufwand so gering wie möglich zu halten, sowie die Einbindung der Stakeholder, die Zusammenarbeit und die öffentliche Transparenz zu erhöhen.

Empfehlungen: gute Planung, Einbindung von Stakeholdern, Transparenz

Die Zusammenführung aller Informationen, die in dieser Untersuchung aus der Literaturrecherche und den Interviews generiert wurden, führte zum Entwurf eines generischen Modells für die Organisation von OBMEAs, das die gesammelten Best Practices einbezieht.

generisches Modell basierend auf „best practice“

Schlussfolgerung

Angesichts der rasanten Entwicklung und der hohen Preise von ATMPs wird der Bedarf an alternativen Erstattungsmechanismen, die die Unsicherheiten rund um den Nutzen dieser Medikamente abmildern, wahrscheinlich steigen.

Wahrscheinlichkeit für OBMEAs steigt mit teuren ATMPs

In der Theorie stellen OBMEAs einen alternativen Erstattungsansatz dar, indem die Risiken gleichmäßig zwischen privaten und öffentlichen Organisationen aufgeteilt werden. Allerdings entsteht durch die mangelnde Transparenz dieser Vereinbarungen ein Ungleichgewicht, das die erfolgreiche Umsetzung in der Praxis behindert. Daher könnte ein höheres Maß an Standardisierung zu vergleichbareren Ergebnissen führen, die gemeinsame Nutzung von Daten erleichtern und die fehlende Transparenz dieser Vereinbarungen abbauen. Bestehende Initiativen zur Zusammenarbeit bieten einen guten Ausgangspunkt für die Nutzung des Potenzials von Real-World-Daten, um die Entscheidungsfindung im Gesundheitswesen voranzutreiben.

OBMEA: Abweichung von Theorie & Praxis, Notwendigkeit der Standardisierung von Datenerhebungen; Transparenz der Ergebnisse und länderübergreifender gegenseitiger Austausch

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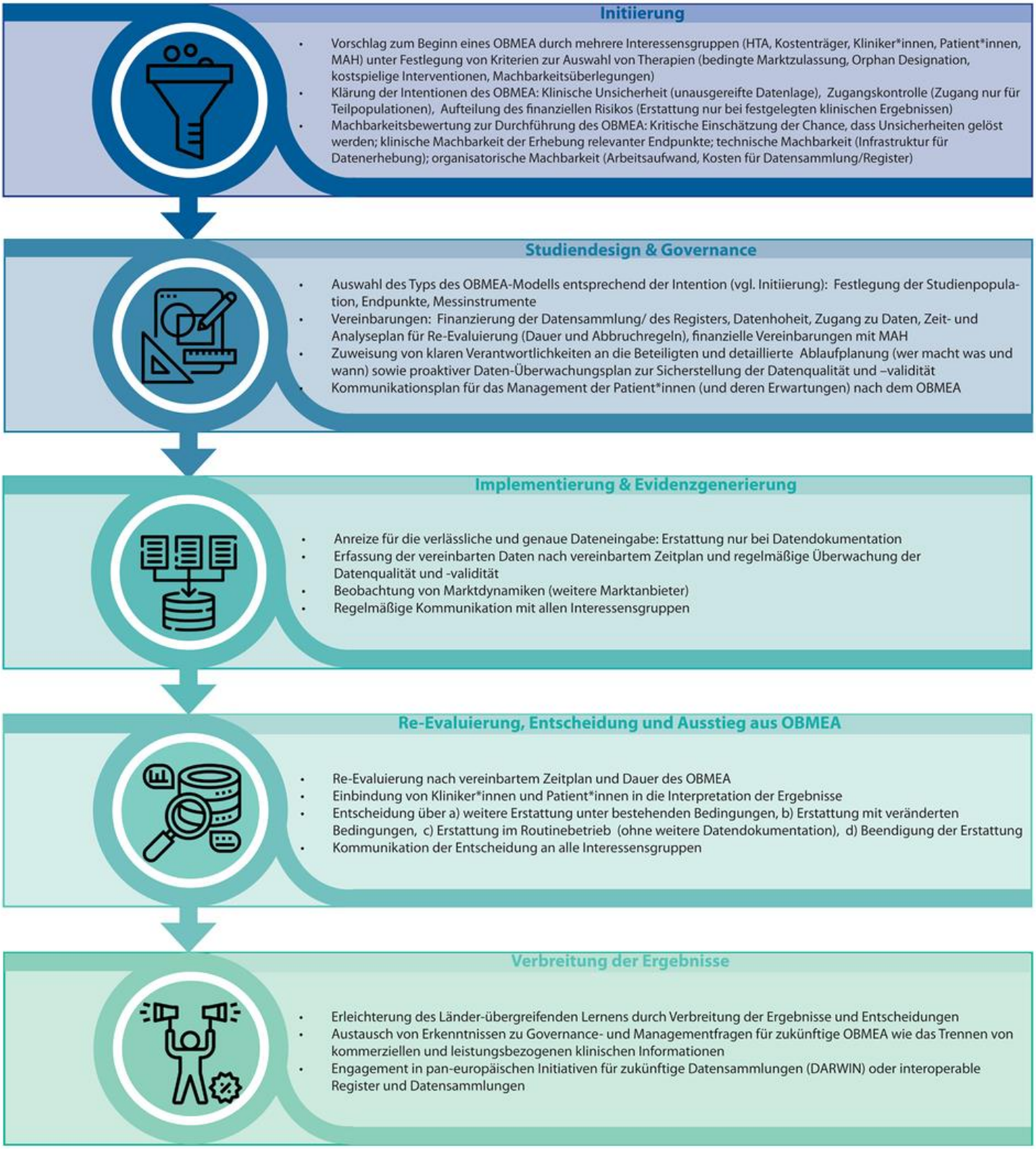

1 Introduction

1.1 Background

Nachhaltigkeit der Finanzierung und Zugang zu neuen Medikamenten

Striving towards a universal health care system that provides effective, safe, and equal access to medical care for every resident is a major objective shared by many nations [1]. However, as the Member States of the European Union (EU) are increasingly struggling with achieving this goal while concurrently safeguarding future financial sustainability and providing sufficient economic incentives for manufacturers to produce new technologies, access to new medicines is at stake [2, 3].

öffentlich finanzierte Gesundheitssysteme unter Druck

The continuing launching efforts of the pharmaceutical industry, introducing new medicine being of either large volume, targeting big population groups or one-time costly therapies, stretch public budgets to its limits. Current figures estimated that drug spending amounts to approximately 20 percent of the overall healthcare expenses in member countries of the Organisation for Economic Co-operation and Development (OECD) [4].

extrem Kosten-intensive ATMPs und Gentherapien

The situation has been exacerbated by the latest scientific advancements in the field of Advanced Therapies Medicinal Products (ATMPs), which are at the forefront of changing the landscape of therapeutic options in medicine [5]. As defined by the European Medicines Agency (EMA), ATMPs encompass gene therapy medicinal products, somatic-cell therapy medicinal products, and tissue-engineered products [6].

hohe Erwartungen: potentiell kurative Interventionen, oft aber ohne Evidenz zur Langzeit- Wirksamkeit zum Zeitpunkt der Zulassung

Associated with high expectations for especially rare genetic disorders, paving the way for alternative treatment possibilities, these therapies claim to deliver a sustained improved, potentially curative, health effect already after a single administration [5, 7]. Despite lacking evidence on the long-term performance at the time of market entry, these therapies come at a high cost, challenging already stretched healthcare budgets and compelling payers to restrict access to these innovations to selected patients [8].

Feb 2021: 12 ATMPs am Markt wegen hoher Kosten, häufig ohne Finanzierung oder Zugang

As of February 2021, twelve ATMPs have been approved by EMA, yet market penetration has been impeded by difficulties in applying the conventional payment methods to ATMPs [7, 9]. Consequently, all of them have failed to reach broad reimbursement and patient access in the five largest EU markets (United Kingdom (UK), Germany, Italy, France, Spain). Four therapies were withdrawn from the market mainly because of insurmountable hurdles for obtaining coverage and obtaining market access [10].

Druck auf Entscheidungsträger insb. bei seltenen Erkrankungen: Preisverhandlungen

Pharma sieht eigene F&E Ausgaben in Gefahr

At the same time, the persistent unmet need for true medical innovations, in particular in the fields of cancer, immune disorders, and rare diseases, intensifies the pressure on decision-makers to strike a balance between funding the increasingly expensive price tags of these therapies, providing accessible healthcare while maximizing budget impact [4, 11, 12]. This might give rise to tensions in price negotiations between health care payers and manufacturers. What public purchasers consider as a reasonable price to ensure patient access, the pharmaceutical sector views as a threat to cover their research and development (R&D) activities [13].

Forschungsstandort vs. Gesundheitspolitik; Wettbewerbsfähigkeit vs. Finanzierbarkeit

EU 2020: Pharmazeutische Strategie, "faire" Preisgestaltung & Transparenz

Trying to serve both interests, public and private ones, by strengthening industries' competitiveness while improving accessibility and availability of innovative medicines and ensuring financial sustainability for healthcare systems of Member States is enshrined as one of the key pillars in the Pharmaceutical Strategy, launched in November 2020 by the European Commission (EC). Since transparency in R&D costs is currently not given, a higher degree of clarity could serve as a basis for pricing discussion of specialty drugs, ensuring a 'fair return' of public investment. Following that, the Pharmaceutical Strategy calls for forming alliances to foster cooperation between authorities and exchanging best-practices on pricing and reimbursement policies to promote value for money of therapies [14].

große Unsicherheiten zum tatsächlichen Wert vieler neuer Therapien

trotzdem Nachfrage nach raschem Zugang

Yet, various sources of uncertainty pose a significant challenge to public payers to accurately evaluate the actual value of potentially innovative pharmaceuticals and thus hamper timely patient access [4, 15]. Owing to the immature clinical data resulting from controlled studies, uncertainties exist around clinical-, cost-effectiveness, and budget impact of recently introduced drugs [4, 16]. Therefore, pushed by the pressing demands of producers, providers, and patient organizations for fast access, payers risk taking hasty inappropriate reimbursement decisions, either approving ineffective technologies or postponing their ruling and refuse access while hoping for better evidence in the future [15].

neue Erstattungsmodelle: Vereinbarungen zu Managed-Entry Agreements (MEA)

Collaborating initiatives between payers and manufacturers, aiming at evenly sharing these risks of uncertainty while allowing access, resulted in introducing new funding schemes, the so-called Managed-entry agreements (MEA) [16]. They are frequently applied for elevating the affordability of oncological and orphan drugs given their highly uncertain inherent nature concerning the financial impact and possible clinical benefit [1]. Several types of these contractual agreements can be found [16].

Performanz- und Ergebnis-basierte Abkommen als Balance zwischen Unsicherheit und Zugang zu Therapie

Current arrangements for expensive cell- and gene-therapies, such as Chimeric antigen receptor (CAR) T-cell therapies, concentrate on outcome-based Managed-entry agreements (OBMEA) that link drug performance to the level of reimbursement. Thereby, real-world evidence (RWE) has established itself to be a powerful tool for supplementing data on efficacy by providing evidence on the health outcomes observed in the real world, helping payers to assess the therapy's value, and securing fair access to potentially effective treatments [17].

1.2 Problem definition and relevance of the study

OECD-Arbeitspapier äußert sich kritisch zu derartigen Abkommen:

undurchsichtig und wenig erfolgreich, Unsicherheiten zum Nutzen zu beseitigen

However, a recently issued OECD Health Working Paper by Wenzl and Chapman (2019) on performance-based MEAs draws a different picture of their uptake. It highlights that such payment schemes commonly fall short in mitigating uncertainty regarding medicines' cost- and comparative-effectiveness. Though in the short-run, MEAs might bring the benefit of allowing access to new therapies, many such contractual agreements are opaque, and results are not publicly available [18]. The confidentiality of prices, debilitating the European price-reference system, and the non-disclosure of evaluations from obtained clinical data is not only ethically questionable but also hinders a well-founded judgment about the achieved impact of MEAs on reducing uncertainty [18, 19]. In particular, for Coverage with Evidence Development

schemes (CED), one type of performance-based MEAs, generating and analyzing data on RWE, is often conducted by the marketing authorization holder (MAH), who has a substantial stake in achieving reimbursement for his drug [18, 20].

häufig für Medikamente für seltene Erkrankungen

Orphan drugs constitute the prime example. In this field, most registries are launched and financed by private institutions. These registries - often drug and not disease-specific - have been primarily initiated for regulatory purposes. However, regulatory agencies might not be capable of assessing the completeness and relevance of presented datasets. Besides, data cannot be made publicly available and openly disseminated without the consent of the MAH [21]. Public payers could significantly benefit from sharing experiences made with such therapies and information on the implementation, measurement indicators of success and performance, etc. Still, confidentiality remains a barrier to mutual learning. Greater transparency would also lead to saving resources by payers, avoiding duplication of work between the Member States by enabling the pooling of data from various sources [18].

Register zur Therapie, nicht Indikationen oft vertraulich = Barrieren für wechselseitiges, grenzüberschreitendes Lernen

aber Notwendigkeit: Daten und Infrastruktur teilen Kriterien zur Beurteilung von RWE

This requires cross-border multi-stakeholder discussions to agree on methods for data sharing, quality criteria for the validation of real-world data (RWD), data analytics, and data infrastructure to develop a system that reaps the greatest benefits of RWE for improving patients' lives [22]. Setting against this background, there is a need for establishing a sustainable alternative for payers determining the value for money of many high-prized gene- and regenerative medicines [22]. The definition of high-priced medicines considerably differs between the countries with no standardized classification of when a drug is considered high-cost [23, 24].

Erleichterung für Entscheidungsträger: Anleitung zu Governance, Verantwortlichkeiten und Ergebnissen von MEA

Having a standardized governance framework in place guaranteeing public access to processes, responsibilities, and outcomes of MEAs might enhance stakeholders' accountability and constitute significant facilitation for payers to interchange data gathered in other health care systems [18].

1.3 Objective and research questions

Zielsetzung der vorliegenden Arbeit:

Konzept für MEA:

Considering the growing global importance of MEAs, enabling access under uncertainty, and the encountered difficulties limiting cross-border public learning, this study aims at conceptualizing a future outcome-based reimbursement scheme for high-prized therapies by providing conditional funding while simultaneously generating publicly accessible data on the RWE of treatment effects for determining the value of therapies.

Anleitung für Organisation von Performanz- und Ergebnis-basierte Abkommen

To successfully launch such new reimbursement models tying public data generation of innovative drugs to possible access schemes that enable the reassessment and price adjustment based on the actual health benefit delivered, decision-makers in health policy require sound advice on specific conditions precedent regarding organizational infrastructure, processes, and responsibilities.

Prozesse, Veranwortlichkeiten, Ablaufplan

In meeting this objective, the study explores the central research question, which reads as follows:

Which organizational infrastructure, processes, and responsibilities are needed for such a public reimbursement model with additional monitoring of patients and data generation?

To sufficiently answer the overarching research question (RQ), it is broken down into four more specific sub-questions:

4 Forschungsfragen:

1. unterschiedliche organisatorische Modelle
2. Module in den Modellen
3. Anwendung der Modelle
4. Erfahrungen

- RQ1: Which (theoretical) models/ frameworks for setting up such new models for reimbursement with data generation do exist?
- RQ2: Of which modules are these models/ frameworks composed/set up? What are their similarities and differences?
- RQ3: For which innovative (gene- or regenerative) therapies are these models/ frameworks applied?
- RQ4: What experiences are made, and what can be learned from countries further advanced in applying these reimbursement models? What needs to be in place before implementing such models regularly?

To set the scene, the paper first gives an overview of current public policy mechanisms to curb the high expenses of pharmaceuticals aiming at achieving a "fair" price for medicines with a specific focus on the feasibility of MEAs. It further situates the role of RWE in decision-making and mentions selected EU initiatives for fostering information sharing. Part two compares the identified practice models for public risk-sharing, analyzing their procedural aspects, learnings, and experiences made in different countries. Derived results are interpreted to outline possible directions and recommendations for role models for future access with data generation.

zunächst aber Überblick über derzeitige Politikmechanismen und -praktiken, "faire" Preise zu erzielen

2 Theoretical framework

2.1 Conceptual approaches to fair pricing and securing public return on public investment

Diskussion zu "fair" Pricing

Since the Member States are facing difficulties ensuring patient access to highly-priced gene- and regenerative therapies, reflecting upon the appropriateness of the traditional pricing system for those drugs seems inevitable. This requires further discussion on what constitutes a fair price for medicine, especially when information on the value of the drug is very limited at the point of approval, and a considerable amount of financing of R&D activities is allocated through public investments [25]. Dabbous et al. (2020) believe that "[…] if drugs are approved based on limited clinical data that demonstrate the potential to generate health outcomes rather than achieved outcomes, the high price for these drugs should also remain a potentiality and not a reality. Therefore, it seems ethical and fair that payers do not agree to such high prices unless the manufacturers are willing to deliver the required effectiveness data" (Dabbous et al., 2020, p.430) [26].

notwendig und ethisch vertretbar, wenn Potential besteht, nicht aber Realität belegt ist

verschiedene Konzepte:

Current debates within and across Europe, trying to determine a fair price level for medical innovations, resulted in several conceptual approaches for fair pricing models [27]. Risk sharing and public funding were among the topics discussed in the World Health Organisation (WHO) Fair Pricing Forum 2017, where it was proposed that "[…] governments should attach conditions to research funding so that the public funding is explicitly taken account of in pricing discussions and the results are made publicly available" (WHO, 2017, p.7) [28]. Risks should equally be shared between the public and manufacturers, possibly leading to lower prices [28].

Konditionen, wenn öffentliche F&E gewährt wurde

keine allgemein konsentierte Definition, aber Umschreibungen wie Erschwinglichkeit, Zugang und finanzielle Nachhaltigkeit

Reviewing available literature on that topic revealed that no consensus on a common definition for a fair price had been established yet [27, 29-32]. Shared characteristics and keywords revolve around affordability, access, and financial sustainability. This also holds for the definition provided in the Fair Pricing Forum 2017, which fits best to the overall objective of this paper, highlighting the importance of a "[…] reasonable return on investment in exchange for an affordable price, which is to say one that does not bankrupt health systems and other payers" (WHO, 2017, p.7) [28].

Konzept von Moon (2020):

Preis wird durch Unter- und Obergrenze begrenzt, der Interessen von Käufer wie Anbieter berücksichtigen

An approach to outline a concept of fair pricing for medicines was proposed by Moon et al. (2020), putting forward the idea of establishing a fair pricing zone determined by a price floor and price ceiling that account for the interests of both buyers and sellers as well as objectives of civil society such as affordability. Sellers are defined by three different groups: R&D engineers, producers, and suppliers. Buyers encompass everyone paying for medicinal products like governments, health insurances but also those reaping the benefits from these health technologies, including patients and the general public at large in case of preventive health measures. Seen from the perspective of sellers, the price floor, meaning the minimum tolerable price by sellers, should be set in relation to R&D expenses, costs of production, dispensation, other expenditures (i.e., drug-registration fees), as well as a reasonable profit. On the flip side, a fair price ceiling represents the willingness to pay of buyers and should reflect their current and projected affordability, reliability of supply with medicines, and associated benefits gained for the individual patient

and overall society. Following that, any price limited by the price floor as the lower and the price ceiling as the upper border is fair as it accounts for the expenses incurred to sellers, allows an acceptable amount of profit, and does not stretch buyers' budget [33].

Berechnungsbeispiele basieren auf Offenlegung von Ausgaben/ Kosten

However, the main shortcoming of this theoretical framework is the prerequisite of transparency about R&D costs, production, and supply. These data are usually not publicly available, limiting possibilities to thoroughly evaluate the fairness in pricing and aggravating the imbalance of asymmetric information in favor of the seller. Yet, attaching conditions to public investment, marketing authorization, or reimbursement to compel access to data might enhance transparency [33].

Voraussetzung: Transparenz schaffen !

Laplane/Mazzucato (2020) zu Konditionen bei staatlichen Förderungen

The following two conceptual models resonate with the idea of imposing conditionalities on the distribution of state resources. The first one, developed by Laplane and Mazzucato (2020), presents an approach for an innovation policy, illustrating the major function of the state as a provider of funds, facilitator, and pacesetter for institutional development. It argues for socializing and evenly splitting risks and rewards between public and private bodies. Creating equal footing on both sides may arbitrate a distorted ratio of powers, diverging beliefs, and foster a shared understanding of value. The model mentions profit sharing and conditionalities as the two main juridical instruments of governments to obtain a solid compensation of investment. Profit-sharing provides a possible means for offsetting potential risks from the investments taken regarding the financial rewards gained. Conditionalities linked to the distribution of public money empower the R&D process to thrive and simultaneously guide benefits to societal needs serving the greater good [34].

Aufteilung von Risiken und Chancen zwischen öffentlichen und privaten Institutionen

Voraussetzung: Einigkeit zum „Wert“ von Innovationen

Mazzucato et al. (2018) zur Transformation des Innovations-systems zur Erfüllung öffentlicher Bedarfe (statt nur Profit-Orientierung)

Realizing public return through conditionalities in the specific context of the pharmaceutical market is mentioned in the second conceptual model issued by Mazzucato et al. (2018). It highlights the role of conditionalities as means to transform the existing structures of the predominantly profit-oriented innovation system into one that yields public value and mirrors societal needs. This is currently hindered by the absence of public accountability and the opacity and concealment of clinical study data, which is detrimental not only for the overall population health, possibly withholding information about the events of adverse drug reactions, but also for the scientific research process per se limiting collaboration and mutual learning [35]. Another problem identified is that the present innovation system provides no mechanisms for securing accessible prices to therapies, also to those that were financed with public money, leading to affordability constraints around the globe. For that reason, an alternative public health-driven R&D model is being proposed grounded in the principles of synergetic cooperation, a fair division of risks and benefits, and an orientation towards long-term goals for sustainable healthcare financing [35].

Voraussetzung: ein F&E Modell, das Public Health Bedarfe identifiziert und Ziele definiert

Bedingungen für Erschwinglichkeit und Zugang öffentlich generierten Wissens stellen

Imposing conditionalities on affordability and access may prevent governments from ‘paying twice,’ once for the clinical development and another time for the reimbursement. Conditions for knowledge exchange ensure that the data produced is not seized by private actors but remains within the organization and stays available to generate benefits to the broader public. Publicly accessible outcomes of clinical studies would limit possibilities for concealing the evidence for financial gains and thus, assist payers in assessing the value of medicines and determining a fair price [35].

The conceptual models mentioned above represent an attempt to define a fair price for medicines and lay down approaches for redesigning the R&D and access process to maximize societal benefits and a reasonable return on public assets. They further stimulate public debate on contemplating if the current healthcare systems are adequately equipped to take up the challenges of securing reimbursement and access to highly-prized ATMPs.

bisherige Konzepte sind erste Vorschläge, das Innovations-system neu aufzusetzen

2.2 Traditional public price control mechanisms

To set the scene, the paper first gives an overview of conventional pricing strategies available to public payers for regulating the high expenses of pharmaceuticals aiming at achieving "fair" prices and affordable access.

traditionelle Preis-Strategien

According to the WHO, four main governmental price control mechanisms prevail in most countries:

4 verbreitete Preis-Kontrollmechanismen

- direct control (e.g., External Reference Pricing (ERP), Value-Based Pricing (VBP)/Health Technology Assessment (HTA)),
- indirect control (e.g., Internal Reference Pricing (IRP), cost-effectiveness thresholds) and
- utilization control (e.g., 'envelope agreements', funding according to predetermined stages of the disease and/or treatment durations)
- a mixture of all three methods [36].

Drawing on two analyses from Vogler et al. (2017, 2018) provides a critical reflection upon the constrained capability of European pricing strategies in achieving broad patient access to health technologies [3, 37].

By using **direct price control** mechanisms, public institutions fix prices by a predefined set of principles or frameworks. Available policy instruments are ERP and VBP [36]. The concept of **ERP**, being defined as the "[p]ractice of using the price(s) of a medicine in one or several countries to derive a benchmark or reference price for the purposes of setting or negotiating the price of a medicine in a given country" is used in most of the European countries (Vogler et al., 2017, p.309) [37]. Yet, there exist vast differences, notably in the extent of application and methodological approach. ERP is commonly used for determining the launch price and serves in theory as an orientation for public payers to compare the prices suggested by the MAH and categorize their own country to it. However, price transparency is frequently reduced because of confidential discounts, impeding payers in having a precise market overview and making well-informed pricing decisions [37]. As ERP refers to the official list prices rather than the confidential discounted ones, payers risk overpaying [3, 37].

direkte Preiskontrolle:

externe Referenzpreise
Nachteil: bezieht sich auf Listenpreise; große Intransparenzen bei „echten" Preisen

VBP has been suggested as a way of fostering access and while incentivizing product innovations that provide an added value. Prices are determined based on the perceived additional benefit a new treatment claims to deliver [37]. This requires an evidence-based assessment process such as HTA or economic evaluation to estimate the added value offered to patients, the overall healthcare system, and society in its entirety [36, 37]. Applying this policy in practice has not been without difficulties. Dissenting views between payers and MAHs on the scope of value and time-consuming evaluations may result

Nutzenbewertung und Kosten-Effektivitäts-evaluationen
Nachteil: zeitaufwändig; Methoden halten großen Nachfrage-druck kaum stand

in restricted or deferred access. Moreover, given the substantial societal pressure in orphan and oncological disease areas where therapeutic options are depleted, public authorities frequently have no choice but have to bear high costs for little proven evidence of additional value [37].

indirekte Preiskontrolle:

Indirect price regulation is exercised by payers through measures that steer choices or price anticipations of MAHs [36]. A prominent example is **IRP** which assembles drugs with similar or equal therapeutic effectiveness within one country into reference groups for which a uniform maximum reimbursement amount is formed [36, 38]. If manufacturers price the drug above the internal reference price, the difference is born by the patients. In this way, IRP does not present a direct means of constraining the pricing freedom of MAHs and distributors [38]. Furthermore, as this policy is mainly applied for generics (except France and Germany), it cannot be considered an adequate instrument for patent-protected costly pharmaceuticals [3]. Another example is **cost-effectiveness thresholds** as used in economic evaluations, reflecting the maximum willingness-to-pay of public authorities for an additional unit of health gained, guiding MAHs towards pricing their products below the threshold to increase the likelihood of obtaining a positive recommendation [36, 39]. However, as previously mentioned, payers tend to reimburse cost-ineffective medicines in the fields of orphan and oncological drugs [3].

interne Referenzpreise Nachteil: referenziert nur auf therapeutisch-gleiche/ ähnliche Produkte, keine Referenz zu „neuen" Medikamente

Kosten-Effektivitäts-Schwellenwerte Nachteil: halten großen Nachfrage-druck kaum stand

Utilization control, the third price control method, goes beyond solely focusing on price regulation, but also on drug volumes. It ensures that the right medicine is used for the right patient and not for someone that might equally be treated with cheaper medical care. Examples include 'envelope agreements' and funding either tied to predetermined stages of diseases or the duration of therapies [36, 40]. 'Envelope agreements' are contracts between payers and manufacturer valid for multiple years that limit the maximum number of medicines a pharmaceutical company is allowed to sell. In case of exceeding this threshold, the MAH has to grant a price discount [40]. For payers, these price caps provide higher financial planning security while guaranteeing access to therapies. Yet, considered from the perspective of manufacturers, the economic unpredictability of this instrument as an increase in sales might result in fewer earnings makes the wider uptake of this scheme undesirable [8]. Since envelope agreements aim to tackle payer's financial uncertainty through reducing expenditure, they can be considered as a subtype of financial-based MEA. MEAs will be further discussed in chapter 2.3.2.4.

Mengen- und Verwendungskontrolle geben Planungs-sicherheit für Zahlerinstitutionen

Instrument auch als finanzielle MEA bekannt

Summarizing the above, it can be concluded that each of these cost control mechanisms entails its benefits and downsides. Looking at the excessive price tags charged for gene- and cell therapies, it seems like none of these mechanisms achieves the balance between establishing a fair price accounting for the interests of both sellers and buyers and securing availability to patients, which highlights the necessity of changing the traditional pricing system [7, 41]

jede der Kontrollmaßnahmen hat Vor- und Nachteile.... wirken aber bei exorbitanten Preisen nicht

2.3 Practical solutions to deal with uncertainty under high prizes

2.3.1 Cross-country collaboration

The limited success of these conventional forms of public price control might have accelerated the emergence of alternative solutions to deal with uncertainty under high prices.

offensichtliche Limitationen der traditionellen Preiskontroll-mechanismen – Erprobung neuer Ansätze:

Systematic voluntary **cross-country collaboration** efforts in numerous fields between public institutions have been put forward as an opportunity to foster patient access to innovative medicines [19]. Key areas encompass tackling information asymmetry, fragmentation across systems, and boosting negotiating power [19]. These are to be addressed through mutual learning and sharing experiences on the success or failure of specific policies in other countries, partnering in technical areas such as horizon scanning and HTA for increasing the scientific evidence basis for more sound decision-making and forming alliances in pricing discussions [3, 37]. Cooperation can take many forms. It could be implemented at the national or trans-national level between two or multiple parties or under the auspices of the EU, such as the organization of the marketing authorization procedure [19]. It can also be embedded in the broader context of cross-agency collaboration in the fields of pricing, procurement, or HTA like the European Network for Health Technology Assessment (**EUnetHTA**) [3, 37, 42].

Länder-übergreifende Zusammenarbeit soll Verhandlungsmacht erhöhen

EUnetHTA
BeNeLuxA(IR)
FiNoSe
….

Further examples worth being mentioned are the Valletta Declaration of Mediterranean Countries, who join forces in horizon scanning, HTA, and negotiations, and the **BeNeLuxA collaboration**, compromising Belgium, the Netherlands, Luxembourg, Austria, and Ireland, that share the same key activities as the Valletta Declaration plus knowledge exchange [35, 42]. Besides, FiNoSe, a Nordic co-operation between the Finnish, Norwegian, and Swedish HTA agencies, aims at conducting joint assessments [43]. These groupings specifically emerged as a reaction to the market entry of high-priced drugs, jeopardizing the fiscal sustainability of Member States and strive towards combining forces to achieve fair prices. Initial successes have been reported by Belgium and the Netherlands, both part of the BeNeLuxA initiative that jointly negotiated a price for Spinraza®. The exact reimbursement level is not disclosed for reasons of confidentiality [38].

viele Barrieren:

Freiwilligkeit
nicht-bindend
Ressourcen-intensiv

In its various forms, collaboration has shown itself to be a promising instrument for policymakers to collectively deal with, i.e., unbalanced bargaining power, opacity around prices, and fragmented markets [3]. Nonetheless, it also has its limitations and requires profound groundwork for ensuring a smooth operation and a long-lasting impact. One aspect is the different guidelines for national drug policies, highlighting the need for cooperative measures to harmonize approaches [42]. Another factor hindering effective collaboration is the lack of interest of big pharmaceutical companies in partnering with these collaborative formations [42]. Besides, the voluntary, non-legally enforceable nature of these joint actions makes it difficult to ensure the involvement of all stakeholders, underpinning the requirement to mobilize appropriate commitment from public institutions and decision-makers to receive sufficient resources for carrying out collaborative activities [3, 42]. Undoubtedly, joining forces between different healthcare systems to counter distortions of power generally point in the right direction of building up common strengths to improve access to medicines [38]. However, additional supplementary policies seem unavoidable.

Potential options to be further explored might include innovative solutions that adopt a holistic approach considering the entire lifecycle of drugs [3].

2.3.2 Using real-world data for innovative access schemes with evidence generation

Terminology

Real-World-Data (RWD) gewinnen an Bedeutung bei mehrmaliger Bewertung von Therapien entlang des Lebenszyklus

Considering the various kinds of uncertainties associated with ATMPs, combined with the enhanced supply of potential sources for data collection, requires rethinking the way HTA activities will be structured in the future. This includes, i.e., reviewing if HTA should shift away from the typical linear approach to a more circular process of reassessing the value of the drug [44].

One possibility might be a longitudinal strategy for evidence generation of treatment effects observed in the real world along the lifecycle of therapies [22]. And in fact, particularly bearing in mind the extreme price tags of recently introduced medical innovations, policy-makers are gradually exploring the possibility of using RWD for coverage and regulatory decisions, acknowledging the significance of obtaining data exceeding the controlled clinical setting with selected patient populations in randomized controlled trials (RCTs) [45, 46]. This is consistent with the common terminology for RWD framed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Real-World Data taskforce in 2007, referred to by several other authors [44, 47, 48], which defines RWD "[…] as data used for decision-making that are not collected in conventional randomized controlled RCTs" (Garrison et al., 2007, p.326) [45].

Unterscheidung zwischen RWD und RWE (real-world-evidence) = Daten vs. Informationen

Further conceptual differentiation between RWD and RWE was undertaken by ISPOR, according to which "[…] 'data' conjures the idea of simple factual information, whereas 'evidence' connotes the organization of the information to inform a conclusion or judgment" (Garrison et al., 2007, p.327) [45]. Put another way, the data alone in its raw form provides no conclusive information but constitutes one element of a study plan. In contrast, evidence is derived from a study plan and interpreted within this context [45].

Sources of real-world data

Quellen von RWD

Types of outcomes to be generated through RWD comprise clinical outcomes (e.g., mortality, morbidity), patient-reported outcomes (PROs) (e.g., health-related quality of life, adherence), and economic outcomes (e.g., resource utilization) [45]. RWD sources identified by Nabhan et al. (2019) and the ISPOR Real-World Data taskforce encompass the following:

1. Complements to RCTs
2. Pragmatic clinical studies
3. Registries
4. Administrative data
5. Health surveys
6. Medical records
7. Social media [45, 46].

komplementäre Daten (zu RCTs): PRO, GesÖk, Anwendungspraktiken

Complements to RCTs generate data on PROs and economic parameters along traditionally conducted RCTs that predominately concentrate on clinical outcomes. This additional information sought by researchers provides, i.e.,

insight into therapeutic practice patterns like dosage regimens. Shortcomings of RCTs have already been mentioned previously [45].

Pragmatic clinical studies are prospective, large randomized trials observing heterogeneous patient groups in real-world practice. They combine the advantage of randomization of RCTs, which reduces the risk of bias in analysing the cause-effect relation between the medicine and health outcome, with the strength of observational trials, studying more diverse patients with potential co-morbidities that increases the possibility of obtaining statistically significant differences in meaningful endpoints. On the downside, the large sample size adds complexity to data collection, increases costs, and may lead to data quality issues [45].

pragmatische klinische Studien

Registries employ an observational prospective research design that records data on clinical parameters, PROs, and economic outcomes in an electronic format. The long-term patient follow-up and the enrolment of diverse populations enable a realistic representation of disease characteristics, treatment effects, adverse effects, and quality of life closer to reality. To this end, registries are sometimes set up for gathering post-marketing surveillance data to address specific remaining uncertainties or answer regulatory requests for receiving conditional marketing authorization. Yet, it should not be overlooked that the missing randomization and standardization of therapies make registries prone to bias, lack of data integrity, and hinders consistent data analysis [45, 46].

Register

The cross-cutting nature of **administrative databases** used for billing reasons and gathering coded information on patient characteristics, diagnosis, treatment plans, and related costs allow the retrospective (sometimes real-time) assessment of claims data on economic and clinical outcomes. The immense dimensions of these data records and the timely and cheap processing of their content highlight the value of administrative data to facilitate the detection of rare events in patients and understand the actual resources used across treatments and indications. However, data protection, data quality, and methodological challenges like biased estimates due to treatment selection threaten the validity of data and hinder the usage for decision-making [45, 46].

administrative Datenbanken

Health surveys compile information on PROs, resource use, costs, and clinical practice patterns of a representative sample group. Their underlying methodological stringency facilitates the generalization of results. Nevertheless, they do not collect intervention-specific data and are also susceptible to bias [45].

Gesundheitsbefragungen

Medical records, whether paper-based medical chart reviews or electronic health records (EHRs), display data on patient characteristics, interventions, diagnostic results, and notes of prescribers. While medical chart reviews have previously been used for obtaining RWD on particular therapies or diseases, the advancement of employing EHRs that include more comprehensive, longitudinal data reduced the costs of analyzing medical records. It should be borne in mind that converting these data to a research readable format poses a challenge [45, 46].

Krankenakte

Through **social media,** a recently emerging source for RWD, patients exchange their unfiltered opinions and experiences during diagnosis, therapies received, and possible side effects. This provides an opportunity for understanding possible reasons behind not adhering to a therapy plan. However, self-reported information is based on subjective perceptions of single patients that do not capture relevant characteristics of all patients, and clinical outcomes are not verified by a second person (e.g., physician) [46]. This might

Soziale Medien

make the source highly prone to influence since individual contributions could willingly lead the patients´ discussion in certain directions.

Managed-entry agreements

Terminology

Begriff des "Managed-Entry-Agreement (MEA)" bezeichnet Erstattung unter kontrollierten Bedingungen & Linderung finanzieller Risken

The aforementioned traditional public price control mechanisms commonly allow three different forms of coverage: full reimbursement, no reimbursement, or restricted reimbursement [12]. The increased introduction of costly medical technologies placed public payers in the challenging position of ensuring access to expensive innovations while achieving value for money which led to the adoption of alternative reimbursement measures such as entering into individual contracts with manufacturers 'managing' the process of securing coverage and controlling financial risks of those technologies [3, 8, 12]. These arrangements can take various names like risk-sharing contracts or access with evidence development [12, 18]. In Europe, the term MEA has become widely accepted [3].

unter Unsicherheit zur Performanz von neuen Technologien

This study refers to the definition established by Klemp, Frønsdal, Facey, and the Health Technology Assessment international (HTAi) Policy Forum Group (2011), which is utilized by many others [16, 18, 49], describing MEAs as "[…] an arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize effective [sic] their use or limit their budget impact" (Klemp et al., 2011) p.79) [12].

strategisches Instrument mit vielen Ausprägungen

Hence, MEAs constitute strategic tools that provide greater flexibility for both manufacturers and payers. Flexibility in mitigating uncertainty around the value of the drug, along with a higher degree of certainty about gaining access to markets for the industry. Facilitating the dialogue and finding a balanced compromise between MAHs and payers allows the necessary leeway for decision-making to turn away from either/or reimbursement and accelerate patient access to medical innovations [49].

Vertragspartner sind: öffentliche Zahlerinstitutionen (Versicherungen), kommerzielle Anbieter (Pharma)

To further establish a common terminology used in this paper, manufacturers encompass any MAH that markets medical technologies while the contractual partners – to mention a few – may include public payers, commercial insurance companies, governmental institutions, or authorities in charge of reimbursement decisions or HTA, are designated as payers. MEAs can be concluded between manufacturers and providers, but for this study, only MEAs between payers and manufacturers will be taken into consideration [18].

verschiedene Taxonomien zur Klassifikation von MEA

Stemming from the different definitions and understandings of MEAs, various taxonomies prevail [16, 18, 49, 50]. The common feature shared by many is the classification into non-health outcome or financial and health-outcome-based agreements. It is claimed by Ferrario and Kanavos (2013) that a lot of taxonomies seem impractical, not sufficiently addressing the complexity of these contracts at the national level. For that reason, they proposed a new typology for Europe employing a polyvalent taxonomy, as shown in Figure 2-1, where the first tier presents the different targets aimed at using MEAs, and the second one outlines the subject of monitoring (e.g., utilization). At the same time, the third level portrays the instruments applied to achieve the predefined goals, and the last tier shows the effect on pricing, reimbursement, and a potential renegotiation [16].

This research will focus on performance or so-called outcome-based MEAs (OBMEAs) since only these schemes incorporate the collection of RWD on health outcomes. A brief overview of this type will be given hereafter.

in diesem Bericht: nur "Outcome-based MEA" (OBMEA)

According to Figure 2-1, OBMEAs either aim at

(a) monitoring the utilization in real life and ensuring value for money by conditioning the refund of the therapy or imposing a retrospective discount to its performance observed under real-world conditions harnessing instruments such as patient registries; or

(b) managing decision uncertainty by providing additional evidence to close evidence gaps through CED schemes. In particular, the latter often involves re-assessments resulting in price adjustments or the conclusion of new contracts [16, 49].

Zielsetzung: Anwendungs-beobachtung, Erstattung an Ergebnisse gebunden, Sammlung zusätzlicher Evidenz

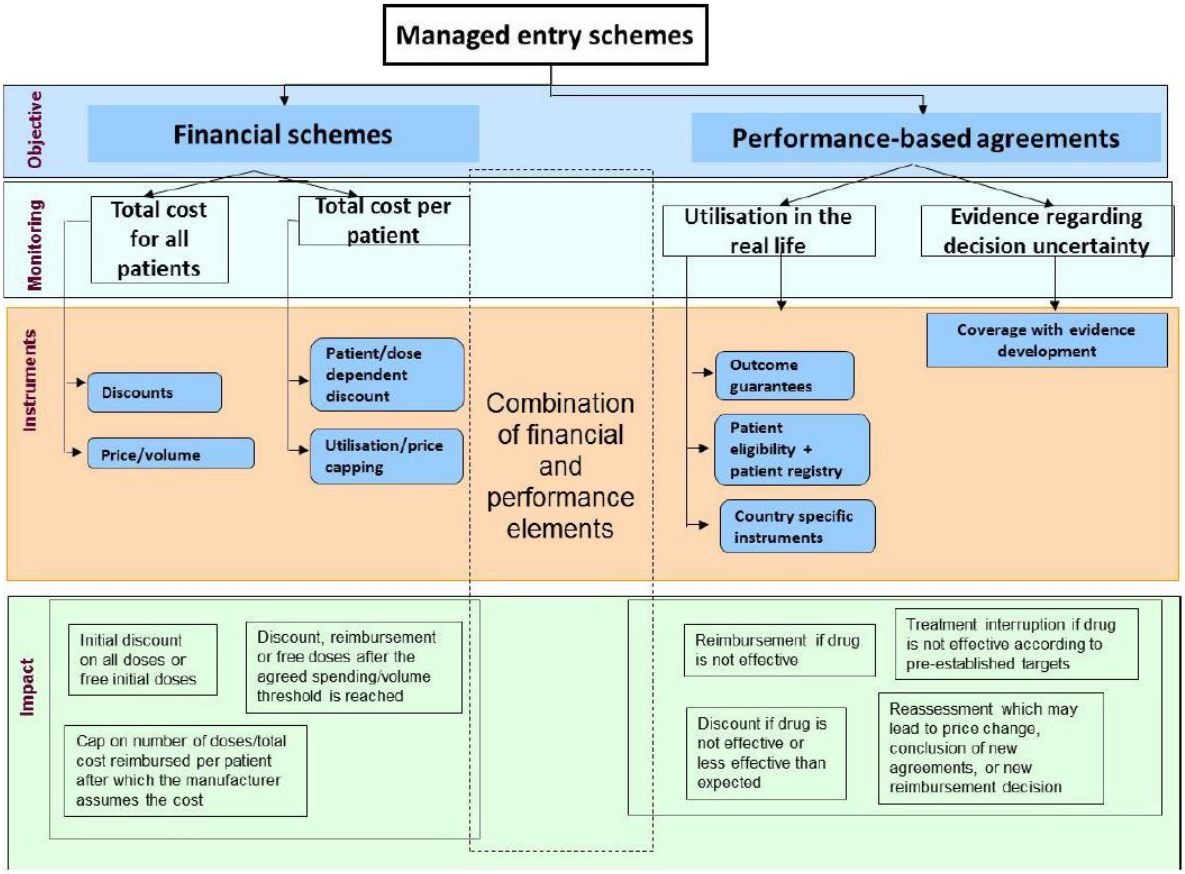

Figure 2-1: Taxonomy of Managed-entry agreements (Ferrario and Kanavos, 2013, p.128) [16]

Managed-entry agreements in Europe

A notable body of scientific literature reviewed the experience European countries had with MEAs [16, 18, 23, 26, 49, 51-53]. Almost all studies agree on one point: MEAs have become a well-established tool operating around the world and especially in Europe, yet their implementation considerably varies from one country to another [4, 26, 52].

zahlreiche Publikationen zu Erfahrungen mit MEA in Europa

große Länder-spezifische Unterschiede bei MEAs

Several factors drive the disparity. First, differences in economic prosperity and health care systems result in applying diverse reimbursement mechanisms [52]. Second, country-specific methodological requirements in HTA generate inconsistent forms of risk-sharing [4]. The feasibility of executing the different possible categories of MEA, as described in the previous chapter, is further determined by structural differences in contextual factors across countries, such as the ability to collect and compile data via reliable IT infrastructure systems [52].

wenig Unterschiede bei Anwendung von MEA: kosten-intensive onkologische und Orphan Therapien

A slightly more homogeneous picture can be observed for the drug application areas of MEAs. Data from the literature demonstrates that most agreements are primarily concluded for cost-intensive medicines targeting oncological and orphan diseases, apart from anti-diabetic medications and therapies treating neurological, rheumatic, and endocrinological disorders [18, 23, 50]. Following a study by Pauwels et al. (2017), hematological drugs offer the most significant potential for MEAs. Around 24% of all agreements considered in the analysis concerned a medicinal product for which MEAs were in place in more than one country simultaneously, yet the content of the contracts was found to be mixed [52].

neben OBMEA auch finanzielle Abkommen: Preisnachlässe und Rabatte

Besides, the number of financial-based agreements has rapidly been expanded in recent decades. Figures entail that this type is or has been applied in two-third of all countries being part of the OECD and EU [18]. Price discounts and rebates are highly popular because of their assumed more straightforward implementation and possible savings for public payers. Conclusively, financial-based agreements mainly serve as cost-containment tools, while for MAHs, they ensure market entry at a high list price to curb parallel trade [26]. OBMEAs are less prevalent, with their main goal often being financial, lowering prices to balance budget impact and enhancing cost-effectiveness. Albeit, they are also used for managing uncertainty regarding the individual performance of therapies [18].

OBMEA sind wenig attraktiv für Zahlerinstitutionen, weil .....

As reported by Bouvy et al. (2018), the industry showed, in general, a greater interest in breaking new grounds with OBMEAs than payers. The lacking appeal of MEAs for public payers, especially schemes with data collection, is due to various reasons, which will be discussed in the following [54].

Feasibility of outcome-based Managed-entry agreements

Erfolg von OBMEA: Verringerung von Kosten und Unsicherheiten zum Nutzen

To be considered successful for payers, OBMEAs need to achieve a considerable decrease in the budget impact, mitigation in the uncertainty around the health effect gained, a more efficient product use, or a mixture of the three [54]. However, practical difficulties inhibit their broader expansion and utilization.

aber: hoher administrativer Aufwand und Kosten

A general hurdle concerning all OBMEAs is the high **administrative effort and costs** associated with data generation requiring reliable information systems not readily available in every country [11, 18, 50, 54]. This holds especially true for schemes employing routine data collection systems. An even greater administrative burden is found in countries like Italy, which created a registry platform for operating MEAs Those schemes heavily rely on healthcare workers for data collection and require ample workforce for analysing the data [18]. Overstraining medical workers frequently leads to human errors in, e.g., filling out necessary forms [26]. Obtaining valuable data of sufficient quality on relevant endpoints can therefore be sometimes challenging [18].

Mangel an konsolidiertem Vorgehen (Dauer der Datensammlung, Konditionen etc.) und Kriterien

Besides, a **missing consolidated approach and governmental structure** of these schemes make them susceptible to tampering attempts after implementation. This stems from lacking standardized criteria on several points: (a) deciding on the requirement and suitability of schemes to resolve uncertainties, (b) defining rules for the duration of data collection, processing the re-evaluation, and adjusting prices as additional evidence becomes apparent, (c) determining conditions for certain reimbursement decisions such as the obligation to set-up a registry [50].

Interessenskonflikte und Rollen der involvierten Parteien

Too much room for interpretation is also left concerning the responsibilities and roles of stakeholders involved in the scheme. Particular attention should be paid to preventing **conflicts of interest** that could occur when the responsibility of funding, data generation, analysis, and dissemination of results lies with the manufacturer. This may lead, i.e., to distorted presentations of observed study outcomes focusing only on positive results, non-disclosing negative ones [50].

Mangel an Transparenz wegen Vertraulichkeit der Daten

A tightly related issue is **opacity** [50]. Concealment of data hinders the exchange of trial findings between different actors involved and the wider research community, so the original target of narrowing down uncertainties is missed [3]. This points to the need to enhance transparency in the broader sense, induce the dissemination of study outcomes, and openly access registries [50]. However, it should be borne in mind that confidentiality of financial modalities marks the backbone of MEAs [52]. Full disclosure of every detail of MEAs seems unrealistic, but achieving a certain degree of openness appears desirable, at least from the perspective of public payers.

Umgang mit öffentlichem Druck

On top of that, payers are coping with **public pressure** exerted by various stakeholder groups, intensifying the challenge of translating evidence-based science into actual policy practice [50]. Expert interviews, carried out in the previously mentioned OECD study on performance-based MEAs, perceived OBMEAs as "[…] a response to pressure by the public and the industry to cover new and high-priced medicines" (Wenzl and Chapman, 2019, p.37) [18]. Given the limited number of alternative options, payers had to enter into these contracts to make expensive drugs available to the public, meeting the pressing demands of patients, relatives, and prescribers for rapid access [18].

Mangel an Folgen: Disinvestment infolge von gering effektiven Therapien

Closely associated with this are possible **disinvestments** that would consequently follow if the data collected proves the ineffectiveness of therapies. However, withdrawing access after treatment has already been applied on patients turns out to be challenging, encountering low public acceptance and incomprehension for revoking interim funding decisions since no standardized processes for smoothing the phasing out of patients are in place [54].

öffentliche Zahlerinstitutionen haben sehr gemische Gefühle zu OBMEAs, aber notwendig in Ermangelung von Alternativen

Following from interviews conducted within the study of Bouvy et al. (2018), public payers and HTA agencies indicated **mixed feelings** about OBMEAs, having doubts if certain contracts meet the initial objective of reducing uncertainties [54]. Nonetheless, there is consensus that due to various financial pressures on healthcare systems like the rising costs of medical innovations being launched, and the lack of alternative approaches, it is believed that MEAs will continue to enjoy great popularity as a practical tool to finance high-cost products with missing data at product launch [11, 26].

Yet, their **sophisticated character** and often ill-advised underlying objectives and strategies make their practical implementation susceptible to errors. This points to the need for an overhaul of the design, corresponding with the common trend observed in health policy practice away from a single assessment going towards several evaluations of an innovation [1, 26]. The movement is expected to forge ahead thanks to the ever-increasing technical possibilities of collecting and exchanging data [1].

Good practice recommendations and real-world evidence initiatives

Scientific harvest on good practice models for MEAs is abundant. Several frameworks and guides exist for executing and reporting high-quality RWE studies, assisting healthcare decision-makers in dealing with RWD for coverage decisions, and increasing transparency to enhance the payer's confidence in RWE [45, 48, 55-57]. However, these pretty generic guidelines provide no specific recommendation on how to tie publicly generated RWE of innovative drugs to possible access schemes that enable the re-assessment and adjustment of the level of reimbursement based on the actual health benefit delivered. Some guidance and recommendations for dealing with issues of OBMEAs, as mentioned in the previous chapter, are given in a few studies which investigate challenges of OBMEAs in general [3, 7, 18, 49, 54].

According to Michelsen et al. (2020), those challenges mainly arise from difficulties balancing the conflicting interests of all parties involved, achieving consensus on financial conditions like agreeing on how to spread reimbursement, the absence of a governance framework, problems with managing existing or setting up new data collection systems and possible national legal hindrances [7]. Drawing on the experience European countries have made with OBMEAs, Wenzl and Chapman (2019) identified the following four key topics of good practices:

1. Devise a strategic way for guiding the application of OBMEAs, making sure that they are only concluded when the value of gaining additional data weighs more than the expenses for bargaining and implementation (a possible decision-tree for MEAs in the context of HTA is presented in Appendix 7.1);
2. Design OBMEAs pursuant to the predetermined uncertainties in question and the sources of data available;
3. Put a governance framework into effect that safeguards transparent processes and enables taking actions in accordance to the additional evidence generated, also possibly facilitating the exit of the scheme;
4. Achieving a certain degree of transparency of the content of MEAs and constraining non-disclosure to sensitive elements of commercial nature like prices [18].

The distinction made between process transparency and content transparency may require further explanation at this point. Effective governance structures secure accountability of actors involved by making some parts of the application process of MEAs public, encompassing information on the initiation of the scheme, data collection and analysis, and decision-making following the evidence available. Other areas to be addressed include, i.e., ownership of data, monitoring, and impartiality. This should prevent conflict of interest and provide unbiased scrutiny [18]. Besides, greater transparency of the contractual terms of MEAs should be achieved. It is recommended that information on the drug performance should be shared with other stakeholders that have a justified public interest. Creating a publicly available knowledge base could enhance cross-border collaboration of payers, HTA bodies, and regulatory agencies on various fields saving resources while limiting overlapping tasks and duplication of work [18].

Gute Praxis bei der Sammlung von Daten für den Zweck einer Erstattung und Re-Evaluierung

Empfehlungen basierend auf Herausforderungen von OBMEA

4 wesentliche Themen:

Abwägung für/ gegen OBMEA: mehr Nutzen als Aufwand

Design von OBMEA zur tatsächlichen Verringerung von Unsicherheiten

Governance mit transparenten Prozessen und Möglichkeit zum Ausstieg aus OBMEA

transparente Datensammlung und Ergebnisse

Transparenz:

Bestimmung von Verantwortlichkeiten
Datenhoheit
Unbefangenheit der Ergebnisse der OBMEA

Standardisierung von Datensammlungen ermöglicht Austausch dieser über Ländergrenzen

Greater standardization of data across countries is also recommended by the OECD Council that calls for developing a framework for health data governance in every country, promoting harmonized norms for data compatibility and the use of standardized data items and formats as well as overcoming obstacles of data exchange [58]. One opportunity for facilitating the compilation of data across the Member States lies within the intercountry collection of clinical trial data, as suggested by Michelsen et al. (2020) and Bouvy et al. (2018) [7, 54]. Establishing interoperable patient registers creates a more efficient data collection and alleviates the administrative burden borne by individual states [7]. Vertical collaboration of public reimbursement and regulatory institutions could be one possible step in this direction [18, 54]. Combining data collection efforts by harmonizing the evidence requested by regulators for conditionally approved therapies with the requirements for RWE demanded by payers may enhance international alignment on data collection [7]. The recently introduced EMA project Data Analysis Real World Interrogation Network (DARWIN) EU is one example of trying to coordinate health data in Europe by developing a viable data management platform for health data exchange, access, and analysis. The overall objective is to establish a pan-European network of different databases containing RWD to enable evidence-based decision-making of regulators with health data from real-life practice [7, 59]. DARWIN is an integral part of building a common European Health Data Space (EHDS), an EC's priority for 2019 to 2025 [60, 61]. Three cornerstones mark EHDS: a governance framework for sharing data, safeguarding their quality, providing a reliable infrastructure while ensuring data interoperability [61].

Etablierung von Patient*innen-Registern

Zusammenarbeit mit Regulator (EMA)

EU-DARWIN: pan-Europäisches Datennetzwerk

internationaler Austausch von Daten

Beyond that, numerous initiatives can be found in Europe and abroad, improving transparency, facilitating international data exchange, and employing RWE for policy-making processes [18, 62]. An excerpt of them is portrayed in Table 2-1.

Verringerung von Daten-Silos

The plethora of initiatives available demonstrates that Big Data has found its way into healthcare decision-making. Using RWE for in particular approval and reimbursement decisions is a rapidly emerging field [47]. Considering the practical difficulties like the administrative burden in capturing and combining RWD sources, it becomes even more important that information is not siloed by single stakeholders or single further technologically advanced countries but mutually shared for the greater public good.

Table 2-1: Selected initiatives on exploring the potential of RWE (table structure adapted from Oortwijn, 2018, p. 23ff. [44])

Organization/ institution	Title	Objective	Further information to be found
EMA	Data Analysis Real World Interrogation Network (**DARWIN**)	Developing a sustainable data management platform for health data exchange, access, and analysis across countries [59].	https://www.ema.europa.eu/en/documents/presentation/presentation-proposal-darwin-eu-data-analytics-real-world-interrogation-network-parlett-ema_en.pdf
European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) (coordinated by EMA)	European Union electronic Register of Post-Authorisation Studies (**EU PAS Registry**)	Open-access registry of non-interventional post-authorization studies (PAS) aiming for, i.e., enhancing transparency and data exchange, restricting publication bias [63].	http://www.encepp.eu/encepp/studiesDatabase.jsp
European Network for Health Technology Assessment (EunetHTA)	The Registry Evaluation and Quality Standards Tool (**REQueST**)	Providing a systematic application tool compromising several general recommendations of good practice for producing high-quality data collection guiding the usability for several registry designs [64, 65]. It should assist: ▪ the owners of registries in evaluating the quality of their data, ▪ international bodies decide whether to implement the generated data for HTA and/or regulatory purposes [64].	https://eunethta.eu/request-tool-and-its-vision-paper/
Innovative Medicines Initiative (IMI) (European Commission/ European Federation of Pharmaceutical Industries and Associations (EFPIA))	Big Data for Better Outcomes (**BD4BO**)	Umbrella project of IMI 2 aiming at unlocking the possibilities of Big Data by aligning different sources and forms of data and enabling adequate analysis [66, 67]. BD4BO is composed of the DO-IT project offering mechanisms of coordination for the following disease-specific programs: HARMONY and HARMONY PLUS (blood cancer, hematologic cancers), ROADMAP (Alzheimer's disease), BigData@Heart (cardiovascular diseases), and PIONEER (prostate cancer), as well as the European Health Data and Evidence Network (EHDEN) which combines health information across the Member States into an integrated data model. The data conversion will be conducted by accredited small and medium-sized firms, respecting all data privacy rights and ethical standards since data ownership won´t be affected [66, 67].	https://www.imi.europa.eu/projects-results/project-factsheets/bd4bo
	Accelerated Development of Appropriate Patient Therapies a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes (**ADAPT SMART**)	Another IMI2 initiative, fostering multi-stakeholder collaboration (HTA bodies, patient representatives, manufacturers, regulatory agencies, payers, scientific community) to encourage the advancement of Medicines Adaptive Pathways to Patients (MAPPs) for helping patients get better access to medical innovations [68, 69]. The concept of MAPP envisages providing the right treatment to the right patients at the earliest possible point where the evolving evidence base on a drug's performance collected throughout its lifecycle guides its application area [68, 69].	http://adaptsmart.eu/home/

The Netherlands Cancer Institute Amsterdam	The Drug Rediscovery Protocol (**DRUP**)	Precision adaptive clinical trial extending the usage of oncological therapies beyond their approved label in patient subgroups by using biomarkers to detect signals of clinical effectiveness. It further incorporates an outcome-based reimbursement model for patients responding to the therapy and shares the knowledge generated for potential policy-making processes in the future [70-72].	https://clinicaltrials.gov/ct2/show/NCT02925234
European Commission (European Union's Horizon 2020 research and innovation program)	Pushing the Boundaries of Cost and Outcome Analysis of Medical Technologies (**COMED**)	Guiding leveraging RWE in the systematic assessment of medical devices. Specifically, work package seven (WP7) envisages developing a proposal for setting up and performing CED schemes for medical devices [73].	https://www.comedh2020.eu/wps/wcm/connect/Site/COMED/Home/
	Improved methods and actionable tools for enhancing Health Technology Assessment (**IMPACT HTA**)	Research project investigating cross-country differences in health effects and expenses accrued, combining data from various sources to enhance methodologies for economic evaluation and measuring the performance of health systems. WP10 aims to create a toolkit to support the implementation of OBMEAs for orphan drugs [74].	https://www.impact-hta.eu/
Rijksinstituut voor ziekte- en invaliditeitsverzekering/Institut national d'assurance maladie-invalidité (RIZIV-INAMI) (National Institute for Health and Disability Insurance in Belgium)	**RWE4Decisions initiative**	International multi-stakeholder initiative pursuing a European-wide network for mutual learning on RWE founded on clear-cut governance processes. It, i.e., should specify the details of the data collection like responsibilities, timeline, methodological approach to ensure that the data is complete and of sufficient quality [75].	https://rwe4decisions.com/

Abbreviations: EMA - European Medicines Agency, HTA – Health Technology Assessment, OBMEA – Outcome-based Managed-entry agreement, RWE – Real-world evidence

3 Research methods

The subsequent chapter outlines the methodological approach followed to answer the research questions posed at the beginning. In the first subsection, the overall design of this study is described, while the second one elaborates in greater detail on the scientific approach adopted towards data collection and analysis. The last subsection reviews ethical considerations necessary to be taken into account for conducting this qualitative research.

methodisches Vorgehen zur Beantwortung der Forschungsfragen

3.1 Research design

Following Green and Thorogood (2004), the characterization of qualitative studies should not solely be contingent on their methods of data collection or the nature of information generated but more on what the investigation aims to achieve. Since the general focus of qualitative research lies on examining reasons behind social phenomena, raising questions about what, in what way, and for what reason something happened instead of trying to measure it, in this context, a qualitative research design was preferred to a quantitative for answering the research questions [76].

qualitatives Forschungsdesign zur Beantwortung von sozialen Phänomenen und Beweggründen

More specifically, this paper applies an exploratory research design. It uses a multi-staged approach by combining primary research, generating qualitative data from semi-structured expert interviews, with secondary data from existing literature. Exploratory work in social science research is defined as "[…] broad-ranging, intentional, systematic data collection designed to maximize discovery of generalizations […]" (Given, 2012, p.2) [77]. Its primary purpose is to illuminate and gain new insights into a topic that has not been investigated in detail so far [78]. Exploratory research further attempts to investigate phenomena from a new perspective, elucidating concepts and developing hypotheses while using research methods such as surveys and interviews [78, 79].

explorativ: semi-strukturierte Interviews zum Erkenntnisgewinn …..

This research explores new ways of linking the funding of highly-priced therapies to publicly generated data on the RWE**,** allowing equal sharing of risks and rewards between public payers and MAHs. Employing qualitative research methods like interviews may help obtain a better understanding of that knowledge field, which is still yet to be explored. Since an in-depth insight from individuals involved in setting up such a reimbursement process was needed, expert interviews were deemed the appropriate research method [80].

…zur Umsetzung von Datensammlungen mit dem Zweck der Erstattung hochpreisiger Therapien

3.2 Data collection

3.2.1 Identification of frameworks

To answer the first research question (identifying frameworks and reimbursement models for OBMEAs), a systematic literature search was conducted, complemented by a manual search in grey literature and a request sent to the

zur Identifikation unterschiedlicher OBMEAs:

International Network of Agencies for Health Technology Assessment (INAHTA) ListServ.

Literature search

systematische Literatursuche

The **systematic literature** search was performed in the Ovid MEDLINE database in February 2021. Details on the specific search strategy employed can be found in Appendix 7.2.1. Inclusion and exclusion criteria for the systematic literature search are summarized in Table 3-1. The reporting of the systematic search follows a simplified version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as outlined in Moher et al. (2009) [81].

Table 3-1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
■ Organizational framework for outcome-based/performance-based MEAs	■ Organizational framework for financial-based MEAs
■ Organizational framework for using RWE in reimbursement decisions and re-assessments	■ Organizational framework for reimbursement decisions not relying on RWE
■ Organizational payment models/risk-sharing agreement model for conditional coverage/funding using RWE	■ Regulatory models for conditional approval using RWE
■ Publications in English, German	■ Publications in any other language than English, German
■ Books, peer-reviewed journal articles, policy reports, guidelines, legal texts, manuals of organizations/HTA-institutions, presentations, etc.	■ Conference abstracts, theses, no full text available, articles not publicly available
■ Countries in the Western world with a universal healthcare system, social healthcare system	■ No coherent healthcare system/ multiple systems in the Eastern World

Abbreviations: HTA - Health Technology Assessment, MEA – Managed-Entry Agreement, RWE – Real-world evidence

graue Literatur Handsuche

In addition, grey literature formed an integral part of enriching the literature search since it was assumed that country-specific frameworks might not necessarily be distributed via traditional publication channels.

To that end, the systematic literature review was complemented by a targeted **manual search** in the following websites:

- Grey Matters (tool for searching health-related grey literature) [82]
- IMPACT HTA country vignettes (part of WP10) [83]
- INAHTA database [84]
- European Commission CORDIS [85]
- Websites of public (research) institutions and HTA bodies (e.g. National Institute for Health and Care Excellence (NICE), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Belgian Health Care Knowledge Centre (KCE), etc.)
- Google Scholar
- PubMed
- Google search

im Februar & März 2021

The hand search was carried out in February and March 2021 and included only articles published in English or German. The search strategy used can be found in Apendix 7.2.2.

Literature selection

Auswahl der Literatur mittels Rayyan

Overall, the literature search resulted in 395 hits. Ovid MEDLINE identified 352 citations; the manual search yielded 43 further references. After deduplication, the 384 records were independently reviewed by two people (KW, CW[1]) using the webtool Rayyan® for screening titles and abstracts. Divergent views were resolved through discussion and dialogue.

Volltextlektüre

In the second step, the eligibility of records was assessed by examining the full text.

Einschluss basierend auf Kriterien n=26

Lastly, articles were incorporated in the final analysis when the inclusion criteria described in Table 3.2.1.1-1 were fulfilled. Apart from that, two other references were included that were sent by the interviewees as supplementary information. The whole process of the literature selection is illustrated in Figure 3-1, a slightly adapted version of a PRISMA flowchart as described in Moher et al. (2009) [86].

[1] Claudia Wild

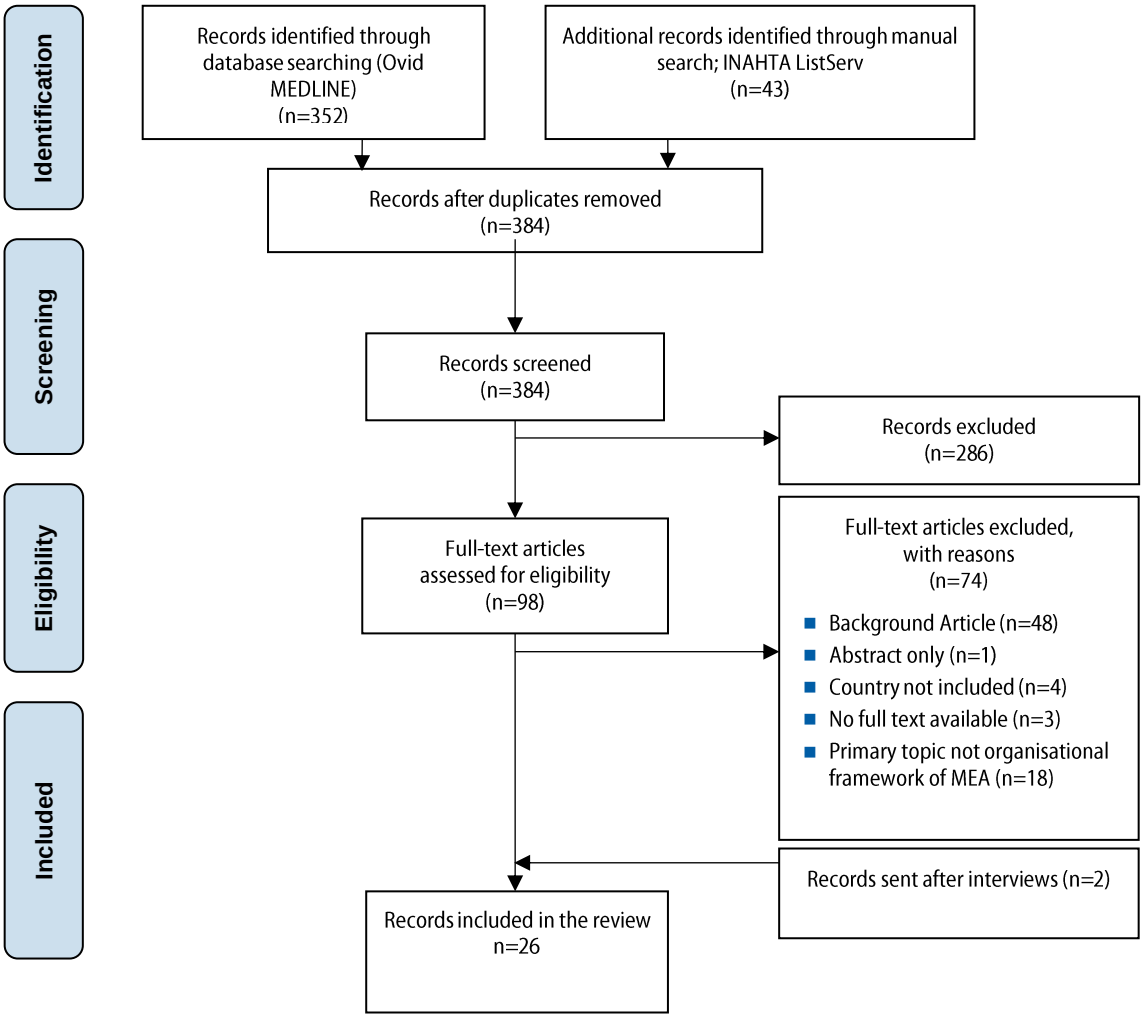

Figure 3-1: Literature selection process (PRISMA Flow Diagram) (adapted from Moher et al., 2009, p.3) [81]

Abbreviations: INAHTA - International Network of Agencies for Health Technology Assessment

INAHTA ListServ

INAHTA Netzwerk Befragung zu nationalen OBMEAs

INAHTA, a network of 49 HTA agencies, aims at facilitating knowledge exchange and mutual learning. Through the INAHTA ListServ, a mailing group comprising all members, queries arising from ongoing or future projects can be shared [86]. To complement the systematic literature review and the manual search on organizational frameworks for OBMEAs, a request was sent to the INAHTA ListServ on the 6th of February, inquiring about if HTA bodies could share guidance documents (process manuals/ handbooks/ frameworks) that explicitly describe how to set up a reimbursement model that provides conditional funding while publicly accessible RWE is generated. The complete request and the responses received are shown in Appendix 7.3

Data extraction

Datenextraktion zu den unterschiedlichen OBMEA-Modellen

After having collected organizational models for OBMEAs, information gained was transferred into data extraction tables as found in Appendix 7.4, distinguishing between the search in the database and the hand search. More specifically, the following criteria were sought:

- Title
- Author
- Date of publication
- Country/Region
- Key points
- Inclusion of an organizational framework
  - Relevant for research question
  - Shortcomings of the framework
  - Aim
- Rationale for exclusion

3.2.2 Elements of the identified framework and learnings

Expert interviews

Expert*innen-Interviews zu Erfahrungen

For obtaining a deeper insight into the specific organizational set-up, therapeutic areas of application, and experiences made with the identified frameworks for OBMEAs (second, third and fourth RQs), semi-structured web interviews with relevant experts from different countries were conducted.
Semi-structured interviews, the most common way of interviewing people in qualitative studies, use pre-defined open and closed-ended questions, giving room for potential additional questions arising from the conversation itself instead of closely sticking word-for-word to a questionnaire [87, 88]. This interview format was chosen because of the right balance between flexibility during the interview process and the comparability of responses.

Leitfaden zu Interviews basierend auf Ergebnissen aus EU-Projekten: COMED, IMPACT HTA etc.

The questions for the interview guideline emerged from the theoretical framework itself and the resulting records from the literature review. In particular, the CED scheme for medical devices developed within the WP7 of the COMED project, the toolkit for OBMEAs of orphan drugs produced in WP10 of IMPACT HTA, and the interim report on the currently developed framework for incorporating RWE into drug funding decisions by the Canadian Real-world Evidence for Value of Cancer Drugs (CanREValue) collaboration provided great guidance [89-91].

zu 23 Fragen zu organisatorischen Inhalten und Erfahrungen mit OBMEA

The interview guideline consisting of 23 open and closed-ended questions follows a three-tiered structure and is displayed in Appendix 7.5.1. After a general introduction of the interviewer, interviewee, and research topic, the first part tries to draw a general picture of OBMEAs in the country of interest. The subsequent section addresses the organizational aspects of the outcome-based reimbursement model by utilizing the four exemplary stages of an OBMEA as described by Frederici et al. (2019): initiation, design, implementation, and evaluation [92]. In the last part, learnings and experiences made with these models are gathered, and recommendations are provided for designing an OBMEA that ties conditional reimbursement to public data generation. The interview guide was sent to the participant approximately one week preceding the interview.

Rekrutierung von Interviewten

It was aimed to recruit at least one interview subject per identified country model. Purposeful sampling ensured that only individuals who are knowledgeable in this field were selected [93]. The main criterion for inclusion was, having experience in setting up an OBMEA scheme. The empirical basis for choosing countries for interviews was provided by the literature review, where relevant background articles revealed countries with experience in applying MEAs.

insg. 11 Interviews aus 8 Ländern

Based on that, a total of eleven interviews were conducted with 15 relevant stakeholders from HTA bodies (8), a negotiation organization (1), a university (1), and a research project (1) representing eight different countries (Italy, Belgium, Germany, Spain, the Netherlands, Scotland, Canada, Sweden). An overview of the participants is given in Appendix 7.5.2. Following from the literature search, England also has experience with OBMEAs. However, it was not possible to schedule an appointment with an expert from NICE. Nonetheless, the British model will be discussed in the results section.

Rekrutierungsstrategie: email Interviews: Zoom, MS-Teams (30-90 Min)

Recruitment strategies entailed approaching experts via e-mail using personal contacts, contacts obtained from the INAHTA ListServ responses, and publicly available contact information complemented through snowball sampling. Interviews were conducted via Zoom or Microsoft Teams and audio-recorded after receiving approval. Ten of them were performed in English, one in German lasting between 30 min and 90 min.

Transkription

A denaturalized approach for transcribing the interviews was pursued because the primary focus was on the content of information, omitting "[….] idiosyncratic elements of speech (e.g., stutters, pauses, nonverbals, involuntary vocalizations)" (Oliver et al., 2005, p.1) [94]. This transcription method is preferred for content analysis, as the researcher's interest is on the content itself, not influenced by contextual factors or language styles [95]. Transcripts were sent to interviewees for review upon request.

3.3 Data analysis

qualitative Inhaltsanalyse nach Mayring

For combining information generated from the interviews, a qualitative synthesis was conducted using content analysis.

Hsieh et al. (2005) described qualitative content analysis "[…] as a research method for the subjective interpretation of the content of text data through the systematic classification process of coding and identifying themes or patterns" (Hsieh and Shannon, 2005, p.1278) [96]. Following that definition, organizing textual material into categories, and reducing the amount of data lies at the core of this method [97]. The same analytical approach is pursued in the general procedural guidance for content analysis as developed by Mayring (2014), shown in Appendix 7.6.1 [97, 98]. This common model needs to be adjusted to the specific textual data generated and the aim of analysis [98]. For this research, structuring content analysis is used, one of the three specific methodological techniques of content analysis [97].

systematische Identifikation von Themen und Kategorisierung

The underlying idea of this approach is to first identify and conceptualize selected content-related aspects in the data, such as specific themes mentioned in the interview, which are then used to describe the material systematically. Based on these aspects, the structure of the overall category system is created. The different themes form the categories [99]. The essential steps of structuring content analysis followed are shown in Appendix 7.6.2.

induktiv und deduktiv ATLAS.ti

Categories were derived both inductively from the data itself and deductively from the interview guideline. After defining the single coding units, the smallest unit of information possible to be analysed, subcategories were developed, and categories defined [98, 99]. The evolved groups were transferred into a category system which was tested and adapted if necessary [99]. The coding scheme can be found in Appendix 7.6.3. Coding was performed by using ATLAS.ti 8, a computer-aided qualitative data analysis software (CAQDAS) that helped to manage and arrange a large amount of data in a systematic way [100].

3.4 Quality of research

Qualitätsbewertung: Total Quality Framework (TQF) nach 4 Kriterien

The quality of research was assessed using the four interrelated elements of the Total Quality Framework (TQF) developed by Roller and Lavrakas (2015), credibility, analysability, transparency, and usefulness. TQF presents a holistic approach taking into account the complete process of research. It strives towards enhancing academic rigor in qualitative studies, placing particular emphasis on quality-related problems on the design, conduct, analysis, and reporting of research [101].

Glaubwürdigkeit

A **credible** data collection process was ensured through the purposeful selection of the sample group according to concepts identified in the literature review. This produced a sound basis for the comparison of interview answers. Yet, sampling was limited by the availability of interview subjects. Internal consistency was achieved through thoroughly developing the interview guide based on the theoretical framework. The semi-structured nature of the interview allowed to gain supplementary information and thus enriched the database.

Auswertbarkeit

Following the TQF approach, the **analysability** of the research focusing on the accuracy of conducting content analysis and a clear interpretation of results was guaranteed. Categories were developed using CAQDAS. It aimed to accurately reflect the content in the final coding process and limit inconsistency and potential biases of the researcher. Inter-coder reliability, which is usually determined by statistical methods, is not sought in TQF but is achieved by dialogues within the research group [101]. However, it was not possible to reach an inter-coding consensus because no other researcher was involved.

Transparenz

The highest level of **transparency** was secured by providing as many details as possible on the design, analysis, and tools used during the study in the appendices, attempting to maximize the transferability of the outcomes to other settings [101].

Nützlichkeit

Ultimately, the **usefulness** of research is fuelled by the previously mentioned three elements, aiming at doing "something of value" with the results generated and further developing the present state of scientific knowledge [101]. Developing a generic organizational model for OBMEAs ensures a high degree of applicability in countries.

3.5 Ethical considerations

ethische Überlegungen:

Common ethical considerations in qualitative studies such as informed consent of participants, anonymity, and data protection were carefully taken into account in this research project [102]. Before the interview, **informed consent** was obtained from the participants. The form can be found in Appendix 7.7. It was developed based on the template for qualitative studies designed by the Research Ethics Review Committee of the WHO [103]. Informed consent is divided into two parts. The first one provides general information on the study, mentions, i.e., the purpose and type of research intervention and how the results of the interviews will be processed. The second part entails the consent certificate where interview subjects could give their permission for audio recording and indicate in what way the researcher was allowed to use direct quotations and personally identifiable information in the final report. Respondents had the option to remain completely anonymous.

informierte Zustimmung

Vertraulichkeit

By signing the form (electronically), they expressed their voluntariness of participation. If interviewees could not sign it beforehand, their consent was orally obtained as part of the audio recording. Data retrieved from the interviews was treated with the appropriate level of **confidentiality** and stored on devices with passcodes. Recordings will be destroyed after graduating from the Master's program.

4 Results

The following chapter provides an overview of the research findings from both the literature review and qualitative interviews. First, the identified reimbursement frameworks are presented, then their modular structure is described in more detail. After indicating for which therapies these models are used, experiences and lessons learned from countries more advanced in their application are illustrated.

Ergebnisse aus Literatur und aus Interviews

4.1 Identified models

The literature search showed the abundance of published papers on MEAs. Yet, most of them failed to provide information on the organizational infrastructure of OBMEA schemes with public evidence generation. From the initial 352 records identified through database searches, only five records met the inclusion criteria. Therefore, a targeted hand search was necessary, which yielded 43 further records.

Vielzahl an Publikationen zu MEAs

Following the small number of responses from the INAHTA ListServ, the lack of standardized rules and operational guidance in this field became further apparent and highlighted the relevance of this research. Two HTA bodies, the National Commission for the Incorporation of Technologies (CONITEC, Brazil) and Instance Nationale de l'Evaluation et de l'Accréditation en Santé (INEAS, Tunisia), reported not having any frameworks for OBMEAs in place, though expressed growing interest in such reimbursement models. INEAS mentioned the complexity of implementation as one possible hindrance to the greater usage of OBMEAs. The Agency for Health Quality and Assessment of Catalonia (AQuAS) (Spain), the Federal Joint Committee (G-BA) (Germany), and Health Improvement Scotland (HIS) (Scotland) were the only INAHTA members that provided information on existing models or models under development.

wenige INAHTA ListServ Antworten zeigte Mangel an Regelwerken und Leitfäden zur Etablierung von MEAs

AQuAS/ Spanien
G-BA/ Deutschland
SMC/ Schottland

- AQuAS referred to the Catalan Health Service (CatSalut) in Catalonia (Spain), which has experience in the systematic collection of RWD to evaluate the effectiveness of therapies.
- Germany, on the contrary, is still in its infancy. The G-BA mentioned the conceptual framework developed by the IQWiG to generate routine practice data and their analysis for the benefit assessment of drugs. However, this framework focuses on evidence generation and is not tied to any reimbursement matters.
- Scotland (Scottish Medicine Consortium-SMC) implemented a new pathway for ultra-orphan medicines with data collection and an interim conditional acceptance decision option for drugs approved on a conditional basis by EMA.

Putting the identified frameworks from all sources together resulted in a total of 26 references showing 16 models. An overview of them regarding their organizational aspects is presented in Table 4-1. A broad distinction was made between country-specific (n=12) and generic models (n=4). The latter category included the OBMEA tools for orphan drugs as designed within the WP10 of IMPACT, a CED scheme for medical devices developed by the

26 Referenzen zu 16 unterscheidlichen OBMEA Modellen

Länder-spezifische und generische Modelle

COMED working group, a framework on how to build and use RWE for coverage decisions, and an article providing recommendations on the organization of data collection and a possible governance structure [7, 57, 90, 91].

Apart from the three countries mentioned above from the INAHTA ListServ, further country-specific models identified were attributed to Italy, England, Canada, the Netherlands, and Belgium. Studying the literature also revealed that Sweden has experience in conditional financing and, thus, as a potential interview candidate [4, 49, 104, 105]. However, no framework could be identified.

Italien

- Three records described the Agenzia Italiana del Farmaco (AIFA) Monitoring Registries in **Italy**, a nationally publicly owned web-based tool for monitoring the appropriateness, use, safety, and efficacy of pharmaceuticals and managing reimbursement according to the data obtained [106-108].

Belgien

- Two articles reviewed the **Belgium** experience made with managing uncertainties through MEAs, called conventions [50]. One presentation from KCE used CAR-T therapies as an example to outline the procedure [unpublished].

Niederlande

- The **Netherlands** has long-term experience with conditional reimbursement schemes. Between 2006-2012 conditional coverage for highly-priced inpatient therapies was implemented [109]. Today a CED scheme exists for “Orphan drugs, conditionals, and exceptionals”, and a research program called “Potentially promising care” for therapies that appear promising in terms of (cost) effectiveness, but further data needs to be collected to prove their value [110-114].

England

- The Cancer Drug Fund in **England** provides another practice model of managing access to cancer drugs while routine data is being collected by the manufacturer that enables the reassessment by NICE. The agreement consists of two parts: a data collection and a confidential commercial arrangement laying down the details of data requirements and the medicine’s price during the term of the scheme [110-114].

Kanada

- In **Canada**, OBMEAs are in a nascent stage. The two Canadian HTA agencies, Institut National d’Excellence en Santé et en Services Sociaux (INESSS) and the Canadian Agency for Drugs and Technologies in Health (CADTH), aim to adopt a lifecycle approach to HTA [115, 116].
- The CanREValue collaboration (also in **Canada**), a publicly financed research project, is currently developing a framework for producing and incorporating RWE into reimbursement of cancer drugs in Canada, enabling the re-evaluation based on the new data generated. Some interim reports are already available, which were included for analysis [117].

Table 4-1: Overview of the models identified from the literature review

Number	Name	Model category	Country	Organization/ University	Category	Organizational aspects	Specific features	Reference
1	Funds Reimbursement of High-Cost Drugs in Gastrointestinal Oncology: An Italian Real Practice 1 Year Experience at the National Cancer Institute of Naples	Country-specific	Italy	National Cancer Institute of Naples	Research	-Description of the AIFA Monitoring Registries which is a government web-based tool for monitoring the appropriateness, use, toxicity, and efficacy of pharmaceuticals and manage reimbursement -Tool is used for operating MEAs	-Proposes to involve a pharmacist with expertise in health policy for managing the monitoring of the registry and thus improve the payment process -Responsibilities of the pharmacists included, i.e., data registration, follow-up, and reimbursement request	Capozzi et al. (2018) [106]
2	The Italian post-marketing registries	Country-specific	Italy	Italian Medicines Agency (AIFA)	HTA body	-Description of the AIFA Monitoring Registries -Highlights more the application of this tool and the computerized data generation with the application of MEAs -Shows how data enters the system, responsibilities within operating the MEAs, and the data aggregation with regional dashboards	-Graphical illustration of the risk-sharing scheme, interrelation of different stakeholders	Xoxi and Pani (2012) [108]
3	Monitoring registries at Italian Medicines Agency: Fostering access, guaranteeing sustainability	Country-specific	Italy	Italian Medicines Agency (AIFA), Universita Cattolica del Sacro Cuor	HTA body, Research	Description of the AIFA Monitoring Registries with a specific focus on its history, aims, and applications MEAs and re-evaluation activities of pharmaceuticals	Taxonomy and typology of MEAs used in Italy	Montilla et al. (2015) [107]

Number	Name	Model category	Country	Organization/ University	Category	Organizational aspects	Specific features	Reference
4	How to improve the Belgian process for managed-entry agreements? An analysis of the Belgian and international experience	Country-specific	Belgium	Belgian Health Care Knowledge Centre (KCE)	HTA	-Belgium experiences made with MEA (challenges, uncertainties addressed, results of conventions) -Legal basis, negotiation process, initiation of the scheme, stakeholders -Elements of the convention, duration, end of the convention -Data collection	-Types of therapies applied -Number, types of conventions -Uncertainties aimed to tackle	Gerkens et al. (2017) [50]
5	The Belgian Experience with immunotherapies and CAR-T temporary reimbursement with MEA	Country-specific	Belgium	Belgian Health Care Knowledge Centre (KCE)	HTA	-Timeline of an MEA scheme -When MEAs are initiated -Responsibility for data collection -Data requested by the Commission -Goal of MEAs (sources of uncertainty)	-	n.a. (un-published)
6	Konzept für eine anwendungsbeglei-tende Daten-erhebung – Onasemnogen-Abeparvovec (Concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social Code Book V (SGB V)	Country-specific	Germany	Institut für Qualität und Wirtschaflichkeit im Gesundheitswesen (IQWIG)	HTA body	-Guidance on the generation and evaluation of routine practice data and their appropriateness for the benefit assessment of drugs in Germany -Definition of criteria for data quality, methodological requirements -Data collection tools, different study designs, requirements for reporting	Providing recommendations for a possible approach to the routine practice data collection according to the German Drug Supply Safety Act (Gesetz für Mehr Sicherheit in der Arzneimittelversorgung) (GSAV)	IQWiG (2020) [118-120]

Number	Name	Model category	Country	Organization/ University	Category	Organizational aspects	Specific features	Reference
7	CADTH 2018–2021 Strategic Plan. Transforming How We Manage Health Technologies in Support of Better Health, Better Patient Experience, and Better Value	Country-specific	Canada	Canadian Agency for Drugs and Technologies in Health (CADTH)	HTA body	-Strategic goal to take on a life-cycle approach to HTA aiming for a higher level of alignment in drug and medical device assessments on a federal, provincial, and territorial level -Planning to develop guidelines for re-evaluations and how to deal with disinvestments -Still at the beginning of conceptualizing a model	-	CADTH (2018) [121]
8	a) A methodology for the evaluation of a disruptive innovative therapy: The example of Kymriah® b) Disruptive therapies - INESSS's perspective	Country-specific	Canada	Institut national d'excellence en santé et en services sociaux (INESSS)	HTA body	-Model of iterative evaluation throughout the lifecycle of technologies -Data synthesis from scientific, contextual, and experimental data	-Application of the model at the specific example of Kymriah® -Conditions for the data collection by MAH	a) Mombo et al. (n.d.) [116] b) De Guise (2019) (un-published)
9	Mapping Canadian Provincial data assets to conduct Real-World studies on cancer drugs	Country-specific	Canada	Canadian Real-World Evidence for Value of Cancer Drugs (CanREValue) collaboration	Research	-Identification of data custodians in Canada -Required elements of data for RWE studies -Capability assessment of Canadian provinces in conducting RWE analysis	Essential data elements RWD Table, Expanded data elements RWD Table for cancer	Chan et al. (2020) [122]
10	Developing a framework for incorporating real-world evidence into drug funding decisions (Interim Report)	Country-specific	Canada	Canadian Real-World Evidence for Value of Cancer Drugs (CanREValue) collaboration	Research	-Preliminary model for planning and selection of RWE projects -Preliminary model of the re-evaluation process -Feasibility considerations for RWE schemes -Considerations for conducting a reassessment	-Timeline for reassessment process and stakeholders involved -Graphical illustration of the drug selection process	Chan et al. (2019) [89]

Number	Name	Model category	Country	Organization/ University	Category	Organizational aspects	Specific features	Reference
11	Registry of patients and treatments of hospital medicines in Catalonia (Spain): 10 years of clinical data	Country-specific	Spain	Catalan Health Service (CatSalut), Vall d'Hebron University Hospital, a, Universitat Autònoma de Barcelona	HTA body, Research	-Description of the Registro de Pacientes y Tratamientos MHDA (Registry of Patients and MHDA Treatments Registry (RPT-MHDA)), a centralized and specific registry for all SISCAT hospitals, to systematically collect information on the use, efficacy, and safety of MHDA under routine clinical conditions	-	Roig Izquierdo (2020) [123]
12	Implementing managed entry agreements in practice: The Dutch reality check	Country-specific	Netherlands	Zorginstituut Nederland (ZIN), Utrecht Institute for Pharmaceutical Sciences, Utrecht Institute for Pharmaceutical Sciences	HTA body, Research	-Reviews experience with CED scheme for financing expensive hospital drugs on a conditional basis, implemented between 2006 and 2012 -Process chart for the conditional financing scheme in the Netherlands -Inclusion criteria for drugs, stakeholder included, duration of the scheme -Criteria for re-assessment, criteria for appraisal, final advice	Reasons for failure of CED scheme	Makady et al. (2019) [109]
13	Conditional reimbursement of health care	Country-specific	Netherlands	Zorginstituut Nederland (ZIN)	HTA body	-Description of the conditional entry of health technologies into the basic benefit package -Criteria for conditional reimbursement -Selection of potential therapies for conditional entry -Time schedule -Eligibility considerations of potential therapies	-	Ligtenberg (2012) [110]

Number	Name	Model category	Country	Organization/ University	Category	Organizational aspects	Specific features	Reference
14	Potentially Promising Care	Country-specific	Netherlands	Zorginstituut Nederland (ZIN), Netherlands Organisation for Health Research and Development (ZonMw)	HTA body	-Description of research program Potentially Promising Care, which enables temporary funding for promising therapies not included in the standard health care package while research data is collected that enables the reassessment by ZIN -Criteria for including therapies -Duration -Who can apply for funding -Evaluation criteria	-	ZIN (n.d.) [111, 112]
15	Conditional inclusion procedure for medicinal products (orphan drugs, conditionals and exceptionals)	Country-specific	Netherlands	Zorginstituut Nederland (ZIN)	HTA body	-Describing the phases for initiating a conditional inclusion scheme: a) Time of submission, dossier requirements b) Intervention selection by ZIN (eligibility criteria), responsibilities of MAH, registry use, duration c) Price negotiation, preparation of the covenant, funding of research, elements of the covenant, monitoring, interim assessment, final assessment	Detailed flowcharts available on the process for starting such a scheme and the process steps during the scheme	ZIN (n.d.) [113, 114]
16	A Guide to the Ultra-Orphan Pathway	Country-specific	Scotland (UK)	Scottish Government	Payer	-Describing the four different steps of the new pathway (Validation, Initial SMC Assessment, Evidence Generation, Reassessment)	Graphical illustration of the process	Scottish Government (2019) [124]

Number	Name	Model category	Country	Organization/ University	Category	Organizational aspects	Specific features	Reference
17	Guidance on the Evidence Generation Phase of the Pathway for Ultra-Orphan Medicines	Country-specific	Scotland (UK)	Scottish Government	Payer	-Describing the evidence generation process -Pre-evidence generation phase: ensuring commitment -Evidence generation phase: data collection plan, data governance, data collection report, costs, time frame -Post evidence generation phase	-	Scottish Government (2019) [125]
18	Guidance to Submitting Companies for Completion of New Product Assessment Form (NPAF) (Interim accepted advice decision option)	Country-specific	Scotland (UK)	Healthcare Improvement Scotland (HIS)/Scottish Medicines Consortium (SMC)	HTA body	-Describing the possible decision option of conditional funding of conditionally approved medicines (alignment between EMA authorization and HTA advice) -Submission process via completing New Product Assessment Form (NPAF) by the MAH (study design, inclusion criteria, etc.) -New Drugs Committee (NDC) issues preliminary advice to SMC if data generation could address key uncertainties -Re-assessment is done by SMC	-	HIS/SMC (2019) [126]

Number	Name	Model category	Country	Organization/ University	Category	Organizational aspects	Specific features	Reference
19	Appraisal and Funding of Cancer Drugs from July 2016 (including the new Cancer Drugs Fund) A new deal for patients, taxpayers, and industry	Country-specific	England (UK)	National Health Service (NHS England)	Payer	-Providing detailed insight into conditional financing via Cancer Drug Fund (CDF) -Components of Managed access agreements: data collection arrangement, commercial arrangement (determining the price) -Criteria for drugs to enter CDF -Patient eligibility, data collection and monitoring, data ownership, funding, duration exiting the scheme, roles and accountabilities for data collection, monitoring, disseminating results, study protocol -Data collection sources (public registries)	-Graphical illustration on the start of the process -Template Managed Access Agreement -Specifications for data collection -Procedural steps for data collection arrangement	NHS England (2016) [127]
20	Barriers and Opportunities for Implementation of Outcome-Based Spread Payments for High-Cost, One-Shot Curative Therapies	Generic	n.a.	Katholieke Universiteit Leuven, Vlerick Business School Ghent,	Research	Providing recommendations on the organization of data collection, implementing a governance structure	Involving an external advisory body to build mutual trust	Michelsen et al. (2020) [7]
21	A framework to guide the optimal development and use of real-world evidence for drug coverage and formulary decisions	Generic	n.a.	Institute for Clinical & Economic Review, Office of Health Economics	HTA body, Research/Consul-tancy	-Presenting a framework for supporting the ideal development and application of RWE for HTA purposes: framing the question, curating the data, establishing methods, verifying analyses, decision-making -Considering contextual factors and the required evidence standards in each single step	-	Pearson et al. (2018) [57]

Number	Name	Model category	Country	Organization/ University	Category	Organizational aspects	Specific features	Reference
22	Coverage with evidence development schemes for medical devices: a policy guide	Generic	n.a.	Pushing the Boundaries of Cost and Outcome Analysis of Medical Technologies (COMED)	Research	Description of the four different phases of a CED scheme for medical devices and aspects to consider in each stage: desirability, design, implementation, evaluation	Comparative overview of CED policies for medical devices in Europe	[90] (unpublished)
23	Checklist for a Rare Disease Treatment. Is an Outcomes-Based Managed Entry Agreement Feasible?	Generic	n.a.	Improved methods and actionable tools for enhancing HTA (IMPACT HTA)	Research	Feasibility criteria for CEDs for rare diseases	-	IMPACT HTA (2021) [91]
24	Template for Adaptation by HTA Bodies. Outcomes-Based Managed Entry Agreement of a Rare Disease Treatment	Generic	n.a.		Research	-Description of the public documentation process for the data collection agreement, determining: >Uncertainties to be resolved >Patient eligibility criteria >Data Management (data collection plan, data sources) >Review by a Monitoring Committee >Re-assessment >Responsibilities of parties (clinicians, MAHs, payer, etc.)	-	IMPACT HTA (2021) [91]
25	Template for Adaptation by HTA Bodies. Monitoring committee terms of reference for an outcome-based managed-entry agreement for rare disease treatment	Generic	n.a.		Research	-Description of the responsibilities of the Monitoring Committee -Governance measures of the Committee	-	IMPACT HTA (2021) [91]

Abbreviations: AIFA – Agenzia Italiana del Farmaco, CADTH - Canadian Agency for Drugs and Technologies in Health, CanREValue - Canadian Real-World Evidence for Value of Cancer Drugs, CAR-T – Chimeric antigen receptor T-cell, CatSalut - Catalan healthcare service, CDF – Cancer Drug Fund, CED – Coverage with Evidence Development, EMA – European Medicines Agency, GSAV - Gesetz für mehr Sicherheit in der Arzneimittelversorgung (German Drug Supply Safety Act), HIS - Healthcare Improvement Scotland, HTA – Health Technology Assessment, IMPACT HTA – Improved methods and actionable tools for enhancing Health Technology Assessment, INESSS - Institut National d'Excellence en Santé et en Services Sociaux (Canadian HTA – Québec), IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), KCE - Belgian Health Care Knowledge Centre, MAH – Marketing Authorization Holder, MEA – Managed-entry agreement, MHDA - Medicamentos hospitalarios de dispensación ambulatoria (hospital drugs for outpatient dispensing), NHS – National Health Service, NDC – New Drug Committee, NPAF - New Product Assessment Form, RWD – Real-world data, RWE – Real-world evidence, SISCAT - Sistema Sanitari Integral d'Utilització Pública de Catalunya (Integrated Public Health System of Catalonia), SMC – Scottish Medicines Consortium, UK – United Kingdom, ZIN - Zorginstituut Nederland (National Health Care Institute)

4.2 Modular structure of models

modulare Struktur der Modelle nach 5 Phasen

The subsequent three chapters elaborate on the qualitative data collected in the expert interviews, providing a deeper insight into the country-specific OBMEA models. This section mainly draws on the individual modules that characterize each model. The results are presented along the five different modules for planning OBMEAs:

Initiierung des OBMEA
Design (Aufsetzen)
Evidenzgenerierung
Re-Evaluierung
Ausstieg aus OBMEA

1. Initiation,
2. Designing the scheme,
3. Evidence generation,
4. Re-assessment, and
5. Exit.

jede der Phasen beinhaltet mehrere Elemente

Those categories were deducted from the interview guideline, the CED scheme for medical devices developed within the COMED project, and the responses received. Each module consists of different single elements that constitute critical features essential to consider during that specific stage. It was noticed that taxonomies significantly differed between countries. Various terms for categorizing MEAs are established. For example, in Scotland, CEDs are not seen as a type of OBMEAs (Respondent (RE) 9). Further information on some country-specific definitions is to be found in Appendix 7.8. Nevertheless, for reasons of consistency, this paper refers to the terminology set out in chapter 2.3.2 (Good practice recommendations and real-world evidence initiatives).

4.2.1 Initiation

erste Phase: Initiierung des OBMEA

The first phase of the organizational model deals with factors to be considered when initiating new schemes: Who is **responsible for nominating therapies for OBMEAs,** how are **potential therapies identified,** and which mechanisms exist for assessing the **operational feasibility** of conducting these payment models.

(mögliche) Verantwortlichkeiten für Initiierung:

A rough distinction is drawn between the two main **parties responsible for initiating** these schemes: public bodies (i.e., HTA agencies, payer) and manufacturers. The first group comprises countries like Canada, Germany, Spain, and Belgium, the latter one Italy, the Netherlands, Scotland, and Sweden.

öffentliche Institutionen oder Hersteller

DE: G-BA
Katalonien: CatSalut
BE: RIZIV-INAMI
CA: pCA, INESS, MAH

- In *Germany*, the G-BA initiates and defines for which drugs the generation of routine practice data and their analysis for the benefit assessment should be started (RE 4).
- For *Catalonia (Spain),* this task is in the remit of CatSalut.
- In *Belgium*, a multi-stakeholder committee independent from RIZIV-INAMI proposes OBMEAs to the Minister of Social Affairs, who makes the final decision (RE 2 and RE 3).
- According to interviewee eleven, in *Canada*, the initiation process involves the provinces which are responsible for reimbursement decisions and the pan-Canadian Pharmaceutical Alliance (pCPA) that conducts joint negotiations for public drug plans [[128], RE 11]. CADTH confirmed these results and stated that the MAH could propose it. The Expert Committee (part of the HTA body) decides whether to include it in its final recommendation upon which the

price negotiations start. But the final decision whether to negotiate OBMEA rests with the negotiating body (pCPA) and payers (RE 5). A representative from pCPA indicated that either the MAH or public payers would propose an OBMEA once the confidential negotiations have started (RE 10). In Québec, the recommendation for conditional funding for Tisagenlecleucel (Kymriah®) and Axicabtagen Ciloleucel (Yescarta®) was made by INESSS. However, the HTA body is not involved in any subsequent arrangements that may be concluded between the MAH and the Ministry of Health (RE 15). In the CanREValue collaboration framework under development, a transparent process is considered allowing multiple stakeholders to bring in potential questions (RE 11).

- In the *Italian* process, the MAH can propose an OBMEA as part of the dossier and discuss it during the price negotiations with AIFA (RE 1).
- For both the "Interim accepted decision option" and the "Ultra-orphan pathway" in *Scotland*, the MAH applies to the Scottish Medicines Consortium (SMC). In the former case, the final decision is taken by SMC. In contrast, for the "Ultra-orphan pathway", after the validation process by SMC, the MAH decides whether to follow the OBMEA or the standard reimbursement route (RE 9).
- In the *Dutch* conditional reimbursement model for "Orphan drugs, exceptional and conditionals", the MAH initiates the process. However, for the "Potentially promising care process", it is an administrative representative of a health care provider (RE 8).

IT: MAH oder AIFA
SCO: MAH oder SMC
NL: MAH oder öffentlich

The **technology selection** for OBMEAs is discussed separately in Chapter 4.3 when the different (gene- or regenerative) therapies for which these models apply are reviewed.

Auswahl der Therapie für OBMEA

The main topics identified for the **feasibility assessment** of these schemes centered around evidence generation (RE 2 and 3, RE 4, RE 10), translating primary endpoints from clinical studies into clinical practice (RE 1), and a priori clear definition of the question to be addressed and outcome measures to be collected (RE 11). The first group entailed considerations on having accessible and available data on the clinical outcomes of interest (RE 10), a feasible data collection (RE 2 and 3), is it realizable within a specific time frame, what data sources exist and which data are missing (RE 4).

Machbarkeitsanalyse:

klare Fragestellung
wichtige Endpunkte
Dateninfrastruktur
Zeitrahmen

- Assessments are conducted, i.e., in *the Netherlands* with the help of a scientific organization that analyses the submitted research proposal of the MAH in terms of feasibility and addressed uncertainties. In addition, an assessment of the research proposal is done by the Advisory Committee on Promising Healthcare Advice (RE 8).
- A similar process is established in *Catalonia (Spain)*. A specific committee evaluates the feasibility for MEAs. In theory, good practice guideline exists laying down criteria for risk-sharing agreements, i.e., the primary outcome must be achieved after six to twelve months, but in practice, they are not strictly applied (RE 6 and 7).
- Another method involving the perspective of a broader range of stakeholders is proposed by INESSS *(Canada)*. In the case of Kymriah® and Yescarta®, it adopted a multidimensional approach consulting clinicians, experts, patients but also hospital managers and citizens with no direct relation to the condition for estimating the effect of introducing these therapies (RE 15).

Komitees unter Einbindung von Stakeholdern, MAH

- In contrast to these views, currently, no feasibility assessment is done in *Scotland*. Since the MAH has the sole responsibility for data collection, SMC is not involved in that process (RE 9).

Table 4-2: Cross-country comparison of module "initiation" in outcome-based Managed entry agreements (OBMEA)

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Responsi-bility initiation	-CTG/CRM, who advises the Minister of Social Affairs -Minister of Social Affairs makes the final decision and starts negotiations -Possible initiation also without proposal by CTG-CRM but by Taskforce MEA (RIZIV -INAMI) and the Minister of Social Affairs -MAH can ask to start negotiations if CTG/CRM did not come to a proposal, but the final decision rests with the Minister	MAH or public payers once the negotiations have started	-Provinces make reimbursing decisions -MAH submits a dossier to INESSS -INESSS recommends conditional funding	-Possible proposal by MAH -Expert Committee (part of the HTA body) decides whether to include it in its final recommendation upon which the price negotiations start -Final decision whether to negotiate OBMEA rests with the pCPA and payers	-Current process: provinces and pCPA -CanREValue proposal: multiple stakeholders	G-BA	MAH proposes OBMEA as part of the dossier and discusses it during the negotiations	-Potentially promising care: administrative representative of a health care provider (i.e., hospital) -Orphan drugs, exceptionals, and conditionals: MAH	-Interim accepted decision option: MAH applies, final decision by SMC -Ultra-orphan pathway: MAH applies, SMC validates if ultra-orphan criteria are met; if so, MAH decides whether the ultra-orphan pathway or the standard pathway should be followed	CatSalut	-In case of financial agreements: raised by the MAH during the application to TLV, which transfers it to the regions -Final decision whether to conclude an agreement rests with the regions -Prospectively thinking: TLV could identify uncertainties, analyzing possible payment models

Feasibility assess-ment	Feasibility of data collection	Accessibility and availability of data on clinical outcomes: available in the public domain (routinely collected, prior authorization forms) vs. setting up a separate data collection which is feasible across the country	-No specific criteria -Evaluation process guarantees the feasibility of the proposed recommendations, consulting the scientific literature and different stakeholders	Refers to pCPA	-Need to define the question/uncertainty precisely -Answerable within the timeframe? -Outcome measurable/already measured? (feasible to define control group)	-What data sources exist? -Which data is missing? -Time frame of data collection -Number of cases	-Feasibility of translating primary endpoints from trials into clinical practice (define responders/non-responders)	-Potentially promising care: assessment of the research proposal of the MAH by a scientific organization in terms of feasibility and addressed uncertainties -In addition: assessment by the Advisory Committee on Promising Healthcare Advice	SMC does not assess the data collection plan developed by MAH	-Assessed by the Expert committee -Good practice guideline [available only in Catalan] specifies: > criteria for risk-sharing agreements > criteria for assessing the clinical and financial dimensions (not strictly followed in practice) > primary outcome must be achieved after six to twelve months	No information

Abbreviations: AIFA – Agenzia Italiana del Farmaco, CADTH - Canadian Agency for Drugs and Technologies in Health, CanREValue - Canadian Real-world Evidence for Value of Cancer Drugs, CatSalut - Catalan healthcare service, CTG/CRM - Commissie Tegemoetkoming Geneesmiddelen/ Commission de remboursement des medicaments (Commission for Reimbursement of Medicinal Products), G-BA - Gemeinsamer Bundesausschuss (Federal Joint Committee), RIZIV-INAMI - Institut national d'assurance maladie-invalidité/Rijksinstituut voor ziekte- en invaliditeitsverzekering (National Institute for Health and Disability Insurance), INESSS - Institut National d'Excellence en Santé et en Services Sociaux (National Institute for Excellence in Health and Social Services), IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), MAH - Marketing Authorization Holder, MEA – Managed-entry agreement, pCPA - Pan-Canadian Pharmaceutical Alliance, SMC - Scottish Medicines Consortium, TLV - Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency), ZIN - Zorginstituut Nederland (National Health Care Institute)

4.2.2 Design of data collection

zweite Phase: Design (Aufsetzen) des OBMEA

The second stage relates to principal decisions to be taken on the specific design of schemes. This concerns the engagement and **commitment** of **key stakeholders,** deciding on a governance body for commissioning and **monitoring** the scheme, defining the **duration** of agreements, reasonable **stopping rules** for exiting the scheme, and a potential **interim assessment.**

Involvierung von 3 Stakeholder-Gruppen:

Vertragspartner (öffentliche Institutionen und MAH),

Beratungsgremien

Datensammlern

The **key stakeholder groups** could be roughly differentiated between the contracting partners, advisory party, and data collection bodies. MEAs were commonly concluded between the MAH and public payer. The role of the manufacturer varied between countries in particular with regard to data collection, but this will be explicitly discussed in chapter Governance of evidence generation (4.2.3).

- However, most countries agreed that the MAH has the final responsibility for providing answers to the uncertainties identified. *Belgium* highlighted the role of the MAH as the most important stakeholder in designing the scheme (RE 2 and RE 3).
- In *Canada*, pCPA, a third intermediate negotiation partner, is responsible for facilitating negotiations across the fragmented structure of the Canadian healthcare system, where single provinces and territories can opt in to join negotiations (RE 5, RE 10).
- HTA bodies mainly fulfill the role of advising public payers but are not directly involved in concluding agreements (RE 12 and RE 13 and RE 14, RE 2 and RE 3).
- Data collection bodies primarily contain healthcare professionals like (hospital) pharmacists, clinicians, general practitioners entering the data into the registry (RE 2 and RE 3, RE 6 and RE 7). In *Canada*, clinicians might not be aware that the data are used for MEAs (RE 10).
- In *Belgium*, sick funds have a central role in storing and collecting data (RE 2 and 3).
- *Italy* uses a pyramidal system of accreditations to manage the dispense and prescription of therapies. First, regions accredit hospitals that are allowed to prescribe certain drugs, while in the second step, health managers accredit physicians and pharmacists that dispense the medications to the patients (RE 1).

Einholen von Komitments:

vertraglich

oder

mittels (negativer) Inzentivs

Ensuring the **commitment** of stakeholders is mainly provided through either a legal requirement or negatively incentivizing participating groups.

- The *Italian* law stipulates collecting data in registries at the national level to prescribe innovative drugs (RE 1).
- *Belgium, Germany*, and *Catalonia (Spain)* tie the data collection to financial motives. Hospital drugs are not reimbursed in *Catalonia (Spain)* if data are not entered into the registry (RE 6 and RE 7). The same applies in Belgium. It is the hospital pharmacist who is negatively incentivized (RE 2 and RE 3).
- In *Germany*, Zolgensma® is not publicly reimbursed if panel physicians do not participate in the collection of routine practice data (RE 4).
- Also, CADTH *(Canada*) raised the point that the most significant incentive would be defining reimbursement criteria requiring data collection and reporting by the MAH (RE 5).

Verantwortung für Monitoring des OBMEA

The majority of respondents reported that a public body, primarily an HTA institution**,** is responsible for the overall **monitoring** of the scheme.

- In *Belgium*, this is done by RIZIV-INAMI (RE 2 and 3),
- in *Italy* by AIFA (RE 1),
- in *Catalonia (Spain)*, it is CatSalut (RE 6 and RE 7),
- *Dutch* OBMEAs are governed by ZIN (RE 8), and
- in *Germany*, the overall responsibility lies with the G-BA (RE 4). However, in the case of Zolgensma®, the registry operator of the *SMArtCARE* database also has a self-interest in overseeing his registry (RE 4).
- No monitoring happens in *Scotland* since SMC is not involved in the evidence generation (RE 9) and
- in *Canada*, where public payers and MAHs are responsible for administering the scheme. Still, no formal guidelines exist (RE 10). This is also the case in Québec (RE 15). Apart from the payer or MAH, an independent third party might also be suited for monitoring as proposed by interviewee eleven from the CanREValue collaboration group. This might build some joint governance, ongoing reporting and increases transparency (RE 11).

Festlegung der Dauer des OBMEA

The **duration** of the scheme varied between countries. Some of them set a maximum duration.

- The *Belgian* royal decree, for example, stipulates that MEAs should not last longer than three years. However, prolongations with stages of three years are possible. On average, these agreements last two years in Belgium (RE 2 and RE 3).
- A similar picture can be observed in *Catalonia (Spain)*, where a renewal of the contract is possible each year up to a maximum duration of four years in total (RE 6 and RE 7).
- The temporary funding of the promising care process in *the Netherlands* is limited to six years. For the "Orphan drugs, exceptionals, and conditionals", the MAH can opt for either seven or 14 years of inclusion in basic health insurance. In most cases, seven years are chosen (RE 8).
- In *Italy*, it is often failed to complete the agreements within the maximum duration set for usually two years. OBMEAs usually last longer than six years (RE 1).
- The evidence generation in the *Scottish* "Ultra-orphan pathway" is defined for a minimum of three years. No prolongation of the scheme is possible for the "Interim accepted decision option". The medicine is conditionally covered until EMA converts the conditional marketing authorization into a full marketing authorization (RE 9).
- Québec *(Canada)* was the only region determining a fixed duration. After three years, Kymriah® and Yescarta® will be subject to re-assessment. Due to the nature of the progression of the disease and the type of health outcomes monitored, it was expected that outcome measures would be demonstrated within that time frame. However, it should be borne in mind that no other assessments have been conducted yet. So, the duration for future therapies on conditional financing will probably be set individually (RE 15).
- The same will likely apply to *Germany*, which is still beginning to use routine practice data for drug benefit assessments (RE 4).
- In *Canada*, the agreements are ongoing and indefinite (RE 10). CADTH suggested that, ideally, deciding upon the duration would

incorporate clinical and patient input to determine the feasibility of data collection and the number of patients required to establish the necessary level of certainty for re-evaluation (RE 5). The fundamental question of setting a standardized or individual-defined timeline was discussed with RE 11 from the CanREValue collaboration. One point to consider was whether to look at short-term endpoints versus longer-term endpoints. It was argued setting a strict timeline might be beneficial in a phase-in period to assess the situation if it is possible to reach the outcomes in time but also stimulating a strict adherence of all stakeholders to a set deadline. If not feasible, the length might be adjusted (RE 11).

Festlegung der "Stopping Rules" und von Zwischenauswertungen

Only selected countries used **stopping rules** and **interim assessments** at regular intervals on the scheme's progression.

- In *Germany*, it is envisaged that for Onasemnogene abeparvovec (Zolgensma®), at least every 18 months, the G-BA intends to review interim results of the data collection, whether they will provide sufficient evidence for the use of benefit assessments, whether the recruitment of patients is as expected and where appropriate the requirements of the routine practice data collection as outlined in the resolution of the G-BA on Zolgensma® are adjusted. Part of this is also performing a futility analysis (RE 4).
- An interim assessment is also conducted in *Catalonia (Spain)*, the *Netherlands*, and *Italy*. In *Catalonia (Spain)*, it is performed each year to decide upon prolonging the scheme (RE 6 and RE 7) and in the *Netherlands* every six months to control the recruitment of patients and the data collected (RE 8). *Italy* applies stopping rules and interim assessments but has not defined a standardized time frame like the two other countries (RE 1).
- In the *Belgium* process, it is distinguished between stopping rules for the agreement defined by the committee and stopping rules for the treatment duration, but interim evaluations per se are not established (RE 2 and RE 3).
- The other countries have either no interim assessment procedure established, or no information was obtained during the interviews.

Table 4-3: Cross-country comparison of module "design" in outcome-based Managed-entry agreements (OBMEA)

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Stakeholders	-MAH: willingness to negotiate, designing the scheme, providing answers to identified uncertainties in time -Sick funds: storing data, advisory role -Pharmacists, hospitals: collecting data -MEA Taskforce (RIZIV-INAMI): negotiations -Decisive role: Minister of Budget, Minister of Social Affairs [50]	-pCPA: conducting joint negotiations for public payers -Clinicians might be involved in data collection but might not be aware that data is used for MEAs	-Multi-dimensional approach for conducting assessments -Broad consultation of stakeholders to clearly define the impact of introducing the therapy -Final decision: independent committee	-pCPA: conducting joint negotiations (opt-in model: provinces/territories can opt into negotiations) -Negotiation partners: MAH + provinces/territories (=payers) (no involvement of patients, clinicians) -HTA committees: recommen-dations to public drug plans	-Contractual parties: MAH + payer -Calls for a broader involvement of stakeholders	-Onasem-nogene: MAH, registry operator, professional societies, G-BA, IQWiG -Written statements and discussions on the developed concept by IQWiG with MAH, other manufactu-rers with similar therapies on the market/coming to the market, registry operators, technical experts	-Pyramidal system using accredita-tions: a) Regions accredit hospitals that are allowed to prescribe certain drugs b) Health manager accredit physicians, pharmacists ->Two-tiered accreditation system enables prescription of drugs -other stakeholders: AIFA (owner of the platform, MAHs)	MAH, patients, HCPs, doctors	-SMC: defining eligibility criteria for drugs -MAH: data collection	-Clinicians, hospital pharmacists, public managers, health economists, CatSalut, payers, MAH -Contracting bodies: >MEAs for Catalonia: CatSalut + MAH >MEA applied throughout Spain: Ministry of health + MAH (gene therapies, ATMPs, "more innovative" therapies, collecting data through the Valtermed registry)	-Contracting bodies (for MEAs in general): regions + MAH -TLV (HTA body) not involved in concluding agreements, conducts assessments

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Commitment	Negative financial incentive in case of missed data entry by hospital pharmacists	No information	No information	-Varies by province/territory -Biggest incentive: reimbursement criteria would require data collection and reporting by MAH	No information	-No "contract" per se -No coverage of Onasemnogene if panel physicians do not participate in the collection of routine practice data	-No "contract" per se -Legal requirement: mandatory data collection by the registry to prescribe drugs	-Potentially promising care: probably no contract -Orphan drugs, exceptionals and conditionals: confidential contract where conditions, clinical endpoints are determined between MAH, patients, healthcare providers, doctors	No information	No reimbursement of drugs for hospitals if data are not entered into the registry	No information
Monitoring	RIVIZ-INAMI	-Not applied -Public payers and MAH are responsible for administering the scheme	-Shared between INESSS and MAH -No established procedure/ process	-Not applied -Ideally: data safety monitoring process to ensure an unbiased perspective on data	Third-party proposed	-Overall responsibil-ity: G-BA (Onasemnogene: MAH commissions registry operator which has its own interest in monitoring the registry)	AIFA	-ZIN (advises the minister to stop the scheme if necessary)	-Not applied (SMC is not involved in data collection)	-CatSalut (hospitals support data validation)	No information

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Duration	-Depending on budget impact and uncertainties -No longer than three years (legal basis) -Pro-longation of 3 years (per stage) possible -On average: 2 years	Ongoing agreements, duration is not defined	-3 years (for Kymriah, Yescarta) -Duration needs to be individually set for other therapies	Ideally: decided through a multi-stakeholder process to raise awareness on the precon-ditions upon which the funding and access is enabled	-Depends on the drug, indication, the aim of the scheme (price change, safety confirmation, outcome confirmation, estimation of event rates) -Considering standardized vs. individual defined duration	Individually defined per therapy (Onasemnogene: 60 months)	-Critical point to determine -No standardized duration, often extended beyond the maximum period of usually two years (commonly last longer than six years)	-Potentially promising care: max. 6 years -Orphan drugs, exceptional and conditional: MAH chooses between 7 or 14 years (at most seven years)	-Interim accepted decision option: until conditional marketing authorization is converted into full marketing authorization (varies considerably) -Ultra-orphan pathway: 3 years	Each year possible renewal of contract (max. 4 years)	With former CED scheme: 2-3 years
Stopping rules	-Stopping rules exist for: > agreement defined by the committee > treatment linked to the duration	Not applied	Not applied	Ideally: multi-stakeholder determination process	No information	Not applied	Evaluation by G-BA on the data obtained at least every 18 months, performing a futility analysis	Applied (i.e., CAR-T after six months)	Not applied	No information	No information
Interim Assessment	Not applied	No information	Not applied yet	No information	No information	No information		Each half-year (learned from previous experience with MEAs)	Not applied	Each year when decided upon prolongation	No information

Abbreviations: AIFA – Agenzia Italiana del Farmaco, CADTH - Canadian Agency for Drugs and Technologies in Health, CanREValue - Canadian Real-world Evidence for Value of Cancer Drugs, CAR-T-cell - Chimeric antigen receptor T-cell, CatSalut - Catalan healthcare service, CED – Coverage with Evidence Development, G-BA - Gemeinsamer Bundesausschuss (Federal Joint Committee), HCP – Healthcare provider, HTA – Health Technology Assessment, RIZIV-INAMI - Rijksinstituut voor ziekte en invaliditeitsverzekering/ Institut national d'assurance maladie-invalidité (National Institute for Health and Disability Insurance), INESSS - Institut National d'Excellence en Santé et en Services Sociaux (National Institute for Excellence in Health and Social Services), IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), MAH - Marketing Authorization Holder, MEA – Managed-entry agreement, pCPA - Pan-Canadian Pharmaceutical Alliance, SMC - Scottish Medicines Consortium, TLV - Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency), ZIN - Zorginstituut Nederland (National Health Care Institute)

4.2.3 Governance of evidence generation

klare Regeln zu Governance

Decisions on the way data ought to be generated are taken in the third phase. This concerns defining the **roles for data collection and data analysis**, including **financial matters**, defining appropriate data sources to be employed for the collection, clarifying **data ownership**, and ensuring the **data protection** of patients.

Finanzierung der Datensammlung und der Datenanalysen

Responses from the interviews on the provision of **funding for data collection and data analysis** demonstrated a relatively unbalanced ratio between public and private financing. In *Scotland, Italy, Québec (Canada)*, and *Germany*, financing is predominantly being provided by the MAH.

- In *Italy*, for instance, the manufacturer pays for a registry on the national platform 30,000 Euros to AIFA for three years (RE 1).
- *Germany* aims to transfer financing ultimately to the G-BA to achieve independence, but currently, for Zolgensma®, this task still lies with the MAH (RE 4).
- MAHs in Québec *(Canada)* have the primary responsibility for financing; however public data from administrative databases might also be used (RE 15). In Québec and the rest of Canada, public bodies have the primary responsibility for financing the scheme (RE 10, RE 11).
- For *Catalonia (Spain)*, CatSalut provides financing (RE 6 and RE 7).
- Financing data collection and data analysis are split into two parties in *Belgium*. Data is collected by the sick funds to whom the MAH pays a lump sum to use for analysis (RE 2 and RE 3).
- In the *Netherlands*, the evidence generation for the "Orphan drugs, exceptional and conditionals" scheme is funded by the MAH, whereas the government subsidizes the "Potentially promising care process" (RE 8).
- Speaking of sharing the financial burden of evidence generation – interviewee eleven from the CanREValue collaboration *(Canada)* recalled the idea of risk-sharing. According to her/his view, any party benefitting from this agreement should contribute to funding (RE 11).

Verteilung von Rollen und Verantwortlichkeiten

The question of financing is tightly linked to the **distribution of roles and responsibilities**.

- Data collection and analysis are shared between public and private institutions in *Canada*. In Québec, the MAH provides new data for the re-assessment process. This evidence base is supplemented by harnessing locally generated experiential and contextual information, comprising administrative medical databases. Hence, data collected by the MAH, the manufacturer performs the analysis, data publicly gathered, INESSS is responsible for data analysis (RE 15). In the rest of Canada, for schemes using prior authorization forms, data is mainly collected through routine invoicing by public payers, and for registry-based models, it is the MAH. The same holds for data analysis (RE 11).
- Data collection in *Italy, Belgium, Catalonia (Spain),* and the *Netherlands* is mainly conducted by different healthcare professionals comprising, i.e., clinicians, (hospital) pharmacists, physicians (RE 1, RE 2 and RE 3, RE 6 and RE 7, RE 8).

- In *Belgium*, sick funds collect raw data while the MAH performs the analysis (RE 2 and RE 3).
- In *Italy* and *Catalonia (Spain)*, public bodies AIFA and CatSalut examine the data obtained (RE 6 and RE 7).
- In the former CED schemes in *Sweden*, the MAH was responsible for collecting and analyzing data (RE 12 and RE 13, and RE 14).
- *Germany* was the only country explicitly mentioning the role of the registry operator in the data collection and analysis. Yet, the final responsibility for the data suitable for the benefit assessment rests with the MAH (RE 4).
- As mentioned earlier, SMC has no insights into the infrastructure of data management in *Scotland* since the responsibility entirely rests with the MAH (RE 9).

Dateninfrastruktur:

Orte der Datensammlung

bestehende oder neue Register

oder

administrative Datensammlungen

The **sources** most often mentioned to generate RWD were registries and administrative data.

- AIFA *(Italy)*, for instance, uses administrative data from clinical practice (RE 1).
- In addition, *Belgium* employs financial data, clinical diagnostic data, and claims data (RE 2 and RE 3).
- Data from public hospitals are collected in the *Catalan* registry. The equivalent on a national level is called the Valtermed registry (RE 6 and RE 7).
- *The Netherlands* also employs registry-based data for both schemes of conditional funding (RE 8).
- In *Germany*, any source that is eligible for collecting data to address the uncertainties can be included. In the case of Zolgensma®, these are data from the *SMArtCARE* registry operated by a professional society (RE 4).
- pCPA *(Canada)* reported customarily utilizing prior authorization forms (RE 10). Interviewee eleven referred to the "Essential Cancer RWD table" (Chan et al., 2020b, p.22f) [122] developed by the Data Working Group of the CanREValue initiative *(Canada)*, listing the minimally required relevant databases for RWE studies such as cancer registries, treatment claims and physician billings. The "Expanded Cancer RWD Table" (Chan et al., 2020b, p.19ff) [122] compares the availability of these data elements among the Canadian provinces. In general, attempts are made by the research group to repurpose the data collected by the provinces for the use of RWE studies and adopting a lifecycle approach to HTA (RE 11).

Datenhoheit

A synthesis of interview responses on the **data ownership** yielded a mixed picture.

- Countries using registry data like, i.e., *Italy* and *Catalonia (Spain),* indicated that data is publicly owned (RE 1, RE 6, and RE 7).
- In *Canada,* databases described in the "Essential Cancer RWD" table are often held by (public) data custodians such as provincial ministries and cancer agencies (RE 11, [122]).
- In *Sweden* and the *Dutch* "Orphan drugs, exceptionals and conditionals scheme", the MAH is the data owner, while in the "Promising care process", it is healthcare providers (HCPs) such as clinicians and physical therapists (RE 12 and 13 and 14, RE 8).
- Sick funds hold the data in *Belgium*, while

- in the *German* routine practice data collection of Zolgensma®, this is done by the registry operator (RE 2 and 3, RE 4).
- However, *Germany* and the representative from the CanRE collaboration group *(Canada)* also pointed out that technically the patient is the data owner (RE 4, RE 11).

Gewährleistung der Datensicherheit und des Datenschutzes

This leads to the question of how countries intended to ensure the **data protection** of patients.

- Using anonymized patient data was one way reported, for example, by pCPA, INESSS (both *Canada*), and *the Netherlands* (RE 10, RE 15, RE 8). The framework currently developed by the CanREValue collaboration intends to use the existing data generation systems in the provinces where privacy issues have already been resolved (RE 11).
- Another approach was utterly relying on administrative data generated from clinical practice, which required no extra approval from an ethics committee or additional informed consent as reported from *Italy* (RE 1).
- In *Belgium*, a third party, a privacy committee, is responsible for ensuring patient data protection and authorizing the use of data for MEAs (RE 2 and RE 3). "It's really a watchdog in what we are doing with the data of the social security" (RE 2).
- *Catalonia (Spain)* uses a specific secured platform to safeguard sensitive information (RE 6 and RE 7).

Table 4-4: Cross-country comparison of module "governance of evidence generation" in outcome-based Managed entry agreements (OBMEA)

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Funding data collection, data analy-sis	-Data collection: Sick funds -Data analysis: MAH (pays a lump sum to sick funds or Healthdata. be to use data to set up registries, i.e.) -Health-data.be is a publicly funded open data platform	-Most cases: routine data collection funded by public programs (part of continuous administrative work) -Some cases: data collection via registries funded by MAH	-Main responsibility: MAH (but also data from administrative databases)	-Varies between provinces, territories, or single institutions (MAHs), depending on who is responsible for data collection	Recall the idea of risk-sharing: divide funding between benefitting parties	MAH	MAH (32k for three years paid to AIFA)	-Potentially promising care: subsidized by the government -Orphan drugs, exceptionals, and conditionals: MAH	MAH	CatSalut	No information
Responsibility data collection	-Sick funds -Hospital pharmacists transfer data from physician to sick funds (financial incentive)	-Public payers for schemes using prior authorization forms -MAH for registry-based models	-MAH provides new data for the re-evaluation process (no specific requirements determined yet) -INESSS supplements evaluation with locally collected experiential and contextual data, comprising administra-tive medical databases	No information (referring to pCPA)	-Most cases: routinely collected data (passive process) -Some cases: prospectively collected data	Registry operators	Clinicians, pharmacists	-Potentially promising care: hospitals, HCPs -Orphan drugs, exceptionals, and conditionals: hospitals -No involvement of MAH	No information	Hospitals	MAH
Responsibility data analysis	Sick funds deliver raw data, further analysis by MAH	-Most cases: routine invoicing by public drug plans -MAH for registry-based models	-Data collected by MAH: MAH -Data collected by INESSS: INESSS	No information (referring to pCPA)	Ideally: cancer agencies	Registry operators (final responsibility that data is suitable for the benefit assessment rests with MAH)	AIFA	No information	No information	CatSalut	MAH

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Data sources/ types of data	Administrative data, financial data, clinical diagnostic data, claims data	Most cases: prior authorization forms	OBMEAs are still ongoing (no information of what data the MAH will submit)	No information (referring to pCPA)	-Trying to repurpose routinely collected data for RWE (lifecycle HTA) -Refers to the report of data working group describing relevant databases (see table "Essential Cancer RWD table") [122]	Any source that is deemed suitable to collect the necessary data for addressing the questions (example Onasemnogene: registry data operated by a profes-sional society)	No observational data but administra-tive data from clinical practice	Registry data for both schemes	No information	-Catalan registry: data collected from public hospitals -Spanish registry: Valtermed	"Could be anything" (MAH responsible for data collection)
Data ownership	Sick funds	No information	-OBMEAs are still ongoing, no re-evaluation conducted yet (probably MAH and publicly owned administra-tive databases)	No information (referring to pCPA)	-Technically: patients -Databases are often held by data custodians (i.e., provincial ministries, provincial cancer agencies) [122]	-Technically: patients -Onasemno-gene: registry operators	AIFA (owner of the registry platform)	-Potentially promising care: clinicians, physical therapists, hospitals -Orphan drugs, exceptionals, and conditionals: MAH	No information	Publicly owned registry	MAH

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Data protection	-Privacy committee responsible for ensuring data protection -Small cell values: grouping of patient data when less than five patients per group	-Use of anonymized patient data -Jurisdictions and federal governments have each their privacy regulations -No involvement of pCPA	Use of anonymized patient data	No information (referring to pCPA)	-Provincial privacy regulations -Since databases are only repurposed, privacy issues have already been resolved	-Part of the concept of the registry -Sometimes additional informed consent required depending on the registry used	Use of administrative data from clinical practice (disclaimer) requires no approval from an ethics committee and no additional informed consent	Use of anonymized patient data	No information	-Use of a specific secured platform to ensure control of sensitive information -No additional informed consent (referred to General Data Protection Regulation (EU) 2016/679 (GDPR)	No information

Abbreviations: AIFA – Agenzia Italiana del Farmaco, CADTH - Canadian Agency for Drugs and Technologies in Health, CanREValue - Canadian Real-world Evidence for Value of Cancer Drugs, CatSalut - Catalan healthcare service, HTA – Health Technology Assessment, RIZIV-INAMI - Rijksinstituut voor ziekte en invaliditeitsverzekering/ Institut national d'assurance maladie-invalidité (National Institute for Health and Disability Insurance), INESSS - Institut National d'Excellence en Santé et en Services Sociaux (National Institute for Excellence in Health and Social Services), IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), MAH - Marketing Authorization Holder, MEA – Managed-entry agreement, OBMEA – outcome-based Managed-entry agreement, pCPA - Pan-Canadian Pharmaceutical Alliance, RWD – Real-world data, SMC - Scottish Medicines Consortium, TLV - Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency), ZIN - Zorginstituut Nederland (National Health Care Institute)

4.2.4 Re-assessment

Re-Evaluierung

The re-assessment stage relates to the evaluation process of the new evidence obtained, focusing on questions like how to structure the **process,** which **assessment criteria** are employed, which mechanisms are used to **ensure** that **the quality of data** is sufficient and complete to address the identified uncertainties and how **market dynamics** such as the market access of similar comparable therapies are taken into consideration.

Festlegung von Prozess zur Re-Evaluierung zu vorweg festgelegtem Zeitpunkt oder MAH-Initiative

The **re-evaluation procedure** in most countries follows a similar pattern. The start is usually marked by the MAH submitting a new reimbursement dossier which contains all evidence collected until a specific time point (RE 2 and RE 3, RE 4, RE 8, RE 9). The duration of evidence generation varies between countries, as indicated in chapter 4.2.2

- In *Germany*, for example, the data collection period for Zolgensma® is set for 60 months. After database closure, the MAH needs to prepare the new dossier within six months (RE 4).
- Subsequently, evaluating the evidence commonly leads to initiating a new HTA process (RE 2 and 3, RE 4, RE 9). Different committees and institutions are in place to make a recommendation to payers or the final authority taking the ultimate decisions upon the use of these therapies.
- The Reassessment and Uptake Working Group of the CanREValue collaboration *(Canada*) drafted a "Preliminary Model of the Reassessment Process" (Chan et al., 2019, p.20) [89] describing the different steps of activities and stakeholders involved. Accordingly, the re-assessment process should be initiated by federal, provincial, territorial drug programs, cancer agencies, or the industry. CADTH and INESSS are foreseen to conduct the re-evaluation review. Based on that, the final recommendations on drug funding should be produced by the expert review committee. During the process, which should last six months, excluding evidence generation, all sources and different data types suitable to answer the initial questions are included for analysis [89].

Kriterien für Re-Evaluierung

Little information was available on the **criteria** applied for re-assessment.

Daten und Literatur
Patientenerfahrungen
Anwendungspraktiken
Bewertung der Endpunkte

- ZIN *(Netherlands*) indicated using the same criteria for the usual reimbursement process of orphan drugs, considering data from research and scientific literature reviews (RE 8).
- *Catalonia (Spain)* also mentioned not changing the criteria for every assessment each year (RE 6 and RE 7).
- Referring once more to the Reassessment and Uptake Working Group of the CanREValue collaboration *(Canada)*, re-evaluating the evidence should consider the following seven factors: addressed evidence gaps identified in the original drug assessment, utilization trends, patient experiences, clinical endpoints, adapting the cost-effectiveness analysis to RWE, updating the funding algorithm and operational aspects such as the sustainability of recommendations [89].

Qualitätsbewertung der neuen Evidenz

Only two countries mentioned having routine measures established to **assure the quality** of the new evidence produced.

- *Catalonia (Spain)* performs regular audits of the data entered by healthcare professionals into the registry (RE 6 and RE 7). Biannually checks to see "[…] that the research is still on track" are carried out in the Netherlands (RE 8).

- No formal process is established in *Canada* and *Belgium*. pCPA mentioned mitigating only the impact of data quality problems through specific mechanisms, while in Belgium, data quality assurance is a "work in progress" (RE 2 and RE 3, RE 10).
- In *Germany*, the generation of high-quality and fit-for-purpose routine practice data is guaranteed by using suitable databases that meet the criteria specified in the conceptional framework (RE 4).
- Whereas in *Scotland* and *Italy*, the responsibility for producing high-quality data lies with the MAH (RE 1, RE 9).

Einbezug von Marktdynamiken (weitere Anbieter)

Different strategies exist on how to handle changing **market dynamics** and innovations in the pharmaceutical sector, particularly the entry of direct competitors.

- In *Belgium*, for example, in case of substantial market changes, a new HTA is induced considering the new therapies. The rapid market dynamics were the main reason for limiting the contract duration for innovative drugs to around two to three years (RE 2 and RE3).
- In contrast, AIFA *(Italy)* retains the opportunity to reopen existing contracts for renegotiations (RE 1).
- In *the Netherlands*, the treatment is compared to the original standard of care and the new comparator where indirect comparisons are possible (RE 8).
- By contrast, the dossier submitted by the MAH in *Scotland* for re-assessment must include the current comparator and follow the existing HTA methodology at the point of re-assessment (RE 9).
- The present concept for the generation of routine practice data does not consider market dynamics. However, recently, the G-BA *(Germany)* has commissioned the IQWiG for developing a concept for generating routine data in an indication area where lots of new therapies enter the market in quite a short time. This should be illustrated by the example of CAR-T therapies (RE 4).

Table 4-5: Cross-country comparison of module "re-assessment" in outcome-based Managed entry agreements (OBMEA)

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Procedure	-MAH submits a new reimburse-ment application containing all data generated -New HTA process (evaluation by CTG-CRM) -New reimburse-ment advice	No reassessment process yet (interested in a lifecycle HTA approach)	No re-assessment conducted yet	MAH can request a re-assessment of a product	-Developed preliminary Model of the Reassess-ment Process: -Process initiated by federal, provincial, or territorial drug programs/ jurisdictions, Cancer agencies, industry -Reasses-sment reviews conducted by CADTH/ INESSS -Recommen-dations for drug funding by the expert review committee -Considering all sources of data if quali-ty is appro-priate and targeted to-wards uncer-tainties [89]	-After 60 months of data collection, database closure -Within six months, dossier preparation by MAH (Onasemnogen e: until 01.07.27) -Standard procedure of benefit assessment -Discount on the amount of reimbursement if an added benefit is not quantifiable based on new data - Reimbursement negotiations	Involvement of the pricing and scientific committee assessing the new data	-MAH submits new dossier -Recommen-dations on cost-effectiveness by promising care com-mittee (potentially promising care), a scientific advisory committee (orphan drugs, exceptionals, and conditionals) -Appraisal committee provides reimburse-ment recommendation, takes on a societal perspective -ZIN provides advice to the Ministry of Health (for drugs that are no hospital care)	-No re-assessment conducted yet -Ultra orphan pathway: >MAH submission for reassessment >SMC re-assessment + advice [124]	Evaluation each year to decide if the scheme should be continued or not	No information
Time frame	Overall duration: 1 year -HTA process + appraisal process within 180 days	No re-assessment conducted yet	No re-assessment conducted yet	No information	About six months	See above	Legal basis: a reassessment after two years (but often lasts much longer)	No information	Ultra-orphan pathway: 22 weeks between the MAH's submission for reassessment and SMC advice [124]	No information	No information

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Assessment criteria	No information	Not applicable	No re-assessment conducted yet	No information	-Evidence gaps which informed the original drug funding recommendation -Utilization -Patient experience -Clinical outcomes -Real-world cost-effectiveness -Changes in the funding algorithm & sequence of therapies -Operational factors [89]	No information	No information	Same criteria as usual reimbursement process	MAH must include the current comparator and follow current HTA methodology at the point of re-assessment	Criteria do not change during the assessment each year	No information
Data quality assurance	"Work in progress," aiming for higher quality control, faster data delivery	No formal processes but mechanisms to mitigate the impact of data quality problems	-No mechanisms for quality assurance in place yet (framework is in progress) -Evaluating data quality is part of the evaluation process	-Data submitted by MAH is reviewed by CADTH -Assessment is shared with the expert committee which analyses and reviews assessment and data	-"Logic checks" -Use of established databases that already control data quality	Part of developing the concept (using high-quality databases)	Responsibili-ty of MAH	Interim checks (twice a year) to see if the "research is still on track"	Responsibili-ty of MAH	Regular audit by hospitals of data entered into the registry	No information

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Market dynamics	-In case of market entry of new therapies, MEA Taskforce sends it back to the committee of reimburse-ment -Start of new HTA that takes new therapies into account (main reason why for new high-priced drugs the duration is set at two years)	No direct impact on the assessment (since using pay for performance schemes) would probably result in a lower patient number being treated with the drug in question	No information	No information	No information	-Not considered in the current concept -On behalf of the G-BA, IQWiG is developing a concept for generating routine data in an indication area in which many new therapies are coming onto the market within a short period (illustrated by the example of CAR-T therapies)	AIFA can revise existing therapies and renegotiate in case of market entry of new comparable therapies	Compare to the original standard of care, try to compare it to a new comparator if an indirect comparison is possible	-Treatment pathway might have changed -MAH must include the current comparator used in NHS Scotland at the point of re-assess-ment in its dossier	Parallel risk-sharing agreements in indication areas with identical identified uncertainties	No information

Abbreviations: AIFA – Agenzia Italiana del Farmaco, CADTH - Canadian Agency for Drugs and Technologies in Health, CanREValue - Canadian Real-world Evidence for Value of Cancer Drugs, CAR-T-cell - Chimeric antigen receptor T-cell, CatSalut - Catalan healthcare service, CTG/CRM Commissie Tegemoetkoming Geneesmiddelen/ Commission de remboursement des medicaments (Commission for Reimbursement of Medicinal Products), G-BA – Gemeinsamer Bundesausschuss (Federal Joint Committee), HTA – Health Technology Assessment, RIZIV-INAMI - Rijksinstituut voor ziekte en invaliditeitsverzekering/ Institut national d'assurance maladie-invalidité (National Institute for Health and Disability Insurance), INESSS - Institut National d'Excellence en Santé et en Services Sociaux (National Institute for Excellence in Health and Social Services), IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), MAH - Marketing Authorization Holder, MEA – Managed-entry agreement, OBMEA – outcome-based Managed-entry agreement, pCPA - Pan-Canadian Pharmaceutical Alliance, , SMC - Scottish Medicines Consortium, TLV - Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency), ZIN - Zorginstituut Nederland (National Healthcare Institute)

4.2.5 Exit of Outcome-Based Managed-entry agreements

Ausstieg aus OBMEA

Finally, the last phase concerns **potential outcomes** and policy implications at the end of OBMEAs, including the question of how to deal with possible **disinvestments** if the data proves the ineffectiveness of therapies.

Optionen für Ausstieg:

Most schemes encompassed the following four basic options (RE 6 and 7, RE 2 and RE 3, RE 15):

a) Continuation with current conditions
b) Continuation with modifications
c) Discontinuation, stop reimbursement
d) Completion, available for routine use, continue reimbursement (possibly changing funding conditions)

Erstattung mit bestehenden Bedingungen

Erstattung mit Änderungen

Abbruch, Beendigung der Erstattung

Erstattung im Routinebetrieb (evtl. mit Änderung der Förderbedingungen)

- Variation exists in countries where no prolongation of agreements is possible, as is the case in *Scotland*. In both prevalent OBMEA types, the drug is either entirely accepted for use, accepted for a restricted patient population, not accepted, or accepted for use on an interim basis again if the conditional marketing authorization is still valid (RE 9).
- Another possible option used in *Italy* at the end of the contract is to transform an OBMEA into a financial agreement (RE 1).
- If the re-evaluation of the new data generated results, in *Germany,* in a non-quantifiable added benefit, a discount on the amount of reimbursement applies. Reimbursement negotiations between the MAH and the National Association of Statutory Health Insurance Funds only start if the added benefit is proven (RE 4).

Disinvestment:

The majority of respondents had little experience concerning **disinvestment** of therapies (RE 1, RE 6 and RE 7, RE 12 and RE 13 and RE 14, RE 9, RE 10, RE 15). This is partly attributable to the fact that, even theoretically, in some countries, there is no possibility of removing the reimbursement status of drugs if they do not deliver the benefits promised.

Abbruch, Beendigung der Erstattung

muss vorbereitet sein

- In *Germany*, this is because the market access and reimbursement of drugs are not linked to a "fourth hurdle." If the benefit assessment reveals that the new drug has a lower added benefit than the appropriate comparator, the price is adapted accordingly (RE 4).
- A similar mechanism exists in *Canada*, where mainly pay-for-performance schemes are used. The discount amount is calculated on the percentage of non-respondence to the treatment (RE 10).
- *Belgium* and *the Netherlands* were some of the few countries where disinvestments had happened (RE 2 and 3, RE 8). Both reported difficulties when stopping reimbursement, justifying the decision to the public. In the previous Dutch conditional reimbursement scheme for hospital drugs, it was decided not to reimburse a therapy since it was proven to be ineffective, which evoked a public outcry spread in the media (RE 8). Commonly, in Belgium, it is sought to ensure that patients have access to alternative therapies. If this is not possible, the cohort will be closed, and no new patients will receive the drug in question (RE 2 and RE 3).

Involvierung von Patient*innen und Medien

Table 4-6: Cross-country comparison of module "exit" in outcome-based Managed entry agreements (OBMEA)

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Nether-lands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Potential outcomes	a) Prolongation without modification b) Prolongation with modification c) Stop convention + removal from listing d) New submission to CTC-CRM (new convention or inscription on the list or removal of the list) [50]	Not applicable	-No re-assessment conducted yet -Possible outcomes: a) Favour-able assessment and removal of conditions b) Maintain some conditions if uncertainties persist c) Unfavour-able assessment and recommen-dation to stop reimburse-ment	a) Reimburse b) Reimburse with conditions c) Do not reimburse	1) Status quo: a) Data confirmed effectiveness, safety, and cost-effectiveness of initial review; no need to change the current reimburse-ment b) Data was insufficient to address uncertainties, requires additional data and subsequent re-assessment 2) Revisit funding criteria or pricing (cost-effectiveness has changed, narrower/broader indication, etc.) 3) Do not continue funding [89]	a) Discount on the amount of reimburse-ment if an added benefit is not quantifiable based on new data b) Reim-bursement negotiations if an added benefit is proven	a) Maintain OBMEA b) Transfor-mation into a financial agreement c) Stop monitoring and open utilisations of the drug without restrictions	No information	Interim accepted decision option: a) Accepted for use b) Accepted for use on interim basis again if conditional MA is still valid c) Not recommen-ded for use d) Accepted for restricted population Ultra orphan pathway: a) Accepted for use b) Accepted for use on an interim basis again if conditional MA is still valid c) Not recommen-ded for use d) Accepted for restricted population NO option to prolong the scheme	a) Continue without modification b) Continue with modification c) Discon-tinue d) Comple-tion	Slight adaptions in reimburse-ment restrictions

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Nether-lands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Disinvest-ments	-No abrupt stop of reimburse-ment (make sure that patients have access to alternative therapies) -Closed cohort: patients already on the therapy can continue but no inclusion of new patients -One case (2 years ago) where reimburse-ment was stopped from one day to another because no agreement was reached	-No history of disinvest-ments -Rebate of the pay for performance scheme is adapted if patient does not respond to treatment	-No history of disinvest-ments, -No strategy how to deal with disinvest-ments	-Disinvest-ments are almost impossible from a political point of view -Disinvest-ment decisions rest with jurisdictions -No standard approach	**Ideally**: a transparent process involving all stakeholders to raise awareness of potential disinvest-ments	No "fourth hurdle" in Germany, no disinvest-ment possible	Happens very rarely	-Difficult not to reimburse a therapy -Experience with disinvest-ments in previous conditional reimburse-ment scheme, stop of reimburse-ment produced a public outcry	No history of disinvest-ments but aware of the potential risk	No history of disinvest-ments (responsibili-ty of the Ministry of Health, not CatSalut)	No history of disinvest-ments

Abbreviations: AIFA – Agenzia Italiana del Farmaco, CADTH - Canadian Agency for Drugs and Technologies in Health, CanREValue - Canadian Real-world Evidence for Value of Cancer Drugs, CatSalut - Catalan healthcare service, CTG/CRM Commissie Tegemoetkoming Geneesmiddelen/ Commission de remboursement des medicaments (Commission for Reimbursement of Medicinal Products), RIZIV-INAMI - Institut national d'assurance maladie-invalidité/Rijksinstituut voor ziekte- en invaliditeitsverzekering (National Institute for Health and Disability Insurance), INESSS - Institut National d'Excellence en Santé et en Services Sociaux (Canadian HTA – Québec), IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), NHS – National Health Service, MA – Marketing Authorization, OBMEA – outcome-based Managed-entry agreement, pCPA - Pan-Canadian Pharmaceutical Alliance, , SMC - Scottish Medicines Consortium, TLV - Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency), ZIN - Zorginstituut Nederland (National Healthcare Institute)

4.3 Areas of application

Anwendungsgebiete: Auswahl der Therapien für OBMEA

große Unsicherheit zum klinischen Nutzen, zur Kosten-Effektivität, zu den Budgetfolgen

Kriterien für Auswahl: z.B. EMA Zulassungen mit:

orphan designation,

conditional marketing authorization,

authorization under exceptional circumstances

This subsection answers research question three, concerning for which innovative therapies these models are applied. As indicated in Table 4-7, currently, no uniform process exists across countries for selecting potential therapies for funding through OBMEAs. Though, it appears that there is some basis of consensus on the underlying rationale for implementing these reimbursement schemes for specific therapies. One of the main drivers repeatedly revealed in the interviews was the high uncertainty around introducing new medicines, often resulting from the limited information available in the pivotal trials (RE 2 and RE 3, RE 5, RE 6 and RE 7). This included unresolved questions around the clinical outcomes, cost-effectiveness, and budget impact. Another criterion was the high prices charged from the MAH (RE 2 and RE 3).

- pCPA *(Canada)* follows a rather opportunistic and pragmatic approach, opting for more complex funding schemes during the negotiations when one negotiation body has a stake in OBMEAs or simply purely financial proposals are deemed unsuitable for that specific drug (RE 10).
- Some countries decided to explicitly target specific groups of medical technologies for these new payment models by using particular conditions to be met, such as an existing orphan designation, conditional marketing authorization, or authorization under exceptional circumstances granted by EMA. These three criteria are, i.e., considered by the G-BA *(Germany)* when deciding for which therapies a generation of routine practice data should be initiated. In addition, essential aspects analyzed are the data gaps at the time of approval and what information can be obtained within a foreseeable period (RE 4).
- Looking at the reimbursement models in *Scotland* paints a similar picture. The "Interim accepted advice decision" requires a conditional marketing authorization while the "Ultra-orphan pathway" includes only therapies fulfilling the ultra-orphan criteria as defined by the SMC (RE 9).
- In *the Netherlands*, a conditional reimbursement route applies for "Orphan drugs, conditional or exceptional authorized drugs" by EMA. Besides, the medicine must address an unmet medical need corresponding to the EMA definition. The other subsidy scheme, "Potentially promising care", is not tied to a specific authorization or orphan drug status but focuses more on the lack of research results being the only reason why a technology has not been included in the basic benefits package yet (RE 8 [111, 112]).
- In *Italy*, AIFA Monitoring Registries are mandatory for innovative drugs. The status of innovativeness is assessed by the AIFA innovation algorithm based on the unmet medical need, added therapeutic value, and quality of clinical trials (RE 1, [129]).
- In contrast to these rather loose and unorganized selection processes, the CanREValue group *(Canada)* is currently drafting a multi-criteria decision analysis rating tool for enhancing transparency and create a more thorough understanding of potential projects ahead. It is based on two principles: the importance and feasibility of the question to be addressed (RE 11).

derzeit ausgewählte Therapien:

CAR-T Zelltherapien
Onkologika
seltene Erkrankungen (SMA-Therapien)
ATMPs

Following the approaches and criteria described above that are used for screening therapies for OBMEAs, it becomes apparent that most of them apply to **ATMPs**. These products come along with numerous uncertainties are often conditionally or under exceptional circumstances approved. Comparing the results from the interviews confirms the picture presented. Gene therapies, orphan drugs, and CAR-T cell therapies were the most mentioned type of technology for which an MEA was in place. However, it is necessary to bear in mind that the confidential nature of MEAs hindered this analysis. Some countries could not provide any details on the specific products financed via MEAs.

- This holds, for example, for pCPA *(Canada)* and CatSalut *(Catalonia, Spain)*. CatSalut indicated that eight risk-sharing agreements are currently in place: seven in the area of oncology and one for a Multiple sclerosis drug. Yet, the responsibility for concluding MEAs for ATMPs lies with the Ministry of Health at the national level.
- The *Belgium* HTA body provided a list of products with MEAs in place (see Appendix 7.8), but no specification on the type of agreement, whether financial or outcome-based, could be given for confidentiality reasons.
- The therapeutic areas most often targeted were **oncological and rare diseases** in general. This coincides with the fact that the framework developed by the CanREValue collaboration *(Canada)* is explicitly designed for cancer drugs. Though, the reasons behind refer more to feasibility grounds concerning data collection. It was reported that a more organized and better-developed infrastructure exists for oncology care than other indications.
- Looking at the specific product level shows that in five countries, at least one of the two **CAR-T cell therapies** Tisagenlecleucel (**Kymriah®**) and Axicabtagen Ciloleucel (**Yescarta®**) approved for the European and Canadian Market is recommended for conditional funding (INESSS) or already reimbursed via an MEA (RE 1, RE 2 and RE 3, RE 6 and RE 7, RE 8).
- Onasemnogene abeparvovec (**Zolgensma®**) was the second most often named drug. In *Belgium*, an MEA is still in discussion; in *Italy*, a payment-at-result agreement is in place, and in *Germany*, this product is the first one for which the novel concept of routine data collection is applied (RE 2 and RE 3, RE 1, RE 4). In *Scotland*, SMC validated Zolgensma® as qualified for the "Ultra-orphan pathway". However, the MAH opted for the standard reimbursement route for orphan drugs and thereby might have reduced, on the one hand, the burden of data collection and, on the other, the risk of receiving a negative recommendation after re-evaluation if the treatment pathway had changed considerably. The medicine is now available for use in NHS Scotland (RE 9).
- The other three most common reported therapies in at least two countries were **Strimvelis®** (Italy, Belgium (ongoing discussion for possible reimbursement)), **Holoclar®** (Scotland ("Interim acceptance decision option"), Belgium (MEA since 2017)), and **Translarna®** (Netherlands (potential candidate for conditional reimbursement), Scotland ("Ultra-orphan pathway")).

Table 4-7: Cross-country comparison of module "technology selection" in outcome-based Managed entry agreements (OBMEA)

	Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE-Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Technology selection/ Prioriti-zation	No specific criteria	-No specific criteria (opportunis-tic approach) -Criteria used by public payers when evaluating proposals: overall feasibility, financial attractive-ness, workload	High uncertainties but also the high potential benefit of therapy	-Refers to pCPA -Need for OBMEA if: >Uncertainty around clinical outcomes >Very high price >Limited cost-effectiveness >Several therapies for the same indication on the market	CanREValue framework: drafting an MCDA rating tool based on the importance and feasibility of the question	-Limited to drugs with orphan designation, conditional marketing authoriza-tion, authorization under exceptional circumstan-ces -Criteria G-BA: available studies at the time of approval (which data are missing), what information can be obtained within a foreseeable time frame	-No specific criteria -Fully innovative and highly-priced drugs -Mandatory registries at a national level for innovative drugs (AIFA innovation algorithm: unmet medical need, added value, and robustness of clinical trials)	-Potentially promising care: promising but unproven (cost)effec-tiveness, proven safety, effica-cy, accept-able risks-benefit level, lack of research results showing that therapy is at least as effective as the standard of care [111] -Orphan drugs, exceptio-nals, and conditionals: EMA authorization (orphan designation, conditional or exceptio-nal MA), unmet medical need, new data will an-swer uncer-tainties,	-Interim accepted decision option: conditional marketing authorization -Ultra orphan drugs: criteria to be considered an ultra-orphan > condition has a prevalence of 1 in 50,000 or less in Scotland, > EMA orphan designation > condition is chronic and severely disabling, and > condition requires highly specialized management [130]	-Primarily determined by identified uncertainties that cannot be solved with data from pivotal trials -Decision is taken by a specific committee for MEAs -No specific guideline	No information
								research can be comple-ted within the period of conditional inclusion (7 or 14 years) [113]			

Abbreviations: AIFA – Agenzia Italiana del Farmaco, CADTH - Canadian Agency for Drugs and Technologies in Health, CanREValue - Canadian Real-world Evidence for Value of Cancer Drugs, CatSalut - Catalan healthcare service, EMA – European Medicines Agency, G-BA – Gemeinsamer Bundesausschuss (Federal Joint Committee), RIZIV-INAMI - Institut national d'assurance maladie-invalidité/Rijksinstituut voor ziekte- en invaliditeitsverzekering (National Institute for Health and Disability Insurance), INESSS - Institut National d'Excellence en Santé et en Services Sociaux (Canadian HTA – Québec), IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), MCDA – Multi-Criteria Decision Analysis, MEA – Managed-entry agreement, OBMEA – outcome-based Managed-entry agreement, pCPA - Pan-Canadian Pharmaceutical Alliance, , SMC - Scottish Medicines Consortium, TLV - Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency), ZIN - Zorginstituut Nederland (National Healthcare Institute)

4.4 Experiences and learnings

Erfahrungen mit OBMEA

Countries reported mixed experiences in the application of these alternative reimbursement models. Overall, more problems than advantages were mentioned during the interviews.

in Interviews mehr Probleme als Vorteile erwähnt

The two most frequently reported **strengths** were effectively addressing various kinds of uncertainties associated with introducing therapies and achieving value for public money (RE 4, RE 6 and RE 7, RE 2 and RE 3, RE 8).

Stärken von OBMEA (in Theorie):

- Along these lines, the *German* concept for the generation of routine practice data was explicitly designed to collect data to address **open questions and uncertainties** that might not be possible with every routine data collection (RE 4).
- *Catalonia (Spain)* reported using these models to reduce uncertainties **around clinical outcomes and economic impact** and adapt the price to the value observed while

Unsicherheiten beseitigen zu klinischem und ökonomischem Nutzen

- *the Netherlands* highlighted the benefit of having more information available at the end to decide on the cost-effectiveness when medicines are conditionally approved (RE 6 and RE 7, RE 8).

in Praxis: Patient*innen-Zugang ermöglichen

- One interview partner from the *Belgium* HTA body summarised the strength of OBMEAs in the following excerpt: "[…] we don't pay for a patient that is a non-responder. […] So, we're really paying for the gain in health" (RE 3).

Erstattung nur bei klinischem Erfolg

- Further benefits revealed included enabling earlier **patient access**, having a centralized registry, and an independent institution for managing data privacy (RE 8, RE 6 and 7, RE 2 and RE 3)

Schwierigkeiten von OBMEA

On the other hand, considerable **difficulties** were reported with the organizational implementation of OBMEAs, most of which were related to the evidence generation phase. Three interview partners mentioned issues with data collection.

Kliniker: Zeitkonsumierend statt Patient*innen-Kommunikation

- One anonymous interviewee highlighted the associated additional burden: "I think that's one of the biggest barriers, it's not automated, it's time-consuming, it's taking peoples time away from doing patient-facing roles. So that's a major barrier in terms of rolling this out to more medicines".

Zeit-verzögerte Datenlieferung

- RE 3 from *Belgium* agreed on that: "[…] it's harder than we thought to have these real live data. […] there is a big delay on the collection of the data."

Einheitlichkeit Qualität und Vollständigkeit der Daten

- *Canada´*s decentralized organization of healthcare, consisting of different territorial and provincial healthcare systems, which in turn have their local laws regarding patient data protection, makes **consistent data collection** increasingly complex (RE 10).

Widersprüchlichkeit der Daten

- Even more, issues were reported concerning the **quality of data** outcomes. The Dental and Pharmaceutical Benefits Agency (TLV) *(Sweden)* and ZIN *(Netherlands)* mentioned that the data submitted by MAH were of low quality, incomplete, and often did not sufficiently address the uncertainties (RE 12 and RE 13 and RE 14, RE 8).

Ressourcen- und Arbeits-intensiv

- *Belgium* is facing similar problems. Data presented by the MAH were often incomplete and not timely. It was reported that the MAH often blames the sick funds for the incompleteness of data since they are often the ones responsible for data collection. However, it was

Disinvestment ist schwierig

emphasized that the final responsibility for answering uncertainties lies with the MAH. Because of the sometimes incomplete data, theoretical schemes are preferred over schemes built on RWD. Another challenge reported was to ensure the clinical relevance of outcomes (RE 2 and RE 3).

- *Italy* struggles with duplicating data between the national monitoring registries held by AIFA and regional registries, causing **discrepancies and incoherence in data.** Besides, the long duration of schemes mentioned earlier may lead to deviations in the drug's clinical value (different percentage of non-responders, survival data, etc.), which affects the outcome of the re-negotiations (RE 1).
- The perceived intensive **operational workload** and **resources required** to set up OBMEAs were identified problems (RE 2 and RE 3, RE 5, RE 6 and RE 7, RE 15). According to interviewee five from CADTH *(Canada)*, the workforce required for collecting, analyzing, and reporting data constituted one barrier for implementing OBMEAs (RE 5).
- Further obstacles were finding the right way to deal with **disinvestments**, handling the sometimes high **political pressure** and negative media in reimbursement removal (RE 8, RE 12 and RE 13 and RE 14).

Mißtrauen und Skepsis, wenn MAH Daten sammelt

Intransparenz wegen Vertraulichkeitsvereinbarungen

Mangel an Interoperabilität verschiedener Datenquellen

- General **mistrust** of OBMEAs constituted another challenge identified. Canadian payers we sceptical about these new schemes, particularly when the MAH collects the data (RE 5, RE 10). TLV *(Sweden)* expressed concerns that the MAH will probably propose outcome-based payment models, "pretending" to reduce uncertainties, but data presented are considered inadequate, i.e., providing too short follow-ups, no reasonable extrapolation of long-term effects, etc. So, in the end, the risks won´t be mitigated enough (RE 12 and RE 13 and RE 14).
- Linked to that, some countries called the **opacity** of those reimbursement models into question (RE 2 and RE 3, RE 9, RE 10). Interviewee ten from pCPA *(Canada)* mentioned that the HTA work is impeded by the confidential nature of these negotiations and final agreements (RE 10). SMC *(Scotland)* raised the point that the publication of reassessment is constrained by the MAH who marks large parts of the reports as confidential (RE 9). As indicated in Table 7-4: Excerpt from of interview answers Table 7-4 (Appendix 7.8), elements of data exchange are pretty limited. Results of the scheme and conditions of the agreement are usually not publicly disseminated.
- Another issue mentioned during the interviews was the lack of **interoperability of different data sources**, thus limiting data coupling (RE 1, RE 2, and RE 3). Any other challenges can be taken from Table 7-4: Excerpt from of interview answers Table 7-4.

Empfehlungen aus Interviews:

Following the problems discussed above, **recommendations** from countries for designing OBMEAs that tie conditional reimbursement to public data generation centred around four main topics:

1. A feasible and pre-specified data collection plan,
2. Stakeholder engagement,
3. Raising public awareness, and
4. Increasing transparency.

Probleme beim Datensammeln durch klare Spezifikationen reduzieren

To mitigate the aforementioned **data collection** issues,

- *Belgium* advised creating systems for capturing the type of RWD you are looking for in a timely manner (RE 2 and RE 3).
- This is consistent with the recommendation provided by interviewee one from *Italy*, calling into mind that OBMEAs are only feasible if you agree on the correct data to collect and plan the data sources which produce high-quality data considering the national, regional, or local level. It was encouraged to make use of existing data collection structures. Further, a minimum dataset should be determined, and a data platform developed to implement OBMEAs (RE 1).
- As learned from the failure of former CED schemes in *Sweden*, OBMEAs require a high level of pre-specification, i.e., data collection, outcomes to be agreed on, organization, timeline, etc. Finding the right balance between defining the well-targeted towards cost-effectiveness but complicated to measure outcomes and more manageable but less exact endpoints might be challenging. TLV pointed at always keeping in mind the underlying rationale of implementing OBMEAs. Is the primary goal to reduce the risk or reduce the price tag? Another lesson learned from the experience with previous OBMEAs was generating data itself instead of putting the responsibility on the MAH since the quality of data submitted was often insufficient (RE 12 and RE 13 and RE 14).
- pCPA *(Canada)* also recommended a great level of pre-specification. INESSS emphasized choosing the right health technology for starting an OBMEA since the burden of data collection should be worth it (RE 10, RE 15).
- Besides, *the Netherlands*, another country drawing on previous experience with conditional funding, suggests regular interim assessment to keep track of data generation (RE 8).

Involvierung und Koordinierung von Stakeholdern:

Patient*innen (und Angehörige)
Kliniker*innen
MAH
Registerbetreiber

von Another topic raised during the interviews was the importance of early **involvement and alignments with stakeholders** on the scheme, comprising, i.e., patients, clinicians, the MAH, registry operators, etc. (RE 1, RE 4, RE 5, RE 6 and RE 7, RE 10). This could include stakeholder engagement in drafting the scheme to ensure broad acceptance and discussion with registry operators to agree on suitable data sources (RE 10, RE 4). Additionally, it was advised to establish partnerships with people who share the same goal and obtain support to manage the administrative burden, like pharmacists' and clinicians' involvement to collect the data entered into the system (RE 1).

frühe öffentliche Bewusstseinsbildung & Kommunikation zur Vorläufigkeit der Erstattung

Related to that, enhancing patient communication and public education on the high costs of treatments, the resulting conditional nature of funding, and possible disinvestment might raise **public awareness**. Since "(…) the patient is the one who has to perform in essence (…)" (RE 2) "(…) we have to be aware that patients might say that it works better, if they think (..), we will get our reimbursement if we say that it works, even if it doesn't work that good. So, I think the whole system on agreements and how public money is used should be enhanced, should be better" (RE 3).

Transparenz erhöhen:

Increasing transparency has also been brought up during the interviews.

Länder-übergreifendes Lernen ermöglichen

- CADTH *(Canada)*, i.e., stressed the need for public transparency, and *Italy* highlighted sharing results for enabling stakeholder participation (RE 5, RE 1).

- Cross-country collaboration between European countries was seen as one possible step in this direction (RE 2 and RE3, RE 8). Especially "[…] in rare diseases we should work internationally. And we should not use public money only from Belgium to invest in a registry, but make it as a whole group" (RE 3). As part of the BeNeLuxA group, Belgium already has some experience with setting up some international registries. One was, for example, established for Multiple sclerosis (RE 3 and RE 4).
- For the joint collection of RWE for highly innovative therapies, increasing transparency, and encourage early dialogue between stakeholders to agree on data to be collected and outcome parameters, reference was made to the *RWE4Decision initiative*. This research project also aims for an international registry (RE 2 and RE 3). However, some doubts were expressed. "It can work, but it's far-fetched. […] But more realistically is to exchange the registry protocols, the registry necessities, […], etc. But that's more easily to realize on an international level than putting an international registry just like that" (RE 2).
- Using foreign registries has also been taken into account in the concept developed for the generation of routine practice data for Zolgensma® in Germany. Having in mind that rare diseases may require the incorporation of registries from other countries, a Master protocol determining the common considerations for data generation and a Master Statistical Analysis Plan (SAP) describing the statistical methods for data analysis should be created to allow the integration of other registry data that meet the requirements such as producing high-quality data. The aim, however, is not to integrate all individual data from different countries into a shared data pool but to standardize the registry evaluations (RE 4).

juristische Basis für OBMEA erarbeiten

Additional recommendations provided from countries were **establishing legislation** for OBMEAs, ensuring that in the case of different healthcare systems, **consistent OBMEAs** are created valid throughout the country (RE 1, RE 5).

5 Discussion and conclusion

This report intended to investigate organizational models for outcome-based Managed-entry agreements (OBMEA). It was found that their implementation considerably varied between countries. Some were further advanced and could call on previous experience, while others have just started to conceptualize OBMEAs. Despite the feasibility constraints reported with their execution, little is known about measures proportionate to overcome practical difficulties. Therefore, the subsequent chapter first summarizes and interprets the findings of the literature search and interviews in light of the theoretical framework, which then results in deriving policy recommendations for harmonizing the organizational process of OBMEAs. Finally, the limitations of this study are discussed, and an overall conclusion is drawn.

Intention des Berichts: organisatorische Aspekte und Erfahrungen mit OBMEA sammeln

Zusammenfassung in diesem Kapitel

5.1 Interpretation of main results

5.1.1 Identified models

The literature search identified 16 frameworks, describing four generic and twelve country-specific models from Italy, Belgium, Germany, Canada, Catalonia (Spain), Netherlands, Scotland, and England. Comparing them showed different levels of maturity and level of detail. Some were still in their infancy, just recently initiated or applied on selected therapies as pilot projects, while others seemed further progressed. The Netherlands and Sweden, for example, have a history of using OBMEAs. In contrast, in Germany, it is the first time to apply the recently developed concept for generating and evaluating routine practice data on a therapy. Also, Canada is still at the beginning of exploring OBMEAs.

16 OBMEAs in Literatur identifiziert:

4 generische, 12 Länder-spezifische Modelle

in unterschiedlichen Einführungsstadien

In general, a lack of standardization to guide the operation of OBMEAs was observed. For example, few had established a uniform infrastructure for systematic data collection. In addition, a clear governance framework defining roles and responsibilities of stakeholders, information flows, and timelines were a rarity, pointing to the need to guide decision-makers on organizational prerequisites required for the successful implementation of OBMEAs. This is in line with the good practices proposed by Wenzl and Chapman (2019) to implement a strategy for guiding the application of OBMEAs and Michelsen et al. (2020), highlighting that a uniform governance approach across several schemes might ease the summative burden of execution [7, 18]. The IMPACT OBMEA tools, identified as one of the generic models, present a sound basis for policymakers to transparently manage the data collection process and increase the accountability of stakeholders.

im allgemeinen: Mangel an Standardisierung wie OBMEAs gut funktionieren können

aber: „Gute Praxis“ Wenzl/ Chapman 2019

und: IMPACT HTA tools

5.1.2 Modular structure of models

modulare Struktur der OBMEA Modelle

The analysis of the interview data confirmed the picture gained from the literature review. Wide variations emerged across countries in the composition of organizational models for OBMEAs.

Rationale für OBMEA
Kontext-Faktoren
rechtliche Voraussetzungen
IT-Infrastruktur

bestimmen OBMEA-Modell

- First, this may be due to different terms and taxonomies employed by countries to describe these agreements. What some categorized as an OBMEA, others did not.
- Besides, contextual factors and the rationale using these policy instruments varied, resulting in different types of OBMEAs applied. For example, countries with a financial-oriented objective were keener on using pay-for-performance schemes like Canada, where OBMEAs were used as an alternative to direct discounting (RE 10).
- Another factor contributing to variation might be having a legal basis for these schemes, as in Italy, Belgium, Germany, and the Netherlands. Legal backing is absent in Canada, which may explain the early stage of OBMEAs.
- The variance in terms of organizational models supports the findings of the literature confirming the picture of heterogeneous levels of implementation of MEAs in Europe [4, 26, 52]. The analysis by Pauwels et al. (2017) highlighted that contextual factors such as collecting evidence via reliable IT infrastructure systems play an essential role in enabling the use of different MEA types [52].

5.1.3 Area of application

Anwendungsbereiche:

Gentherapien,
Orphan Drugs
(Onkologika, seltene Erkrankungen)

Data from the literature were also in line with the responses from the interviews on the types of therapies most often targeted by these reimbursement models. Studies indicated that most agreements were reached on high-cost therapies, often for oncological or orphan diseases [18, 23, 50]. The interviewees confirmed these results, frequently mentioning gene therapies, orphan drugs, and CAR-T cell therapies as the primary target of OBMEAs with oncological and rare diseases as the most often addressed therapeutic areas. However, countries followed no standardized approach for choosing potential candidates for conditional financing. Instead, the selection seemed rather pragmatic and intuitive, focusing on cost-intensive drugs with high levels of uncertainty, which were commonly therapies with an orphan designation, conditional marketing authorization, or authorization under exceptional circumstances.

Kosten-intensive Therapien

5.1.4 Experiences and learnings

Erfahrungen:

Entscheidung für OBMEA will gut überlegt sein, weil Ressourcen-intensiv und häufig ohne klare Ergebnisse

Interviewees appraised the potential of OBMEAs, such as addressing uncertainties and achieving value for public money. Yet, benefits were outweighed by practical difficulties encountered in implementation. OBMEAs were perceived resource-intensive and cumbersome, with data collection placing a significant administrative burden on public systems. Besides, the lack of quality assurance mechanisms and the inadequate data submitted by the MAH fueled the common mistrust of payers towards OBMEAs. This was also demonstrated by Bouvy et al. (2018), where public payers and HTA agencies expressed concerns about whether OBMEAs could reduce uncertainties [54]. Besides, following Michelsen et al. (2020), studies showed that scepticism of payers is often caused by the insufficient quality of data [7]. Other feasibility issues reported in the interviews, such as the lack of standardization, opacity, and low public acceptance of disinvestments, have been confirmed in the literature and are seen as a possible explanation for public payers' reluctance to adopt data collection schemes [11, 18, 50, 54]. For example, after the failure of CED schemes, Sweden currently only pursues financial-based agreements.

Empfehlungen, Schwierigkeiten frühzeitig zu mildern

Based on the experiences countries made with OBMEAs, recommendations entailed, i.e., pre-specifying data collection, increasing stakeholder engagement, and enhancing public transparency by collaboration between countries. This is consistent with the findings of Vogler et al. (2018), who highlighted knowledge exchange as a policy tool for overcoming information asymmetry [3].

5.1.5 Outcome-based Managed-entry agreements - a fair pricing approach?

OBMEA als alternative Strategie der Preiskontrolle

theoretisch gute Idee

öffentliche Institutionen sollen Bedingungen stellen (Mazzucato 2018)

When placing the findings of this research within the overall context of decision-making and reflecting upon the general relevance of OBMEAs as a policy tool for fair pricing, ambiguous conclusions emerge. Given the increasing pressure on finite healthcare budgets and the emergence of highly-priced ATMPs, an area where traditional public price control mechanisms have failed, the importance of alternative reimbursement models is likely to increase. The theoretical foundation of OBMEAs, providing conditional reimbursement and allowing an equal sharing of risks between MAHs and public institutions, presents a sustainable solution for pricing these expensive drugs. The idea of risk-sharing and imposing conditionalities to public investment is also supported in the WHO Fair Pricing Forum 2017 [28]. Additionally, Mazzucato et al. (2018) proposed attaching conditions on knowledge exchange to secure access to the data produced in research to generate benefits to the broader public, which would help payers evaluate the medicines and negotiate a fair price [35].

Critically reviewing the research findings against this backdrop raises the question of whether the identified OBMEA models follow the conceptual idea of risk-sharing. It appears that much control over evidence generation rests with the MAH. As registry and administrative data were the most frequently cited data sources, many of which may be publicly owned, the fair distribution of responsibilities and authorities seems only partially implemented. Yet, it should be noted that some countries explicitly entrust the MAH with the evidence generation because of the high administrative and technical effort involved. Therefore, a crucial point of such schemes is finding a sustainable way to relieve the burden of data collection. One possible approach could be introducing a generic model for OBMEAs which standardizes the organizational processes to achieve greater transparency, alignment, and interchangeability of data.

praktisch verwirklicht sich die "gute Idee" nur bedingt

Datensammlung und –kontrolle oft durch MAH

ev. Lösung: generisches Modell, Länder-übergreifend, standardisiert

5.2 Recommendations

To answer the overarching question of advising health policy which organizational infrastructure, processes, and responsibilities are needed for OBMEAs, all findings are synthesized into a guiding organizational model, drawing on the good practices in other countries. This guidance is to be understood as a generic approach. It gives each country the freedom to adopt the model according to its contextual factors such as legal framework and national data infrastructure.

The breakdown in five different stages from the initiation of the scheme, design, evidence generation, re-assessment and exit, and dissemination of results is based on the structure of the interview guideline. Unlike other frameworks, the last stage has been purposely included as an additional element to pave the way for mutual learning between countries.

The model is presented in *Figure 5-1*.

Empfehlungen für

Prozesse
Infrastruktur
Verantwortlichkeiten

nach 5 Phasen von OBMEA

generisch

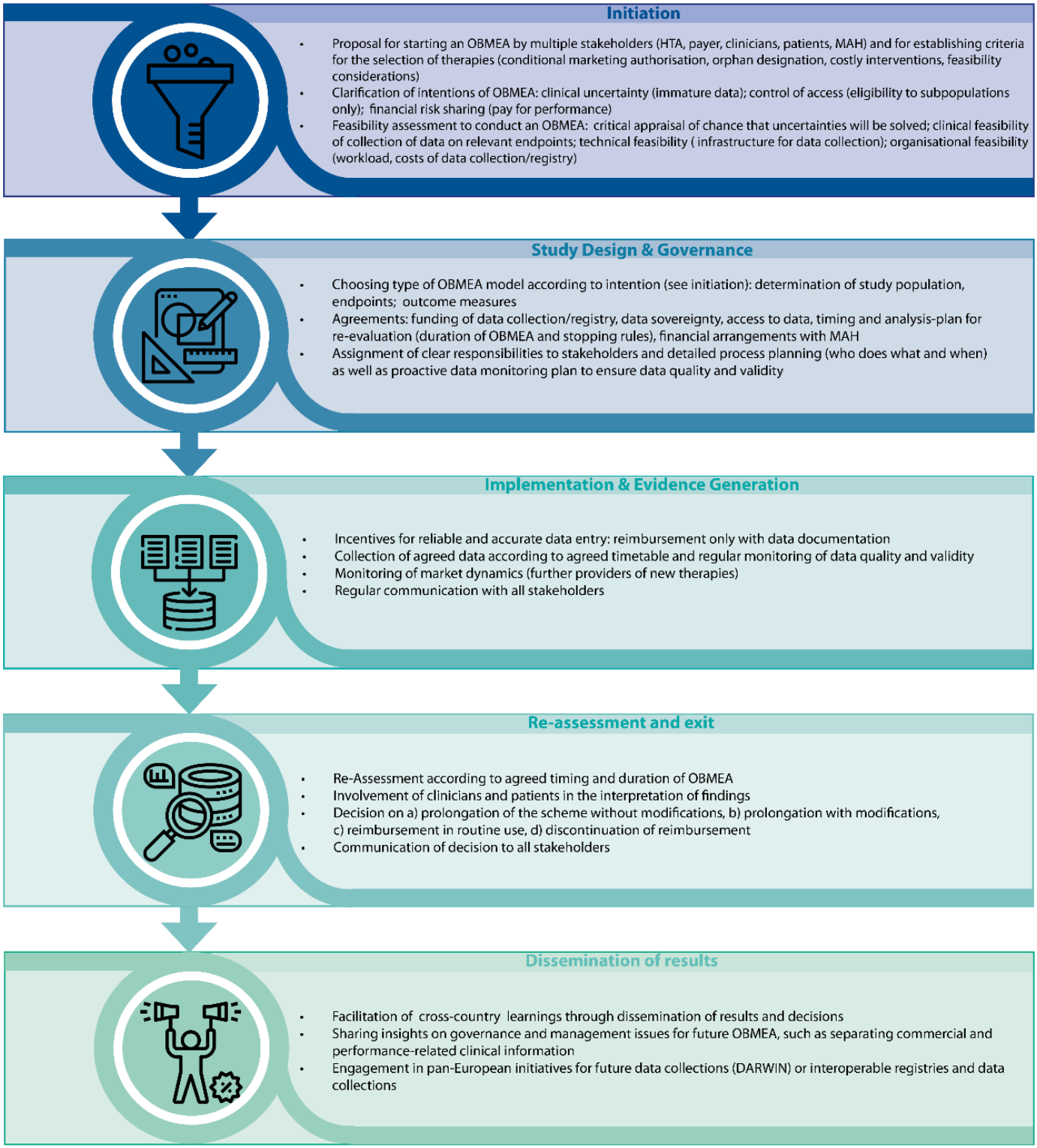

Figure 5-1: Generic organizational model [own figure]

5.2.1 Initiation: introduction, selection, and prioritization

Introducing OBMEAs should not be limited to a single party but involve various interest groups as the early stakeholder engagement was seen as a critical success factor for OBMEAs.

Initiierung durch verschiedene Stakeholder als kritischer Erfolgsfaktor für OBMEA

- Following *Figure 5-1*, one possible way is for the MAH to propose an OBMEA in the dossier submitted to request reimbursement.
- The second option could be for the HTA body to initiate such a scheme. Possible candidates might be identified early on through screening activities such as horizon scanning using uncertainties of different nature, a certain authorization status granted by EMA like conditional approval as potential indicators, or focusing on certain types of technologies such as orphan drugs, a certain level of expected public spending or therapeutic area.
- A third group might be clinicians and patients who know best about treatment gaps and ongoing studies [89].

The importance of **identifying the evidence gap** at the beginning was also highlighted in the procedural sequence for planning, collecting, and analysing routine practice data, as developed by the German Network for Health Services Research (DNVF). Accordingly, the definition of the research question forms the basis for designing the study and data collection. The process steps, outlined in Figure 7-4 (Appendix 7.9.1), guide decision-makers in employing routine practice data to estimate treatment effects [131].

klare Fragestellung zum Evidenzbedarf

Sorting out suitable therapies for OBMEAs from the collected pool requires pre-defined **selection** criteria. One of the OBMEA tools produced within the EC-project IMPACT HTA (WP10) is a comprehensive checklist assessing the **feasibility** of CED schemes for rare disease treatments. The list is found in Figure 7-6 (Appendix 7.9.2). Criteria encompass, i.e., a data collection plan and/or protocol outlining the research questions, design of the scheme, and data sources [91]. The data collection could be developed by the MAH and (public) registry holder and be approved by HTA bodies and payers. Apart from the IMPACT HTA checklist, the CanREValue collaboration also produced feasibility considerations displayed in Figure 7-7 (Appendix 7.9.2), highlighting the importance of a suitable comparator, relevant outcome measures, and required financial support for conducting the scheme [89]. The final decision whether a product is selected for an OBMEA or should follow the standard route of reimbursement assessment should be made by HTA bodies and payers.

nach Auswahl der Therapie für OBMEA soll Machbarkeitsanalyse folgen

In the next step, due to resource constraints of public budgets, identified therapies for OBMEAs should be **prioritized**. The CED scheme developed within the COMED project proposes to set priorities considering the burden of disease, unmet need, budget impact, and expected clinical benefit [90]. The uncertainties identified could then be further grouped into clusters like “unavailability” (absence of observations), “indirectness” (no head-to-head comparison in diverse settings), and “imprecision of evidence” (few observations) [90, 132]. The categorization into these three reasons of uncertainty by Pouwels et al. (2019) is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework and the classification by the ISPOR-SMDM (Society for Medical Decision Making) Taskforce. GRADE uses, i.e., criteria such as imprecision, indirectness, and inconsistency to evaluate the certainty in evidence while the ISPOR-SMDM Task-

da OBMEAs Ressourcen-intensiv sind:

Priorisierung von jenen Therapien, wo größter Nutzen zu erwarten ist

force differentiates between methodological uncertainty, stochastic uncertainty, structural uncertainty, parameter uncertainty, and heterogeneity. An overview of these terms used by the ISPOR-SMDM Taskforce is found in Figure 7-8 (Appendix 7.9.3). Classifying the different levels of uncertainty may help payers and HTA bodies to decide which therapies should be targeted first [90, 132].

5.2.2 Design: OBMEA type, data collection, stakeholder, and governance

Aufsetzen des OBMEA

The second stage of designing the scheme involves determining the **type of OBMEA, stakeholders** involved, **data collection,** and **monitoring** mechanisms.

Entscheidung für Typologie fällen:

klinische Unsicherheit beseitigen oder Kontrolle des Zugangs oder der Kosten ?

The decision on the specific category of OBMEA employed relates to the overall purpose of the scheme. Therefore, payers and HTA bodies need to choose the **type of OBMEA** after defining the goal. Since different taxonomies for OBMEAs exist, recommendations can only be general. Common drivers of OBMEAs to be distinguished are managing clinical uncertainty, access control, and cost reduction. A mixture of all might often result in pay-for-outcomes schemes, while CEDs mainly focus on collecting RWE to decide on a therapy's effectiveness.

Spezifikationen: Patient*innen-Population, relevante Endpunkte

Indikatoren für Erfolg des OBMEAs festlegen

Further specification of the model design includes deciding on the **study population**, making the product available for pre-defined patient groups registered in a study (only in research), or all patients eligible for this treatment (only with research). The decision often depends on the type of uncertainty targeted [90]. Besides, **outcome measures** must be defined to assess the performance of the therapy. These should be clinically and patient-relevant and readily measurable [90]. Establishing a disease-specific core minimum outcome-set on some parameters, i.e., mortality and disease progression, might help in that respect [7]. **Indicators** measuring the overall **success** of the scheme, signalling whether the predefined uncertainties can be answered after data collection, should also be determined.

Kommunikations-strategie planen:

Dauer des OBMEAs Entscheidungs-optionen bei Beendigung (auch Disinvestment)

Possible decision rules at the end of the scheme, including a clear **communication strategy** to patients about potential disinvestments, must be agreed upon by all stakeholders. Apart from that, when determining the **duration** of the OBMEA, countries need to weigh upon setting a fixed length for all schemes or deciding on a case-by-case basis. The latter often seems preferable since the timeframe is highly dependent on the research questions to be answered and the timeframe for data collection, which might substantially differ between technologies [90].

Involvierung aller Stakeholder weitere wesentlicher Erfolgsfaktor

Verteilung von Rollen und Verantwortlichkeiten

The engagement of a range of **stakeholders** is vital for the success of OBMEAs. Contract concluding parties mentioned during the interviews were often limited to the MAH and the payer. However, parties involved in data collection, such as clinicians and patients, must also be included to build consensus, ensure their commitment, and document their responsibilities. A template for a possible agreement can be found in Figure 7-9 (Appendix 7.9.4), describing the public documentation process for data collection and assigning responsibilities to stakeholders. For example, payers commit to paying the agreed price of the therapy while the MAH undertakes the re-assessment process and pays any expenses arising during the procedures, patients consent to the collection of patient-reported outcomes, and clinicians enter the data and answer data inquiries within a specific timeframe [91].

IT-Dateninfrastruktur: öffentlich aufgesetztes Register

Routinedatenerhebung

Kriterien für Eignung und Qualität der Daten

Any open-accessible **data source** that is suitable for answering uncertainties should be included in the analysis. Using existing **data collection infrastructures** keeps the additional effort to a minimum. These could comprise, i.e., publicly managed registries or routinely collected administrative information from claims data. However, administrative databases must be treated cautiously because clinical outcomes might not be sufficiently displayed [7]. Brandes et al. (2016) concluded that the appropriateness of claims data is determined by the type of uncertainty. In Germany, for example, they might be used to answer open questions on the utilization and incurred expenses in real life [133]. The concept for the generation and analysis of routine practice data for benefit assessments developed by IQWiG drafted a list of criteria for assessing the suitability and quality of data produced by registry-based studies distinguishing between obligatory requirements for securing data quality, general criteria for registry studies, and criteria related to the research question. The list is found in Figure 7-10 (Appendix 7.9.4) [119, 131]. Additionally, the REQueST tool can support to assess the quality of registries and whether data fit for HTA purposes [64].

internationale Kooperationen zur Verbreiterung der Datenbasis

„Core Datasets“:

Koop mit EMA
Koop mit klin. Fachgesellschaften

Beyond using national data sources, **international cooperation in data collection** will significantly improve the available evidence base for assessing the value of therapies [7]. Therefore, it is encouraged to build interoperable registries that facilitate the pooling and analysis of datasets to make valid judgments on small patient populations. Interoperability can be on semantic, technical, and legal/operational aspects. For example, the European Joint Programme rare diseases proposes to use common ontologies and core datasets [134]. Collaboration can also happen horizontally. For example, aligning the post-approved data collection process of conditionally authorized therapies between regulatory and reimbursement agencies, intended with the interim-accepted decision option in Scotland, might save resources [7].

Interoperabilität nationaler und internationaler Datensammlungen

Interoperability is not only desirable across countries but also within a country. Ideally, a national reliable **data infrastructure** might be based on automated, interconnected data collection systems, enabling incorporating different IT systems into standardized data formats. The AIFA monitoring registries could serve as a role model for a central national data platform [7].

Finanzierung der Datensammlung klären

Recalling the idea of risk-sharing, **funding** for data collection should be provided by the parties benefitting most from the agreement. Since preferably publicly managed and financed databases should be used, it would be fair to charge a fee from the MAH as practiced in Italy (RE 1). Another possibility might be outsourcing the whole data collection process to an independent not-for-profit institution, strengthening trust among stakeholders [7].

Datenhoheit mit Zugang (unter Gewährleistung von Datenschutz) zu Daten für öffentliche Forschung

Collecting and using patient data for OBMEAs must follow country-specific and European **data privacy** laws as the General Data Protection Regulation (GDPR) [7]. If possible, only anonymous aggregated patient data should be used, avoiding obtaining any additional informed consent. Establishing a specific institute for handling privacy regulations, such as in Belgium, could help ensure data protection. **Data ownership** should primarily be in public hands to have full decision-making authority over its use and dissemination.

Monitoring der Datensammlung: regelmäßige Überprüfung der Datenqualität, -validität

Lastly, implementing continuous **monitoring** activities ascertains internal control of the scheme and allows for timely and targeted pre-emptive action. First, this concerns ongoing quality assurance mechanisms of data validity during the evidence generation, including, i.e., regular audits and sample testing by registry owners. Routinely conducting interim assessments at least

every six months should verify, if stopping rules, a set of ex-ante decision criteria on when to terminate the scheme, have been met. In that way, it is possible to revise priorities, identify data collection issues, non-compliance of stakeholders, and early signs for a necessary extension of the duration.

Governance-Prozess und –Struktur unter Einbindung der Stakeholder

Secondly, establishing an efficient joint **governance process** for the overall implementation tracks the scheme's successful completion. This could follow a similar **governance structure** proposed by Michelsen et al. (2020) (see Figure 7-11, Appendix 7.9.5). According to which a steering committee composed of HTA, MAH, payers, and providers are responsible for setting out and managing the general conditions of the OBMEA while regularly updating all stakeholder groups on the status of the scheme, securing the highest possible level of transparency. In addition, an impartial perspective on the OBMEA should be ensured through an external advisory committee consisting, i.e., of researchers, IT specialists, HCPs, and patient organizations. Possible tasks could entail assisting in assessing the relevance and feasibility of the OBMEA, reviewing the data collection plan, and mediating any conflicts [7]. The importance of an advisory committee and its potential roles in overseeing data collection is also outlined in the template "OBMEA Monitoring committee" in Figure 7-12 (Appendix **Fehler! Verweisquelle konnte nicht gefunden werden.**).

regelmäßige Updates und Information zum OBMEA

5.2.3 Implementation and evidence generation

Implementierung der Datensammlung:

Implementing the scheme marks the start of the evidence generation phase, characterized by several **interim assessments** which necessitate the **regular reporting** of the MAH on the process of data collection to HTA bodies or a monitoring committee as previously described.

vorab vereinbarte Zwischen-auswertungen, regelmäßiges Reporting

These interim analyses may reveal that **market dynamics** require adjustments of the data collection process. For example, in the case of the market entry of direct competitors, contractual terms should allow to re-open or modify the conditions of the agreement as practiced in Italy and proposed by Michelsen et al. (2020) ([7], RE 1). This may be more likely in schemes with long duration or high-profit therapeutic areas such as oncology.

Berücksichtigung von Marktdynamiken wie etwa zusätzlicher Anbieter

Since lacking quality of data was a common problem described in the interviews, measures are necessary to **incentivize accurate data entry**. Compliance could be enhanced by making data entry a requirement for the reimbursement of HCPs, as it is already practiced in some countries. At the same time, given the increased complexity of these administrative tasks placed on HCPs, there is a need for offering additional training on proper data collection [7]. Establishing a minimum dataset in data collection, as shown in Figure 7-9 (p.6) (Appendix 7.9.4), is intended to unburden clinicians and patients [91].

Inzentivs für genaue Dateneingaben setzen

5.2.4 Re-assessment and exit

Re-Evaluierung und Ausstieg aus OBMEA

Upon completing data collection, the MAH will hand in a new reimbursement dossier, including all evidence collected. The appropriate comparator is the standard of care at the time point of re-assessment to ensure that changing market dynamics are taken into account. The submission of the new dossier induces the second HTA (=re-assessment). Evaluation criteria should consider whether the data is of sufficient quality to close the evidence gaps and makes a final judgment about the value of the therapy.

Kriterien für Erstattungsentscheidungen nach OBMEA vorab festlegen

The re-assessment process might result in one of the following five recommendations:

Optionen für Ausstieg:

a) Prolongation of the scheme without modifications
b) Prolongation of the scheme with modifications
c) Positive recommendation for routine use
d) Positive recommendation for routine use for a restricted patient population
e) Negative recommendation, discontinuation of reimbursement (closed cohort)

Erstattung mit bestehenden Bedingungen

The first two possibilities should be considered, if endpoints were not reached within the timeframe and interim assessments already pointed to a potential extension for various reasons. For example, one might revisit the scheme because of the changes of product characteristics such as indication area and patient population, new data sources, or the entry of competitive products. However, prolongations should be set to a maximum of three times to avoid that the MAH uses OBMEAs as an instrument for infinitely extending reimbursement for ineffective drugs.

Erstattung mit Änderungen

In the remaining three options, the OBMEA will be closed.

Erstattung im Routinebetrieb

- A positive recommendation for routine use is issued if data provided at re-assessment sufficiently answered the uncertainties and confirmed the value of the drug in routine practice.
- The therapy could also be available for a restricted patient population if RWE revealed the effectiveness for a selected group.

Erstattung für eingegrenzte Patient*innen-Population

In both cases, reimbursement is continued, a final price is set considering all evidence available. In federated healthcare systems, such as Canada, it is recommended to conduct joint negotiations to increase bargaining power and possibly achieve lower prices while realizing greater consistency [128].

Abbruch, Beendigung der Erstattung

Financing is stopped if additional data proves the ineffectiveness of a therapy. The cohort is closed, allowing treated patients to continue to receive the drug. Stakeholders should be involved in the interpretation of findings. In particular, raising awareness of the conditional nature of funding is indispensable in minimizing adverse public reactions after disinvestments.

5.2.5 Dissemination of results

Verbreitung und Kommunikation jedenfalls der klinischen Ergebnisse des OBMEA

Vertraulichkeit – wenn – nur über kommerzielle Informationen (Preise)

As currently scarcely practiced, additional thoughts must be given to how information gained from OBMEAs could be disseminated to benefit other countries and facilitate learning from each other. Despite significant interest expressed in the expert interviews, little is shared due to reasons of confidentiality. If at all, available information is limited to the existence of an MEA while details on the performance and results are lacking [18]. Full transparency of MEAs will probably remain an elusive utopia. However, a balance must be struck between the MAH´s demands for the confidentiality of business information and the public payer's objective to disseminate results for mutual learning with other countries. As practiced in England with the Cancer Drug Fund, one possible mechanism is to have two separate agreements that distinguish between commercial and performance information. The non-disclosed commercial arrangement determines the price, while the published data collection arrangement outlines the planned process of evidence generation [18].

Empfehlung für zentrale Datenbank über alle MEAs, damit Austausch von Information rasch möglich ist

Aufgabe für DARWIN/ pan-European Health Data Space

One way, as suggested by Wenzl and Chapman (2019), was building a centralized database accessible by all participating countries to document for which products MEAs exist, what outcome measures are used, what findings data analyses produced, and which final decisions were taken at the end of the scheme. Besides, ongoing and planned initiatives offer possibilities for cross-border data exchange [18] For example, an initial step to build a pan-European Health Data Space is made by the EU project DARWIN, which intends to develop a sustainable data management platform for health data exchange, access, and analysis across countries. DARWIN is currently intended to be used for only regulatory purposes [59]. Yet, future endeavors of streamlining regulatory and reimbursement requirements on data collection might leverage the full potential of data exchange. Looking further ahead, publicly maintained international registries may represent the ultimate goal for data sharing and preventing the concealment of unfavorable data from studies.

5.3 Limitations

Limitationen des Berichts:

Literatursuche nur in 1 Datenbank

keine Verwendung (weil kein Zugang) von vertraulichen Informationen

Reported findings must be considered with some limitations in mind. Methodological constraints were related to the literature review, sample selection, and restricted sample size.

The systematic search was conducted only in one database. However, the few resulting references included reflected that country-specific models are not distributed via traditional publication channels. This was sufficiently compensated by a comprehensive hand search in grey literature and the request sent to the INAHTA Listserv. Nonetheless, the analysis was limited to the information publicly available or documents sent by the countries. Given the opaque nature of MEAs, this may have led to some existing frameworks missed. Moreover, the language was limited to English and German, excluding models in the local language.

In addition, due to time constraints, only a certain number of interviews (n=11) were conducted, which could potentially affect the external validity of results. The selection of interview partners was driven by the availability of information and access to experts. Thus, it was not possible to recruit a representative from the Cancer Drug Fund in England. However, given the resource constraints many public agencies in the healthcare sector might face due to the outbreak of COVID-19, the recruitment of 15 interview subjects to gain a deeper insight into eleven country models was deemed sufficient. Yet, it should be noted that the comparability of interview responses was limited because the number of participants per interview varied from one and to three experts. The interview guideline addressed different areas of expertise which sometimes required the involvement of several people. Besides, not all questions could be answered by every participant. This can be explained by the fact that some countries were more advanced with OBMEAs than others, or information asked for was confidential.

nur 11 Interviews, nicht alle Länder abgedeckt

The report produced general recommendations for future policy-making that do not consider the local context of countries, such as the legal framework. Therein again lies a strength. A generic organizational model can be adapted to any country-specific environment.

allgemeine, nicht Länder-spezifische Empfehlungen

Since MEAs involve various groups of stakeholders and this research covered only the HTA and public payer perspective, future studies are needed to gain further insights from other stakeholders such as MAHs, registry holders, and patient representatives on the feasibility of the recommendations produced.

Zahler- und HTA Perspektive

5.4 Conclusion

Based on the experiences gathered with (good) practice organizational schemes for risk-sharing, a generic role model for the organization of outcome-based reimbursement is recommended, providing possible directions for decision-makers to ensure future access to highly-priced drugs through public data generation. The conceptual idea behind OBMEAs providing conditional funding while collecting further evidence to prove the value of therapies presents a fair pricing approach. Yet, the administrative burden, particularly around data collection, the lack of transparency, and the missing governance structure, hinder their effective implementation. This study attempts to enhance alignment and increase the feasibility of such schemes by providing policymakers a roadmap on the organizational implementation. It is advised to take advantage of cross-country collaboration initiatives laying the groundwork for information exchange to systematically leverage the wealth of data available in healthcare and create a uniform health data space.

Schlussfolgerung:

OBMEA-Konzeption wird als Erstattungsstrategie zunehmen

Gestaltung ist aber von Bedeutung

jedenfalls zuerst Machbarkeit prüfen und dann Transparenz garantieren

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7 Appendix

7.1 Managed-entry agreement decision tree

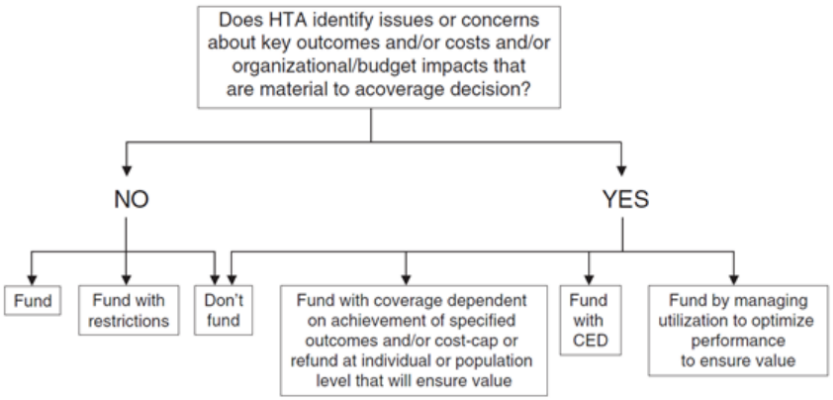

Figure 7-1: Managed-entry agreement decision tree (Wenzl and Chapman, 2019, p.49)[18]

7.2 Search strategy

7.2.1 Search strategy for Ovid MEDLINE

Database: Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations and Daily <1946 to February 18, 2021>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <2016 to February 18, 2021>

Search Strategy:

Query number	Searches	Results
1	price*.mp.	54890
2	pricing*.mp.	8398
3	pay*.mp.	155361
4	buy*.mp.	16117
5	purchas*.mp.	48858
6	1 or 2 or 3 or 4 or 5	259958
7	exp Reimbursement Mechanisms/	41267
8	reimburs*.mp.	59454
9	exp Financing, Organized/	273976
10	financ*.mp.	210310

11	grant$1.mp.	27659
12	fund$1.mp.	40492
13	funding.mp.	91669
14	7 or 8 or 9 or 10 or 11 or 12 or 13	561689
15	6 and 14	71036
16	real world evidence.mp.	3602
17	RWE.ti,ab.	568
18	real world data*.mp.	9833
19	16 or 17 or 18	12960
20	15 and 19	210
21	(model* or framework* or frame work*).mp.	5798689
22	exp Models, Organizational/	21801
23	21 or 22	5798689
24	20 and 23	79
25	((organi#ation* or real world evidence or RWE or real world data*) adj3 (model* or framework* or frame work* or evidence or technolog* assessment* or HTA*) adj5 (reimburs* or financ* or funding or coverage* or managed entry agreement* or MEA$1 or grant* or pay* or buy* or purchas*)).mp.	342
26	managed entry agreement*.mp.	119
27	disruptive therap$3.mp.	20
28	24 or 25 or 26 or 27	552
29	remove duplicates from 28	364
30	limit 29 to (english or german)	352

Search date: 11.02.2021

7.2.2 Search strategy for manual search

Search term	(optionally) combined with
(Outcome-based) Managed-entry agreement(s)	Organisation
Reimbursement model	Organisational framework
Payment model	Real-World Evidence
Conditional coverage	Real-World Data
	Post-launch evidence generation
	High-priced therapies

7.3 INAHTA ListServ

7.3.1 Request sent to INAHTA ListServ

Dear INAHTA-members,

The AIHTA (Austrian Institute for HTA) has been commissioned by Austrian payer institutions to develop a future outcome-based reimbursement scheme for expensive drugs (gene-therapies, ATMPs, …) providing conditional funding while simultaneously generating publicly accessible data on the real-world evidence of treatment effects.

We are currently looking for procedural an organisational guidance (process manuals/ handbooks/ frameworks) in other countries that explicitly describe how to set up such a model with specific regard to:

- *Sources of data used*
- *Data governance/ownership*
- *Data infrastructure*
- *Processes*
- *Responsibilities*

We would highly appreciate your support and are looking forward to your response until Feb 25th 2021.

Many thanks in advance.

7.3.2 INAHTA ListServ Responses

Table 7-1: Summary of responses received from the INAHTA members

Country	HTA body	Response	Framework	Links to documents
Spain	Agency for Health Quality and Assessment of Catalonia (AQuAS)	Not responsible for upharmaceutical assessments anymore Provided documents (only in Catalan) from colleagues from the pharmaceutical assessment	a) Definition of criteria and conditions to use pharmaceutical products in Catalonia, the use of the registry and financing b) A guide that defines the scheme of payment for results c) Article summarizing the experience made within ten years of registry of patients and their therapies used	a) https://catsalut.gencat.cat/ca/proveidors-professionals/farmacia-medicaments/programa-harmonitzacio-farmacoterapeutica/normativa/ b) https://catsalut.gencat.cat/web/.content/minisite/catsalut/proveidors_professionals/medicaments_farmacia/acords-risc-compartit/guia-definicion-criterios-aplicacion-esquemas-pago-resultados-epr.pdf c) https://www.elsevier.es/es-revista-medicina-clinica-2-avance-resumen-registro-pacientes-tratamientos-medicamentos-hospitalarios-S0025775319306086
UK (Scotland)	Healthcare Improvement Scotland (HIS)	The Scottish Medicines Consortium (SMC) is the national source of advice on the clinical and cost-effectiveness of all new medicines for NHS Scotland SMC has no outcome-based reimbursement scheme specifically for expensive medicines However, there is a discreet process for ultra-orphan medicines for extremely rare condition and an interim (conditional) acceptance decision option In both processes, the new medicine is available for prescribing while further data on effectiveness must be collected by the company to inform a future SMC reassessment and a decision on routine access in NHS Scotland Data collection requirements for the ultra-orphan process are the responsibility of the Scottish Government (and not SMC) along with the marketing authorization holder	a) Ultra-orphan medicines for extremely rare conditions b) Interim acceptance decision option	a) https://www.scottishmedicines.org.uk/how-we-decide/ultra-orphan-medicines-for-extremely-rare-conditions/ b) https://www.scottishmedicines.org.uk/how-we-decide/interim-acceptance-decision-option/
Germany	Gemeinsamer Bundesausschuss (Federal Joint Committee) (G-BA)	Framework for additional data generation that aims at drugs with conditional EMA approval The methodological framework relies mainly on registries This framework will be applied for the first time to Onasemnogen-Abeparvovec for SMA (Zolgensma), but for data generation only, this has no impact on reimbursement	Concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social Code Book V (SGB V; 2020)	a) https://www.iqwig.de/projekte/a20-61.html
Brazil	National Committee for Health Technology Incorporation into the Brazilian public health system (CONITEC)	No model and/or specific frameworks related to an outcome-based reimbursement scheme for expensive drugs Nevertheless, they expressed interest and said that this theme is at their attention and would like to get involved in such a debate.	Not in place	-
Tunisia	Instance Nationale de l'Evaluation et de L'Accréditation en Santé (National Authority for Assessment and Accreditation in Healthcare) (INEAS)	Expressed growing interest in this type of managed entry agreement but never been used yet given implementation's complexity There is no guidance nor any platform for that yet	Not in place	-

Abbreviations: NHS – National Health Service, SMA – Spinal Muscular Atrophy, UK – United Kingdom

7.4 Data extraction tables literature search

Table 7-2: Data extraction table of the search in Ovid MEDLINE

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
1	Risk sharing in managed entry agreements—A review of the Swedish experience	Andersson, E. et al.	2018	Sweden	-Reviews existing risk-sharing agreements, describe the type of uncertainty dealt with, and to analyze the incentives created -Main driver behind risk sharing in Sweden so far have seem to be affordability rather than managing uncertainty	no	-	-	-	exclude	Background article
2	Managed-entry Agreements: Possible	Baron-Papillon, F. et al.	2014	No specific country	-A broader, more flexible approach to vaccines access, including MEAs, can address the needs of budget holders and other external stakeholders as well as manufacturers	no	-	-	-	exclude	No full text available
3	Alternative payment models: a changing landscape	Beasley, D.	2015	USA	- Accountable Care Organization (ACO) programs in the USA -ACO are groups of healthcare providers and hospitals that jointly provide coordinated care of the patient population with the goal of giving higher quality while reducing the cos	no	-	-	-	exclude	Primary topic not organisational framework of MEA
4	Using claims data for evidence generation in Managed Entry Agreements	Brandes, A. et al.	2016	Germany	-Use of routinely collected claims data for managed entry agreements (MEA) -Information asymmetry between manufacturere and payer -Legal basis for MEAs in Germany -Overview about value-based typology of MEA und data needs of different MEAs -Secondary data (claims data, hospital data) for financial MEA -Primary data (RCTs, registries) for OBMEA -SHI data are unlikely to be of use in conditional coverage agreements (CED or CTC) as well as in health outcome-based RSA using intermediate clinical endpoints such as biomarkers or tumor progression -Claims data are better suited to MEA addressing uncertainty regarding the utilization and costs -In schemes where safety aspects or clinical effectiveness are assessed, the role of claims data is limited because clinical information is not included in sufficient detail -The suitability of claims data depends on the source of uncertainty and, in consequence, the	no	-	-	-	exclude	Background article
5	Managed Entry Agreements for Pharmaceuticals in the Context of Adaptive Pathways in Europe	Bouvy, J. et al.	2018	Europe	-Suitability of MEA for adaptive pathways in Europe -OBMEA were not commonly used for products with conditional MA -Barriers and enablers to develop workable MEAs	no	-	-	-	exclude	Background article
6	Real-world evidence use in assessments of cancer drugs by NICE	Bullement, A. et al.	2020	UK	-How RWE has factored into NICE appraisals of cancer treatments -RWE has been shown to have a clear role in decision making, by addressing data gaps in cost-effectiveness analyses submitted by companies, and ultimately being used to inform decision-making -Mentions Cancer Drug Fund	no	-	-	-	exclude	Background article
7	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	Buyukkaramikli, N. et al.	2021	UK	-Sequential decision-making process in England & Wales -Typology of managed entry agreements for oncology drugs across European countries -Each MEA type has a different implication	no	-	-	-	exclude	Background article

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
8	Funds Reimbursement of High-Cost Drugs in Gagstrointestinal Oncology: An Italiane Real Practice 1 Year Exeprience at the National Cancer Institute of Naples	Capozzi, M. et al.	2018	Italy	-Description of AIFA Register: a government web-based tool in order to monitor appropriateness, use, toxicity and efficacy of pharmaceuticals -The AIFA Registry was established in 2005 and completely renewed in 2013 through the data collected, the benefit/risk and cost/effectiveness ratios of pharmaceuticals. -Application of MEA requires the correct use of monitoring, in accordance with very specific requirements and deadlines regarding the restaging of the disease, the number of therapy cycles, the monitoring and reporting of therapy response, the timely communication of adverse events, and correct follow-up information -Pharmacist was committed to entry, manage and discuss with clinicians the basal data, prescription appropriateness, drug requests, response monitoring, toxicity reporting, "end of treatment" module -Reimbursement process can be improved when a health policy reimbursement professional Pharmacist is integrated in the multidisciplinary team along with clinicians	Yes	Description of AIFA registry and how to improve the reimbursement process	No information on how reassessment process works	-Monitor appropriateness, use, toxicity and efficacy of pharmaceuticals-->assess the patient's eligibility for treatment, collects epidemiological data, drug safety and efficacy profile	include	
9	Developing a framework to incorporate real-world evidence in cancer drug funding decisions: the Canadian Realworld Evidence for Value of Cancer Drugs (CanREValue) collaboration	Chan, K. et al.	2019	Canada	-Developing and testing a framework for Canadian provinces to generate and use eal-world evidence (RWE) for cancer drug funding in avconsistent and integrated manner '-Description of 5 working groups: (1) Planning and Drug Selection; (2) Methods; (3) Data; (4) Reassessment and Uptake; (5) Engagement	no	-	-	-	exclude	Background article
10	Generating comparative evidence on new drugs and devices after approval	Cipriani, A. et al.	2020	no specific country	-Data generated from Post-marketing studies are often insufficent, poor quality -Most new drugs have industry-initiated post-marketing studies; however, the majority of these are conducted in therapeutic areas outside of the approved indication -Authors propose seven key guiding principles that provide necessary incentives for pharmaceutical and device manufacturers to generate comparative data in the post-marketing period -Electronic health records, administrative data, and clinical registries currently exist in silos in health-care systems. Efforts are underway to build collaborative data infrastructures by linking and	no	-	-	-	exclude	Background article
11	Use of real-world evidence in cancer drug funding decisions in Canada: a qualitative study of stakeholders' perspectives	Clausen, M. et al.	2020	Canada	-Stakeholder perspectives on the current state of RWE in Canada to inform a Canadian framework for use of RWE in cancer drug funding decisions -RWE had value in cancer drug funding decisions, cultural shift is required, infrastructure for real-world data is currently inadequate for decision-making, and there is a need for committed investment in building capacity to collect and analyze RWE, need for increased collaboration among key stakeholders -Barriers to use of RWE in decisionmaking, including lack of expertise in RWE methodology, lack of universally accepted methodologic standards, challenges in accessing data and issues of bias and	no	-	-	-	exclude	Background article
12	Managed Entry Agreements: Policy Analysis From the European Perspective	Dabbous, M. et al.	2020	Europe	-Defintion, current landscape of MEAs in Europe and analysis of the main hurdles they face in implementation, providing a policy perspective -Recent emergence, classification, current use, and implementation obstacles of MEAs in Europe	no	-	-	-	exclude	Background article
13	The current performance-linked and risk sharing agreement scene in the Spanish region of Catalonia	Darbà, J., Ascanio, M.	2019	Spain (Catalonia)	-Seven managed entry agreements were analyzed -Main involved disease area is oncology -Mainly Pay-for Performance, nothing about data collection	no	-	-	-	exclude	Background article

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
14	Use of Real-World Evidence in US Payer Coverage Decision-Making for Next-Generation Sequencing–Based Tests: Challenges, Opportunities, and Potential Solutions	Deverka, P. et al.	2020	USA	-Payers concerns about RWE studies -Potential solutions for advancing use of RWE -Three categories of innovation that may help address the current undersupply of RWE studies for next-generation sequencing (NGS)-based testing: (1) increasing use of RWE to inform outcomes-based contracting for new technologies, (2) precision medicine initiatives that integrate clinical and genomic data and enable data sharing, and (3) Food and Drug Administration reforms to encourage the use of RWE.	no	-	-	-	exclude	Primary topic not organisational framework of MEA
15	Concise Review: The High Cost of High Tech Medicine: Planning Ahead for Market Access	Driscoll, D. et al	2017	USA/Europe	-General information on cell therapies -Performance based managed entry agreements coupled with post-launch evidence generation can help overcome challenges around product uncertainty at launch and reduce market access delays	no	-	-	-	exclude	Primary topic not organisational framework of MEA
16	Innovative pharmaceutical pricing agreements in five European markets: A survey of stakeholder attitudes and experience	Dunlop, W. et al.	2018	France, Italy, Germany, Spain, UK	-Survey of payer stakeholders to determine what kinds of innovative agreements are currently used, anticipated future usage, attitudes, and drivers of adoption -Positive attitude towards new schemes, innovative agreements are likely to be used when they reduce total costs or reduce uncertainty	no	-	-	-	exclude	Primary topic not organisational framework of MEA
17	Determinants of Managed Entry Agreements in the context of Health Technology Assessment: a comparative analysis of oncology therapies in four countries	Efthymiadou, O., Kanavos, P.	2020	Sweden, Australia, England, Scotland	-Uptake of MEAs between countries -Determinants of MEAs	no	-	-	-	exclude	Background article
18	Real-world evidence to support Payer/HTA decisions about highly innovative technologies in the EU—actions for stakeholders	Facey, K. et al.	2020	No specific country	-RWE4Decisions initiative -actions that each stakeholder could take to improve use of RWD in this setting	no	-	-	-	exclude	Background article
19	The Implementation of Managed Entry Agreements in Central and Eastern Europe: Findings and Implications	Ferrario, A. et al.	2017	Central and Eastern Europe	-Definition, use of MEAs -Small number of health outcome-based agreements involving monitoring of clinical outcomes in our study (are resource intensive to implement and require good IT systems with electronic clinical records linked to reimbursement systems to be successfully enacted)	no	-	-	-	exclude	Background article
20	Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden	Ferrario, A., Kanavos, P.	2014	Belgium, England, NL, Sweden	-Objecives of different countries for pursuing MEAs and *legal basis* of policy -Types of MEAs used in different countries -Definition of MEAs	no	-	-	-	exclude	Background article
21	The impact of managed entry agreements on pharmaceutical prices	Gamba, S. et al.	2020	no specific country	-Impact of MEAs on list prices (prices before the deduction of any discount) -Introduction of an MEA leads to a higher list price -Manufacturer would react to the possibility of an MEA being introduced by raising the proposed price of all products, some of which may end up having no MEA. Hence, the opportunity for the payer to introduce an MEA, given the proposed price, causes an increase in the list price. -Drives up prices on average by more than 5%.	no	-	-	-	exclude	Background article

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
22	A Strategy to Support Efficient Development and Use of Innovations in Personalized Medicine and Precision Medicine	Garrision, L. et al.	2019	No specific country	-Rewards for innovation should be value based and flexible over time and across indications as new evidence emerges -Value should be based on ex-ante willingness to pay and should include, at its core, the value of health gain in terms of the length and quality of life -Splitting the rewards among inputs that are complementary in a static sense, reward systems for personalized medicine/precision medicine (PM/PrM)	no	-	-	-	exclude	Primary topic not organisational framework of MEA
23	Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report	Garrision, L. et al.	2007	No specific country	-Framework to assist health-care decision-makers in dealing with RW data related to coverage and payment decisions	no	-	-	-	exclude	Background article
24	Experience with outcomes research into the real-world effectiveness of novel therapies in Dutch daily practice from the context of conditional reimbursement	Gaultney, J. et al.	2015	Netherlands	-Feasibility and usefulness of observational data (example bortezomib) -CED scheme but data collected was insuffcient to adress all types of evidence -Quality of the evidence was low due to missing data, existing treatment variation and the dynamics in care during a new drug's initial market uptake period	no	-	-	-	exclude	Background article
25	Barriers fo Access to New Medicines: Searching for the Balance between rising costs and limited budgets	Godman, B. et al.	2018	No specific country	-C onsider potential ways to optimize the use of new medicines balancing rising costs with increasing budgetary pressures to stimulate debate especially from a payer perspective -Limitations of OBMEA -European experiences with MEAs	no	-	-	-	exclude	Background article
26	Potential approaches for the pricing of cancer medicines across Europe to enhance the sustainability of healthcare systems and the implications	Godman, B. et al.	2021	Europe	-Narrative discussion principally among payers and their advisers regarding potential approaches to the pricing of new cancer medicines costs of medicines in 2023 -Advantages, disadvantages of MEAs -Elements of fair pricing	no	-	-	-	exclude	Background article
27	Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?	Godman, B. et al.	2015	No specific country	-Challenges of funding new high priced medicines -Proposed model to optimize the managed entry of new medicines dividing the process into pre-launch peri-launch and post-launch activities -Pre-launch with horizon scanning and budgeting. Peri-launch activities include the critical evaluation of the role, value and place in therapy of new medicines with post-launch activities including evaluating prescribing against guidelines and quality indicators as well as addressing concerns with interface management where these exist.	no	-	-	-	exclude	Background article
28	The HTA Risk Analysis Chart: Visualising the Need for and Potential Value of Managed Entry Agreements in Health Technology Assessment	Grimm, S. et al.	2017	No specific country	-Quantifying risk associated with specific MEAs -HTA risk analysis chart, helps decision makers identify those situations by presenting a standardised visualisation to show the need for and potential value of different classes of MEA schemes.	no	-	-	-	exclude	Primary topic not organisational framework of MEA
29	Real-world evidence for coverage decisions: opportunities and challenges	Hampson, G. et al.	2018	USA	-Current uses in USA: RWE is currently being utilized in drug development decisions: regulatory approval decisions, post-approval monitoring, payer coverage decisions (initial decisions and reassessments) and for outcomes-based contracting -challenges of RWE, opportunities	no	-	-	-	exclude	Background article

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
30	The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal	Hettle, R. et al. (NHS)	2017	UK	-Mock technology appraisal' to assess whether changes to its methods and processes are needed -Conclusion: existing methods available to estimate the implications of this uncertainty are sufficient. Ways of sharing the risks between the NHS and the therapy manufacturers should be investigated further.	no	-	-	-	exclude	Primary topic not organisational framework of MEA
31	Lessons learned from the reimbursement policy for immune checkpoint inhibitors and real-world data collection in Taiwan	Huang, L. Y., Gau, C.-S.	2020	Taiwan	-Use MEAs to establish a national registry for immunotherapy patients in Taiwan	yes	-Provides a perspective to improve the quality, consistency, and transparency of decision making -Creating a national registry	-	Enhance the accessibility of advanced therapy	exclude	Country not included
32	Use of Real-World Data Sources for Canadian Drug Pricing and Reimbursement Decisions: Stakeholder Views and Lessons for Other Countries	Husereau, D. et al.	2019	Canada	-Value of RWE in pricing and reimbursement decisions -Barriers to optimal use of RWE in pricing and reimbursement, current initiatives that may lead to its increased use, and what role the pharmaceutical industry may play in this	no	-	-	-	exclude	Background article
33	Post-marketing health technology monitoring. The analysis of an experience from a clinical perspective	Ibargoyen-Rota, N. et al.	2011	Basque Country	-Coverage under review programme in Spain -System for monitoring aphaeresis in ulcerative colitis (SiMAC) -First system designed to monitor the use of a new technology -Points out problems of participants, installing the application and sending data to central database	no	-	-	-	exclude	Background article
34	Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries	Jorgensen, J. et al.	2020	Germany, England, Scotland, Italy, France, Spain	-Overview of the reimbursement schemes used for Kymriah® and Yescarta® in France, Germany, Italy, Spain, and the UK -In France and the UK, reimbursement is on the condition of collecting additional data (at the cohort level) and subject to future reassessments; elsewhere, rebates (Germany) or staged payments (Italy and Spain)	no	-	-	-	exclude	Background article
35	Annuity payments can increase patient access toinnovative cell and gene therapies under England'snet budget impact test	Jorgensen, J. et al.	2017	England	-Problem of gaining reimbursement for ATMPs -How the net budget impact test recently introduced in England can affect patient access to high-value, one-off cell and gene therapies, and how managed entry agreements can improve access -NICE taxonomy of MEAs	no	-	-	-	exclude	Background article
36	Raising the Impact of Real World Evidence	Kalra, D.	2019		- Growing scale and reputation of big health data, the ways in which good governance principles and better quality data are creating reusable data at scale, how platforms and tools are enabling better quality evidence generation, and the perspectives of different stakeholders towards the positioning of RWE in decision making	no	-	-	-	exclude	Conference abstract

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
37	Establishing the cost of implementing a performance-based, managed entry agreement for a hypothetical CAR T-cell therapy	Kefalas, P. et al.	2018	UK	-Quantify the cost of implementing a performance-based MEA at the hospital level -Showing the admininistrative burden of OBMEA -Cost of implementing a performance-based MEA at the hospital level: SoC: £447,353, compared to £1,117,024 for the novel therapy with MEA, and £245,317 without MEA (higher cost associated with the SoC compared to the novel therapy without an MEA, arises from the higher frequency of infusions requiring payments and the associated mandatory data capturing requirements for oncology therapies -MEA for CAR-T with and without a MEA (frequency of monitoring) -if the target therapy area lacks an existing data collection infrastructure, the total MEA implementation burden would further increase --> case to be made for joint government and industry investment to create such infrastructure	no	-	-	-	exclude	Background article
38	What principles should govern the use of managed entry agreements?	Klemp, M. et al.	2011	No specific country	-Definition of MEA; rationale, principles to govern use of MEAs -MEA decision tree based on HTA	no	-	-	-	exclude	Background article
39	The Role of Real-World Evidence in UK Reimbursement: Case Study of Lenalidomide in Myelodysplastic Syndrome Deletion 5q	Lee, D. et al.	2018	UK	-Cost-effectiveness model of lenalidomide -Search for real-world evidence should be initiated prior to submission of technologies to health technology assessment authorities -A willingness to provide reassurance on outcomes with future data collection may reduce delays in new therapy reimbursement.	no	-	-	-	exclude	Primary topic not organisational framework of MEA
40	Real-world data for health technology assessment for reimbursement decisions in Asia: current landscape and a way forward	Lou, J. et al.	2020	Asia	-Framework is currently lacking in Asia -Proposal to establish an international collaboration among academics and HTA agencies in the region: the REAL World Data In ASia for HEalth Technology Assessment in Reimbursement (REALISE) working group, which seeks to develop a non-binding guidance document on the use of RWD/RWE to inform HTA for decision making in Asia	no	-	-	-	exclude	Primary topic not organisational framework of MEA
41	Implementing managed entry agreements in practice: The Dutch reality check	Makady, A. et al.	2019a	Netherlands	-Reviews eperience of 4-year CED scheme for expensive hospital drugs between 2006 and 2012	yes	Reassessment of therapeutic value, appropriate use, cost-effectiveness and budget impact	No description about data collection, data sources etc.	-Provide uniform access	include	
42	Conditional Financing of Drugs in the Netherlands: Past, Present, and Future - Results From Stakeholder Interviews	Makady, A. et al.	2019b	Netherlands	-Stakeholder experiences in implementing CF in practice -CF either did not meet its aims or only partially did so, there was agreement on the need for new policy to address the same aims of CF in the future --> replace CF with a scheme that resembles adaptive pathways -Recommendations for better CED design	yes	-Identical process chart for conditional financing scheme as presented in Makady et al 2019a	-	-	exclude	Background article
43	Real-World Evidence: Useful in the Real World of US Payer Decision Making? How? When? And What Studies?	Malone, D. et al.	2018	USA	-How RWE was perceived and used in managed care environments, including pharmacy and therapeutic (P&T) decisions -Features of RWE studies such as the study design (e.g., prospective vs. retrospective cohorts), type of analytic methods, population, outcomes (e.g., safety vs. efficacy), and data sources (e.g., claims vs. EHRs) that make certain studies more useful to payers -RWE was useful for monitoring safety, conducting utilization management, and examining costs, but was less likely to be considered in P&T decision making, principally because of timeliness.	no	-	-	-	exclude	Country not included

Appendix

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
44	Barriers and Opportunities for Implementation of Outcome-Based Spread Payments for High-Cost, One-Shot Curative Therapies	Michelsen, S. et al.	2020	No specific country	-Barriers and opportunities of different MEA categories -Spread payments: Correcting Payments for Achieved Real-World Outcomes -Conflicting interests and incentives of stakeholders during outcome-based agreements	yes	-Organization of data collection -Governance structure	-No information on re-assessment process	Build a framework that details every step of the process with specification of stakeholders' roles, responsibilities, interests and	include	
45	Monitoring registries at Italian Medicines Agency: Fostering access, guaranteeing sustainability	Montilla, S. et al.	2015	Italy	-Describes the Italian pharmaceutical context and the aims and functioning of AIFA Monitoring Registries, focusing on the applications to the Managed Entry Agreements (MEAs) and HTA approaches	yes	-Description of AIFA Monitoring Registries System, its overhaul, current use		-Allow the evaluation of the pharmaceuticals' performance in clinical practice and may promote innovation and quicker access to medicines at affordable prices, for the benefit of patients	include	
46	Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries	Morel, T. et al.	2013	Belgium, England, Italy, NL, Sweden, (France, Germany)	-Description of MEAs in different countries -MEA Definition von HTAi Policy Forum -MEA backgound information: taxonomy, therapeutic classes, geographical spread, rationale, evolution over time -Italy was the country with the highest number of schemes (n=15), followed by the Netherlands (n=10), England and Wales (n=8), Sweden (n=5) and Belgium (n=4). - No MEA was identified for France and Germany due to data unavailability. Antineoplastic agents were the primary targets of MEAs. 55% of the identified MEAs were performance-based risk-sharing arrangements; the other 45% were financial-based	no	-	-	-	exclude	Background article
47	It is important to note that RWD will never replace the more traditional and more robust RCT data; however, the emerging trend is to incorporate data that are more generalizable. Introduction	Mullins, D. et al.	2011	no specific country	-Suggests best practices for conducting and reporting comparative effectiveness research using "real-world data" (RWD)	no	-	-	-	exclude	Primary topic not organisational framework of MEA
48	Real-world Evidence—What Does It Really Mean?	Nabhan, C. et al.	2019	No specific country	-Sources of RWE, definition -Strengths and limitations of RWD	no	-	-	-	exclude	Primary topic not organisational framework of MEA
49	An evaluation of managed entry agreements in Belgium: A system with threats and (high) potential if properly applied	Neyt, M. et al.	2020	Belgium	-Strengths and weaknesses of managed entry agreements (MEAs) in Belgium -Snowball effect: an increasing non-transparency -Pharmaceutical companies are free to choose how they collect data in a MEA -All Belgian MEAs include a confidential appendix	no	-	-	-	exclude	Background article
50	HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries	Nicod, e. et al.	2019	England, Scotland, European-level	-New HTA initiatives in England, Scotland and at European-level - HTA process for ultra orphan drugs -Mechanism of Coordinated Access to orphan medicinal products (MoCA) --> a collaborative process that involves a sustained dialogue between the OMP developer, a group of payers and other stakeholders from various European countries	no	-	-	-	exclude	Background article

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
51	The value of innovation in decision-making in health care in Central Eastern	Novakovic,T. et al.	2017	Central and Eastern Europe	-RWE is an important component for successful reimbursement in the Czech Republic -->free access to anonymised public information and there has been a significant rise in the number of registries in recent years.	no	-	-	-	exclude	Background article
52	Managed Entry Agreements for Oncology Drugs: Lessons from the European Experience to Inform the Future	Pauwels, K. et al.	2017	Europe	-Regulation and application of managed entry agreements (MEA) for oncology drugs across different European countries -Acknowledge market dynamics (market entry of new, better drugs)	no	-	-	-	exclude	Background article
53	A framework to guide the optimal development and use of real-world evidence for drug coverage and formulary decisions	Pearson, S. et al.	2018	No specific country	-Famework for optimizing the development and use of real-world evidence (RWE) in drug coverage decision-->'best practices' or 'standards' for RWE	yes	Conceptual framework to guide optimal development and use of real world evidence for coverage and formulary decisions	-	Develop a shared understanding of the best way to develop RWE that will ultimately be useful in informing coverage and formulary decisions	include	
54	Market Access and Reimbursement: The Increasing Role of RealWorld Evidence	Pietri, G., Masoura, P.	2014	no specific country	-Only ten guidelines were found from 73 European HTA agencies or governmental authorities which cited RWD as a source for evidence	no	-	-	-	exclude	No full text available
55	Characteristics of Managed Entry Agreements in Australia	Robinson, M. et al.	2018	Australia	-Number of MEAs in Australia -Having two or more MEAs for an MIP is a common situation in Australia. -The reasons may include having different uncertainties addressed for the same medication indication pairs (MIP) or the manufacturer requesting an additional MEA to enable a higher published price over and above the MEA implemented to address an uncertainty.	no	-	-	-	exclude	Primary topic not organisational framework of MEA
56	Rationalizing the introduction and use of pharmaceutical products: The role of managed entry agreements in Central and Eastern European countries	Rotar, A. et al.	2018	Central and Eastern Europe	-Role of MEAs-->limit budget impact of drugs, uncertainty about clinical outcomes was a lower priority -Good taxonomy of MEAs regarding uncertainty	no	-	-	-	exclude	Background article
57	Using Certification to Promote Uptake of Real-World Evidence by Payers	Segal, J. et al.	2016	USA	-A process of third-party certification of RWE -Good Housekeeping Seal of Approval mechanism for the transparent review and certification of either prospective or retrospective observational research studies -Results of observational studies conducted by manufacturers would be voluntarily submitted for review and certification by a third party that uses a transparent and rigorous process to evaluate the investigations and to confirm that they sufficiently fulfill criteria to produce internally valid results	no	-	-	-	exclude	Background article
58	Managed Entry Agreements in UK, Italy and Spain	Trolley, C. Palazzolo, D.	2014	UK, Italy, Spain	-Compare Managed Entry Agreements (MEAs) in the UK, Italy, and Spain, and analyse the type of MEAs, number of agreements, and therapy areas	no	-	-	-	exclude	No full text available
59	Managed entry agreements for pharmaceuticals in Australia	Vitry, A., Roughead, E.	2014	Australia	-Australia's past and more recent experience with managed entry agreements	no	-	-	-	exclude	Primary topic not organisational framework of MEA

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
60	How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries	Vogler, S. et al.	2017	Europe	-Description of pricing policies in Europe with regard to their ability to ensure affordable access to medicines	no	-	-	-	exclude	Background article
61	Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?	Vogler, S. et al.	2018	Europe	-Most frequently applied policies for new high-priced medicines as well as some alternative approaches lack of transparency on 'real' prices	no	-	-	-	exclude	Background article
62	Application of Managed Entry Agreements for Innovative Therapies in Different Settings and Combinations: A Feasibility Analysis	Vreman, R. A. et al.	2020	no specific country	-Feasibility analysis of MEA for innovative studies -How it could be applied (financial/outcome-based), on what level (individual patients/target population), in which payment setting (centralized pricing and reimbursement authority yes/no), for what type of therapies (one-time/chronic), within what payment structures, and whether combinations with other MEAs were feasible	no	-	-	-	exclude	Background article
63	Integrative Review of Managed Entry Agreements: Chances and Limitations	Zampirolli Dias et al.	2020	South America	-Definition MEA, callenges and bnefits, use in Europe, ky considerations for MEA from payer perspective, advantages, disadvantages for OBMEA	no	-	-	-	exclude	Background article

Table 7-3: Data extraction table of the manual search

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
1	How to improve the Belgian process for managed-entry agreements? An analysis of the Belgian and international experience	Gerkens, S. et al. (Belgian Health Care Knowledge Centre (KCE))	2017	Belgium	Lessons to be learned from the European and Belgium experiences made with MEA (challenges, uncertainties addressed, results of conventions)	yes	-Mentions legal basis -Outlines negotiation process, stakeholders involved -Duration of the convention	No specification on reassessment procedure, data collection	-	include	
2	Transforming How We Manage Health Technologies in Support of Better Health, Better Patient Experience, and Better Value	Canadian Agency for Drugs and Technologies in Health (CADTH)	2018	Canada	Adopt a Life-Cycle Approach to Health Technology Assessment	yes	Broad ideas of a conceptual framework	Still at the beginning of conceptualizing	-Align drug and medical device review processes with federal, provincial, and territorial priorities throughout all phases of the technology life cycle -Implement programs for reassessment and disinvestment -Advance initiatives across the health technology life cycle that will improve access, appropriate use, and affordability	include	
3	Mapping Canadian Provincial Data Assets to Conduct Real-World Studies on Cancer Drugs	Chan, K. et al. (Canadian Real-World Evidence for Value of Cancer Drugs (CanREValue) collaboration))	2020	Canada	-Map the available provincial data assets in Canada -Provides an assessment of databases and data elements relevant to the conduct of cancer-specific RWE studies in each province	yes	-Key data custodians -Necessary data elements needed for real-world studies -Province's assessment of their capability to conduct real-world analysis	No details on reassessment process	Strategy to identify and harmonise data elements from each province	include	
4	Developing a framework for incorporating real-world evidence into drug funding decisions: CanREValue Collaboration Policy Working Groups Interim Report 2019	Chan, K. et al. (Canadian Real-World Evidence for Value of Cancer Drugs (CanREValue) collaboration))	2019	Canada	-Potential use of RWE for various stakeholders -Preliminary model for planning and selection of RWE projects -Preliminary Model of the Reassessment Process -Considerations for assessing the feasibility of a potential RWE project -Considerations for conducting reassessment	yes	Includes reassessment process, assessing feasiblity and selecting RWE projects	Not many details on data collection	High-level overview of the preliminary framework that has been developed by the two policy working groups (RWE Planning and Drug Selection WG, RWE Reassessment & Uptake Working Group)	include	

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
5	A methodology for the evaluation of a disruptive innovative therapy: The example of Kymriah®	Mombo, N.N., et al. (Institut national d'excellence en santé et en services sociaux (INESSS))	n.d.	Canada (Québec)	Strategies used to address immature evidence in the assessment of Kymriah®	yes	Evaluation cycle of innovative technologies at INESSS	No specific details on reassessment process	Recommendation how to ensure access to patients despite uncertainties of therapies	include	
6	Coverage with evidence development schemes for medical devices: a policy guide	Pushing the Boundaries of Cost and Outcome Analysis of Medical Technologies (COMED)	unpublished	No specific country	Develop a taxonomy of CED schemes for medical devices in Europe	yes	How to set-up and perform CED schemes for medical devices	Designed for medical devices	Develop a policy guide for those wishing to design and implement CED schemes in the future	include	
7	Konzept für eine anwendungsbegleitende Datenerhebung – Onasemnogen-Abeparvovec (Concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social Code Book V (SGB V; 2020))	Institut für Qualität und Wirtschaflichkeit im Gesundheitswesen (IQWIG)	2020	Germany	-Reviewing of suitability of registry data for reimbursement purposes -Criteria for checking quality of data	yes	Description of process steps for a data collection of routine practice datafor the purpose of the benefit assessment	Focus on evidence generation not re-assessment	Close evidence gaps	include	
8	Checklist for a Rare Disease Treatment. Is an Outcomes-Based Managed Entry Agreement Feasible?	Improved methods and actionable tools for enhancing HTA (IMPACT HTA)	2021	n.d.	Checklist to determine if an OBMEA is appropriate	yes	Feasibility criteria	-	Guide implementation of OBMEAs to aid demonstrating the potential and value of orphan medicinal products	include	
9	Template for Adaptation by HTA Bodies. Outcomes-Based Managed Entry Agreement of a Rare Disease Treatment	Improved methods and actionable tools for enhancing HTA (IMPACT HTA)	2021	n.d.	Template for public documentation of an OBMEA data collection agreement	yes	Data collection agreement, responsibilities, Inclusion of patients, re-ppraisal decisions	-		include	
10	Template for Adaptation by HTA Bodies. Monitoring committee terms of reference for an outcome-based managed-entry agreement for rare disease treatment	Improved methods and actionable tools for enhancing HTA (IMPACT HTA)	2021	n.d.	Terms of reference template for a monitoring committee responsible for overseeing implementation of an OBMEA	yes	Monitoring committee overseeing the scheme	-		include	

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
11	The Italian post-marketing registries	Xoxi, E., Pani, L.	2012	Italy	Shows the computerized´automated workflow of the AIFA Monitoring registries	yes	Combining computerized data generation with the application of MEA schemes	Provides no information on the re-assessment process	Sharing costs and responsibilities among manufacturers, public payers and healthcare providers	include	
12	Conditional reimbursement of health care	Ligtenberg, G. (Zorginstituut Nederland (ZIN) previously: College voor zorgverzekeringen (Health Insurance Board) (CVZ))	2012	Netherlands	Describes the conditional entry of health technologies into the basic benefit package	yes	-Rationale for conditional reimbursement -Critical success factors for conditional entry schemes -Selection of potential therapies for conditional entry -Time schedule -Eligibility considerations of potential therapies	Provides no guidance on how to adjust the price/reimbursement	Outlines how to design conditional entry in the basic insurance package	include	
13	A Guide to the Ultra-Orphan Pathway	Healthcare Improvement Scotland (HIS)/Scottish Medicines Consortium (SMC)	n.d. (application of new pathway since 2019)	Scotland (UK)	-Describes the different steps of the new pathway (Validation, Inital SMC Assessment, Evidence Generation, Reassessment) -Illustration of the process	yes	Clear process flow	To be used only for ultra-orphan drugs?	Informs stakeholders on the new guidance	include	
14	Guidance on the Evidence Generation Phase of the Pathway for Ultra-Orphan Medicines	Healthcare Improvement Scotland (HIS)/Scottish Medicines Consortium (SMC)	n.d. (application of new pathway since 2019)	Scotland (UK)	-Pre-evidence generation phase: ensuring committment -Evidence generation phase: data collection plan, data governance, data collection report, costs, time frame -Post evidence generation phase	yes	-Complements information provided in the ultra orphan pathway document, focusing on data collection	To be used only for ultra-orphan drugs?	Guidance on data collection in the evidence generation phase of the ultra-orphan pathway	include	
15	Guidance to Submitting Companies for Completion of New Product Assessment Form (NPAF) (Interim accepted advice decision option)	Healthcare Improvement Scotland (HIS)/Scottish Medicines Consortium (SMC)	2019	Scotland (UK)	-All medicines approved on conditional basis by EMA are eligible for an interim accepted decision provided that additional evidence is generated as requested by EMA -New Drugs Committee (NDC) issues preliminary advice to SMC if data generation could address key uncertainties -Reassessment is done by SMC -Company must provide a patient acess scheme application	yes	-describes conditional funding -Interconnection between EMA authrization and HTA advice	No details on data management /transparency	Alignment of SMC assessment with conditional marketing authorisation granted by EMA	include	

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
16	The development of pharmaceutical expenditure in Sweden - Managed Entry Agreements is an increasingly important tool for cost control as well as for early and equal access	Tandvårds- och läkemedelsförmånsverket (The Dental and Pharmaceutical benefits agency) (TLV))	n.d.	Sweden	-General facts about MEAs in Sweden -Role of MEAs -Products under MEAs	no	-	-	-	exclude	Background
17	Framework for analysing risk in Health Technology Assessments and its application to Managed Entry Agreements	Grimm, S. et al. (Decision Support Unit, commissioned by The National Institute for Health and Care Excellence (NICE)	2016	England (UK)	MEA Risk Analysis Framework: analyzing risk in HTAs and applying this framework to proposed MEA schemes, to assess the value of alternative MEA schemes, evaluate systematically the decision risk in terms of Payer Uncertainty Burden and Payer Strategy Burden in technology appraisals	no	-	-	-	exclude	Background
18	Access to Cancer Medicines Coalition – CDF update	Fernley, R. (National Health Service (NHS England))	2019	England (UK)	-Presents new Cancer Drug Fund (CDF) -CAR-T therapies funded via CDF	no	-	-	-	exclude	Primary topic not organisational framework of MEA
19	Appraisal and Funding of Cancer Drugs from July 2016 (including the new Cancer Drugs Fund) A new deal for patients, taxpayers and industry	National Health Service (NHS England)	2016	England (UK)	New framework for CDF	yes	-Criteria for entering CDF -Appraisal timetable -Data collection agreement, CDF Commercial agreement -Exit CDF	To be used only for cancer drugs	-Faster patient access -Drive stronger value for money -Offer a new fast-track route to NHS funding via an accelerated NICE Appraisal process and a new CDF managed access scheme	include	
20	The use of Real World Data for the estimation of treatment effects in NICE decision making	Bell, H. et al. (Decision Support Unit, commissioned by The National Institute for Health and Care Excellence (NICE)	2016	England (UK)	-Guidance on the use of real world data (RWD) for the estimation of treatment effects in NICE decision making -Definition of study design required, protocol and statistical analysis plan at the outset -Study protocol defines the appropriate population and the requisite data to be collected	no	-	-	-	exclude	Background

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
21	Commissioning through evaluation programme	The National Institute for Health and Care Excellence (NICE) website	n.d.	England (UK)	Collecting new data (clinical and patient experiences) while giving access to patients in the programme	no	-	-	-	exclude	Primary topic not organisational framework of MEA
22	Widening the evidence base: the use of broader data and applied analytics in NICE's work	The National Institute for Health and Care Excellence (NICE)	n.d.	England (UK)	-Highlights the need to develop a framework for the use of data analytics and elements that should be covered -Provides no recommendations	no	-	-	-	exclude	Primary topic not organisational framework of MEA
23	Sources and synthesis of evidence	The National Institute for Health and Care Excellence (NICE)	2020	England (UK)	Explains current use of RWE and limitations of RCTs	no	-	-	-	exclude	Primary topic not organisational framework of MEA
24	The NICE methods of health technology evaluation: the case for change	The National Institute for Health and Care Excellence (NICE)	2020	England (UK)	Puts i.a. emphasis on the role of a comprehensive evidence base, including non-RCTs and real-world evidence, and the circumstances in which different types of evidence have strengths or limitations	no	-	-	-	exclude	Background
25	Real-world evidence: perspectives on challenges, value, and alignment of regulatory and national health technology assessment data collection requirements	Sievers, H. et al.	2021	Germany	-Discusses stakeholder views on challenges and value of RWE -Divergence between regulatory and HTA data requirements in light of the German regulation for more safety in drug supply (GSAV)	no	-	-	-	exclude	Background
26	A framework for regulatory use of Real-World Evidence	Berger, M. et al.	2017	n.d.	RWE to inform regulatory decisions (definition, challenges, development of RWE)	no	-	-	-	exclude	Primary topic not organisational framework of MEA
27	Real-World Evidence Generation and Evaluation of Therapeutics	Downey, A. et al.	2017	USA	Workshop of different stakeholders discussing opportunities and challenges for integrating RWE into the development and evaluation of therapies	no	-	-	-	exclude	Country not included

Record Number	Title	Author	Date of Publication	Country/Region	Key points	Includes an organisational framework for OBMEAs	Relevant for research question	Shortcomings	Aim/context of framework	Include/Exclude	Rationale
28	Managed Entry Agreements for Pharmaceutical Products in Middle East and North African Countries: Payer and Manufacturer Experience and Outlook	Maskineh, C. et al.	2018	Middle East, North Africa	Describes current MEAs and perceived challenges in Middle East and North Africa	no	-	-	-	exclude	Country not included
29	Managed entry agreements for pharmaceuticals: the European experience	Ferrario, A. Kanavos, P.	2013	Europe	-Use of MEAs in Europe (number of arrangements, indication area, etc.) -Develop a own taxonomy of MEA	no	-	-	-	exclude	Background
30	Managed Entry Agreements in the context of Medicines Adaptive Pathways to Patients	Wilsdon, T Barron, A.	2016	n.d.	Conducting interviews to understand how MEAs have been used for products with conditional marketing authorization (or under exceptional circumstances)	no	-	-	-	exclude	Background
31	Access to High-Cost Medicines in Europe	Vogler, S.	2018	Europe	Challenges and possible solutions to ensure affordability anda access to highly expensive health technologies	no	-	-	-	exclude	Background
32	Onkologika: Übersicht zu Nutzenbewertungen und Refundierungspolitiken in Europa	Grössmann, N. et al.	2016	Europe	-Taxonomy MEAs -Pros and Cons of MEAs -Benefit assessment of oncology drgus in different countries (using MEAs) -Example of AIFA Registriers Monitoring	no	-	-	-	exclude	Background

7.5 Expert interviews

7.5.1 Template interview guideline

HTA Austria
Austrian Institute for Health Technology Assessment GmbH

INTERVIEW GUIDE

Interviewer	Kathrin Wohlhöfner
Interviewee(s)	
Position(s)	
Country representing	
Interview date	
Interview time	

Structure:

- **I. Opening**
- **II. Body**
  - a) Outcome-based managed entry agreements (OBMEAs) in your country
  - b) Organisational model
    - *A. Initiation*
    - *B. Design*
    - *C. Implementation*
    - *D. Evaluation*
  - c) Learnings and recommendations
- **III. Closing**

PART I: Opening

- Introduction of the interviewer, research topic, interviewee
- Informed consent form

PART II: Body

a) Outcome-based managed entry agreements (OBMEAs) in your country

1. Which gene- or regenerative therapies are currently funded via OBMEAs or foreseen to be funded?
2. Which types of OBMEAs are used in your country?

b) Organisational model

Exemplary stages of an OBMEA scheme:

[1]

[1] Adapted from Federici, C. et al (2019). Available from https://www.comedh2020.eu/wps/wcm/connect/309e7eab-767d-4b92-9af1-e0375441b269/AIES_COMED_WP7_C+Federici.pdf?MOD=AJPERES&CVID=mVbHZkh [cited 11.03.2021]

A) Initiation of a scheme
- *Technology selection*
  3. Who makes the initial proposal for funding potential therapies via OBMEAs?
  4. Which criteria for selection and prioritization of therapies are applied?
  5. How do you pre-assess the feasibility of the scheme?

B) Designing the scheme
- *Key stakeholders*
  6. Which stakeholders are typically involved in the scheme and what are their roles?
  7. Is there a publicly available study protocol and/or registration in place?
- *Time frame*
  8. How do you decide on the duration of the OBMEA and reasonable stopping rules?
- *Funding*
  9. Who provides funding for data collection and analysis?
- *Standard operating procedures (SOPs)*
  10. Are there SOPs in place that describe the different steps of activities, persons involved and information flows for operating an OBMEA?

C) Implementing the scheme
- *Data management*
  11. Which sources for data collection are used and who owns them?
  12. Who is responsible for data collection?
  13. Who is responsible for data analysis?
  14. How do you ensure the data protection of patients?
- *Monitoring*
  15. Who is responsible for monitoring the scheme?

D) Evaluating the scheme
- *Re-assessment*
  16. How does the reassessment process work and what are possible outcomes?
  17. How do you ensure that the quality of data is sufficient and complete to adequately address the identified uncertainties?
- *Policy impact*
  18. How do you deal with possible disinvestments if the data proves the ineffectiveness of therapies?
  19. How do you deal with similar/potentially better therapies entering the market?
- *Transparency*
  20. Is a publication (with public access) of the results planned?
  21. Which details of the scheme are publicly available and could be shared with public payers/HTA bodies in other countries?

c) Learnings and recommendations

22. What are the strengths and limitations of the OBMEA used in your country?
23. What recommendations could you provide for designing an OBMEA that ties conditional reimbursement to the public data generation?

PART III: Closing of the interview

- Thanks for the interview
- Possible questions

7.5.2 Overview interview partners

Interviewee(s)	Entela Xoxi (Respondent 1)
Position(s)	Research consultant at Catholic University of the Sacred Heart Member at IMPACT HTA WP10 Data Source Prioritisation Committee Member at IMI European Health Data & Evidence Network (EHDEN) Former AIFA Registries coordinator
Country representing	Italy
Interview date	19.03.2021
Category	Consultant
Interviewee(s)	Marc Van de Casteele (Respondent 2) Inneke Van de Vijver (Respondent 3)
Position(s)	MVD: Coordinator expertise pharmaceuticals at National Institute for Health and Disability Insurance (RIZIV-INAMI) IVV: Acting President of Taskforce Managed Entry Agreements National Institute for Health and Disability Insurance (RIZIV-INAMI)
Country representing	Belgium
Interview date	09.04.2021
Category	HTA body
Interviewee(s)	Thomas Kaiser (Respondent 4)
Position(s)	Head of the Department of Drug Evaluation at the Institut für Qualität und Wirtschatlichkeit im Gesundheitswesen (IQWiG)
Country representing	Germany
Interview date	13.04.2021
Category	HTA body
Interviewee(s)	Heather Logan (Respondent 5)
Position(s)	Vice-President of Pharmaceutical Reviews at Canadian Agency for Drugs and Technologies in Health (CADTH)
Country representing	Canada
Interview date	14.04.2021
Category	HTA body
Interviewee(s)	Marta Roig Izquierdo (Respondent 6) Mercè Obach Cortadellas (Respondent 7)

Position(s)	MRI: Pharmacist in Catalan Health Service (CatSalut) MOC: Pharmacist and scientific adviser at Catalan Healthcare service (CatSalut)
Country representing	Catalonia, Spain
Interview date	15.04.2021
Category	HTA body

Interviewee(s)	Angèl Link (Respondent 8)
Position(s)	Senior advisor and deputy secretary Advisory Committee Package at (ACP) Zorginstituut Nederland (ZIN)
Country representing	Netherlands
Interview date	20.04.2021
Category	HTA body

Interviewee(s)	Noreen Downes (Respondent 9)
Position(s)	Principal Pharmacist at Scottish Medicines Consortium (NHS Healthcare Improvement Scotland)
Country representing	UK (Scotland)
Interview date	23.04.2021
Category	HTA body

Interviewee(s)	Daniel Sperber (Respondent 10)
Position(s)	Senior Economist at Pan-Canadian Pharmaceutical Alliance Office (pCPA)
Country representing	Canada
Interview date	23.04.2021
Category	Negotiation organisation

Interviewee(s)	Anonymous Interviewee (Respondent 11)
Position(s)	Member of the Canadian Real-world Evidence for Value of Cancer Drugs (CanREValue) collaboration
Country representing	Canada
Interview date	28.04.2021
Category	Research project

Interviewee(s)	Douglas Lundin (Respondent 12) Andreas Pousette (Respondent 13) Anders Viberg (Respondent 14)

Position(s)	DL: Chief Economist at Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket - TLV) AP: Health Economist at Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket - TLV) AV: Senior Analyst at Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket - TLV)
Country representing	Sweden
Interview date	04.05.2021
Category	HTA body

Interviewee(s)	Yannick Auclair (Respondent 15)
Position(s)	Scientifique principal, Bureau – Méthodologies et éthique at Institut national d'excellence en santé et services sociaux (INESSS)
Country representing	Québec, Canada
Interview date	10.05.2021
Category	HTA body

7.6 Qualitative content analysis

7.6.1 General content analysis

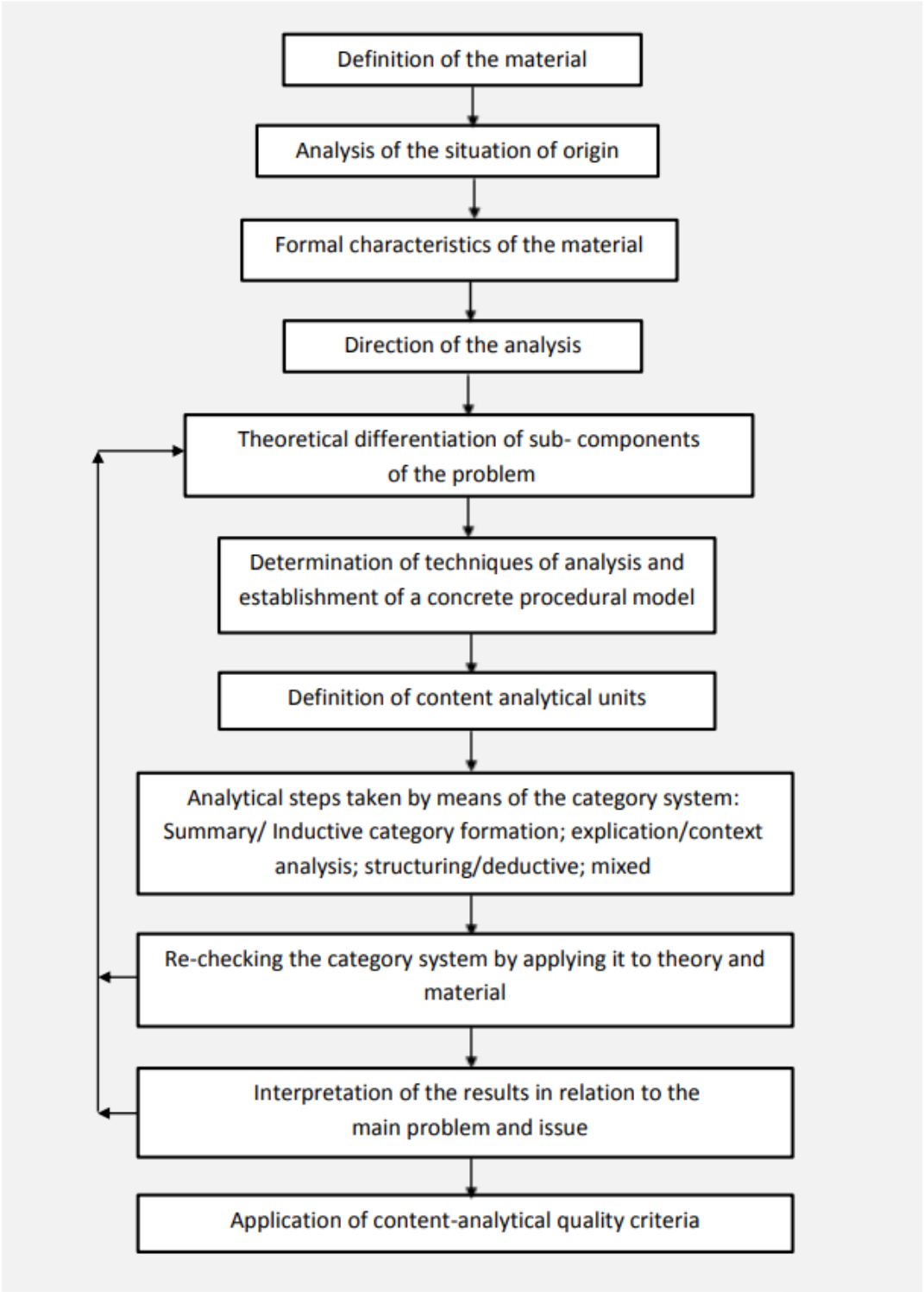

Figure 7-2: Procedural guide for content analysis according to Mayring (Mayring, 2014, p.54) [98]

7.6.2 Structuring content analysis

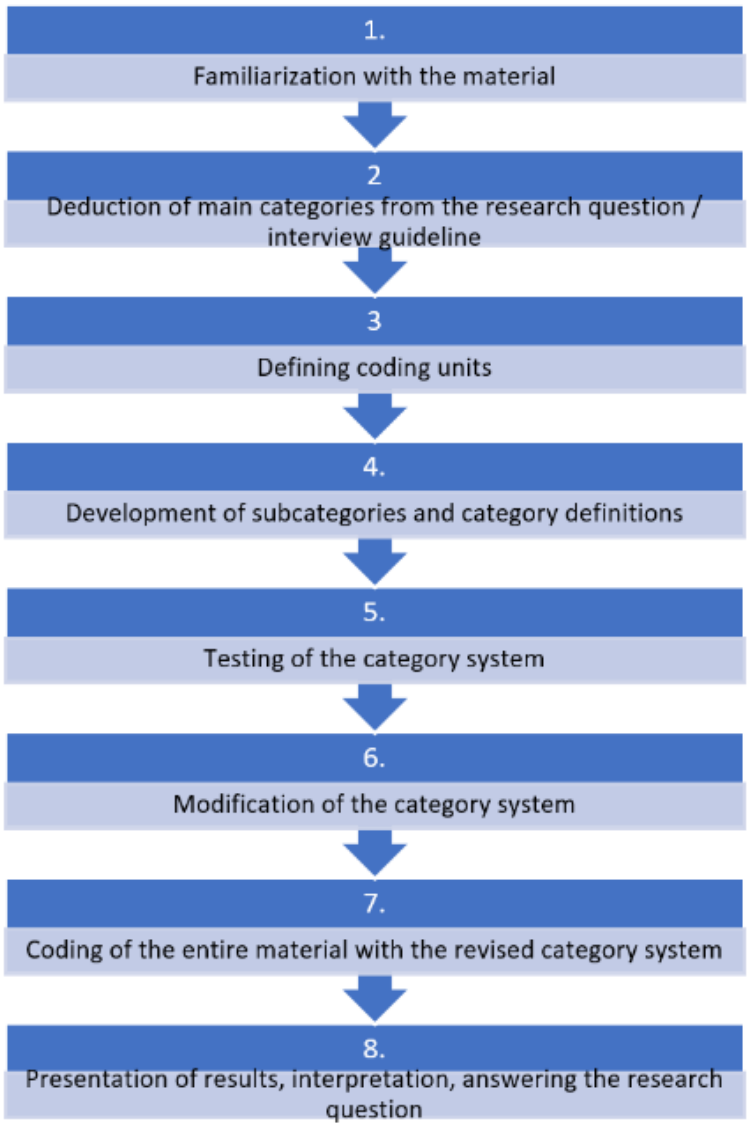

Figure 7-3: Process steps of structuring content analysis (own figure based on Schreier, 2014) [99]

7.6.3 Codes used for content analysis

Category	Code	Inductive/Deductive	Frequency
Introduction	Responsible party for initiation	Deductive	17
	Technology selection/prioritization	Deductive	15
	Feasibility	Deductive	12
Design	Duration	Deductive	11
	Stakeholder involved	Deductive	29
	Ensuring commitment of stakeholders	Deductive	6
	Interim assessment	Deductive	13
	Stopping rules	Deductive	10
	Monitoring	Deductive	12
Evidence generation	Funding data analysis	Deductive	9
	Funding data collection	Deductive	10
	Responsibility Data analysis	Deductive	10
	Responsibility Data collection	Deductive	16
	Data sources	Deductive	15
	Data ownership	Deductive	6
	Data protection	Deductive	9
Re-assessment	Procedure re-assessment	Deductive	23
	Time frame re-assessment	Deductive	7
	Criteria re-assessment	Deductive	3
	Quality assurance mechanisms	Deductive	11
	Market dynamics	Deductive	9
Exit	Outcomes re-assessment	Deductive	8
	Disinvestments	Deductive	13
Contextual factors	Country-specific definition OBMEA	Inductive	5
	Legal framework	Inductive	9
OBMEAs in use	Types OBMEAs	Deductive	31
	Rationale implementing/design OBMEAs	Inductive	8
	Therapeutic area	Deductive	30
	Example OBMEA model for specific therapy	Inductive	10
Transparency	Study protocol/registration	Deductive	13
	Standardization/SOPs	Deductive	12
	Dissemination of results	Deductive	47
Strengths	Addressing uncertainties	Inductive	2
	Centralized registry	Inductive	1
	Earlier patient access	Inductive	1
	Independent institution for data privacy	Inductive	1
	Pooling resources	Inductive	1
	Value for money	Inductive	3
Limitations	Lack of transparency/confidentiality	Inductive	3
	Data outcomes (incomplete/time lag	Inductive	10
	Mistrust	Inductive	2
	Interoperability	Inductive	2
	Political pressure disinvestments	Inductive	1
	Methodological issues	Inductive	1
	Defining clinical outcomes	Inductive	2
	Workload	Inductive	5
	Data collection issues	Inductive	3
Recommendations	Experience with former OBMEA schemes	Inductive	10
	Learnings/critical success factors	Deductive	20
	Cross-country collaboration	Inductive	7
	European initiatives	Inductive	3

Figure 7-4: Coding scheme [own figure]

7.7 Ethical considerations - informed consent form

HTA Austria
Austrian Institute for Health Technology Assessment GmbH

INFORMED CONSENT FORM

PART A) Study Information

Name of Principal Investigator	Kathrin Wohlhöfner
Name of Organization	Austrian Institute for Health Technology Assessment GmbH (AIHTA)
Name of Project	(Good) practice organizational models of public funding of high-prized therapies using Real-World Evidence sdf
Purpose of the Research	This research aims at exploring possible future organizational models for outcome-based managed-entry agreements (OBMEAs) providing conditional funding of highly prized therapies by giving access and equally generating data on the real-world evidence of treatment effects. Based on the learnings and experiences other countries have made with these reimbursement models, policy recommendations will be produced on the requirements of an organizational infrastructure, processes and responsibilities to ensure a successful implementation on a regular basis.
Type of Research Intervention	You will be participating in a semi-structure web-interview in English/German, lasting about 30-45 minutes.
Participant Selection	After reviewing available literature on organisational frameworks for OBMEAs in other countries, your country/organization was among the ones identified. We believe that your participation would deepen our knowledge to better understand the organization of OBMEAs in your country.
Participation (Benefits, Risks)	You will not receive any remuneration or other personal benefits for taking part in this research. Yet, your participation will contribute to develop recommendations for policy-makers on how to organize the reimbursement of expensive therapies and enabling patient access while not endangering financial sustainability of public budgets. Participation does not present any harm to interviewees.
Confidentiality	The interview will be audio-recorded. Your responses will be kept confidential. Transcripts will only be made available to the research team and the co-reader based at the Erasmus University of Rotterdam since this research also serves as a master thesis. The final report may use parts of the transcription file, yet your identity won´t be revealed or associated with any interview responses if you don´t want to. Any data and documents related to this interview will be stored on the principal investigator's password-encrypted computer and will be destroyed after five years upon completion of the study.
Sharing the Results	Final results of the overall research will be published as an AIHTA project report on its website (www.aihta.at).
Right to Refuse or Withdraw	Your participation is entirely voluntary. You can refuse participation, skip any question or stop the interview at each time by informing the researcher without fearing any negative consequences . The transcript of the interview can be sent to you for review if you wish so.
Contact Person for any questions	Kathrin Wohlhöfner kathrin.wohlhoefner@aihta.at

HTA Austria
Austrian Institute for Health Technology Assessment GmbH

PART B) Certificate of consent

1. **Confidentiality of data**
   - ☐ I agree that my full name and position is mentioned in the final report
   - ☐ I agree that my position is mentioned in the final report
   - ☐ I prefer to have not mentioned my name and position in the final report

2. **Use of quotations**
   - ☐ I agree to the non-anonymized use of quotations in the final report
   - ☐ I agree to the anonymized use of quotations in the final report
   - ☐ I do not agree to the use of any direct quotations in the final report

3. **Audio recording**
   - ☐ I agree to have the interview audio recorded
   - ☐ I do not agree to have the interview audio recorded

My signature below indicates that:

- I am voluntarily participating in this research
- I have read and understand the information above and had the opportunity to ask questions
- I understand that I can discontinue my participation at any time

You will receive a signed copy of this form.

Name of Participant _____

Signature of Participant _____

Date _____

Name of Principal investigator _____

Signature of Principal investigator _____

Date _____

2

7.8 Cross-country comparison of interview answers

Table 7-4: Excerpt from of interview answers

		Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
Contextual factors	**Legal framework**	General legislation on MEAs (Art. 81/111 Royal Decree)	No information	No information	No information	No information	§35a Abs. 3b SGB V (legislative change)	-Mandatory by law: innovative drugs must have a national registry that at least demonstrates appropriate use -Scientific Technical Committee determines the status of innovativeness	No information	No information	No information	No information
	Country specific definition OBMEA	No information	No information	No information	No information	No information	No information	-OBMEAs are linked to performance-based risk-sharing -New form: payment at results	No information	CEDs are not necessarily seen as a type of OBMEAs	No information	CED termed as conditional approval of reimbursement (additional evidence required in the future)
OBMEAs in use	**Therapeutic Area**	-High priced medicines in general (no specific indication) List of ATMPs with MEA): 1. ChondroCelect® (product withdrawal in EU) 2. Glybera®: (refused for reimbursement) 3. MACI® (no request for reimbursement was submitted) 4. Provenge® (no request for reimbursement was submitted) 5. Holoclar® (ongoing MEA since 2017) 6. Imlygic® (refused for	-Scope of drugs is confidential -In general: highly-priced drugs with uncertain evidence (i.e., EDRD expensive drug for rare disease)	-Yescarta®, Kymriah®, Luxturna® (conditional recommendation for Yescarta®, Kymriah®, re-evaluation after three years) -Some other rare disease treatments that received a favorable recommendation for re-	Discussions about possible OBMEAs on Kymriah® and Yescarta®, but no implementation at the time when the interviewee was involved in that process	Frameworks targets explicitly cancer drugs: more feasible to collect data (infrastructure and the organization of cancer care is sometimes more organized than for other indications)	No example yet, (process for Zolgensma® has just started (next step: agreeing on a study protocol and SAP)	-Gene therapies and advanced therapies First ATMP: Strimvelis® (payment by results) -Currently: Yescarta® and Kymriah® (CAR-T therapies) and Zolgensma® (payment at the result) -CAR-T therapies: payment after six and twelve months in case of clinical remission -Zolgensma®: payment once a year	-Conditional reimbursement: 1 CAR-T therapy -3 potential candidates: Ataluren, Larotrectinib, Entrectinib	-Interim acceptance decision option: Holoclar® (regenerative therapy) -Ultra-orphan pathway: Ataluren, Afamelanotide, Nusinersen (only SMA II and III, SMA I is available as routine practice), Voretigene, Volanesorsen,	-8 Risk-sharing agreements: >7 for oncology drugs >1 for Multiple sclerosis (drug names are confidential) -Gene therapies or ATMPs fall under the responsibility of the Ministry of health (not CatSalut)	-No funding of any gene or regenerative therapies via OBMEAs -Other types of agreements might exist between the regions and MAH: >Positive recommendation for use issued by the regions: Kymriah®, Yescarta® >Negative recommendation for use issued

		Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
		reimbursement) 7. Strimvelis® (still in procedure) 8. Alofisel® (refused for reimbursement) 8. Yescarta® (ongoing MEA since 2021) 10. Kymriah® (ongoing MEA since 2019) 11. Luxturna® (ongoing MEA since 2021) 12. Zynteglo® (still in procedure) 13. Zolgen-sma® (still in procedure)		imburse-ment on the condition that a clinical follow-up is carried out (Spinraza®: no tempo-rary status like for Kym-riah® and Yescarta®, no conditional recommen-dation with subsequent re-evalua-tion, focus on reducing costs and conducting a follow-up of the clinical data)						Burosumab, Cerliponase alfa (prospec-tively under the ultra-or-phan path-way)	(Dupixent®, CAR-T thera-pies, drugs for cystic fi-brosis), col-lection of data via the national reg-istry Valtermed	by the regions: Luxturna®, Zyn-teglo® >Ongoing dis-cussion: Zolgensma®
OBMEAs in use	**Types OB-MEAs**	-Population-based and individual-based schemes -Further to be distin-guished between "real" and "theoretical based" schemes >Rare: "Real" OBMEAs-- >based on clinical data observed in the real world >More common: "The-oretical based" OB-MEAs: based on data from clinical trials	-No CED schemes -Very rare: Pure OB-MEA on a patient level, full refund for non-re-sponder patients, matching the confi-dential price to the outcomes of that pa-tient -Most com-mon: pay-	-No imple-mentation of OBMEAs yet (still at the beginning) -Conditional funding of some gene therapies and regener-ative thera-pies	Refers to pCPA	No information	-There might exist individ-ual agree-ments be-tween health insurers and MAHS -BUT: Con-cept for the generation of routine prac-tice data and their analysis for the bene-fit assess-ment is gen-erally not linked to re-imbursement restrictions	2 Types: a) Old type: Pay-ment by results (used for cancer drugs, pay-back scheme, MAH pays 100% back in case of non-response) b) New type: Pay-ment at results (used for ATMPs, success fee scheme, regions, hospitals pay only in case of success)	-3 Types: Legal basis for: a) Promising care process (since 2020) b) Orphan drugs, excep-tionals, and conditionals (since 2019) No legal basis: c) Orphan drug arrangement (orphan drug is proven effec-tive, but clinical uncertainty (long term ef-fectiveness, or absence of starting and	-CED schemes -Interim ac-cepted deci-sion option, ultra-orphan pathway -Other types of MEAs may exist, but SMC is not in-volved in that, confi-dential infor-mation	Pay-for-out-comes model: pay-ment only for respond-ers to the treatment	No examples of OBMEAs

		Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
			for-performance schemes used as an alternative to straight discounting				-One exception: G-BA can decide that the prescription of drugs covered by the SHI is bound to participating in this data collection of routine practice data (as decided in the case of Onasemnogene)		stopping criteria and/or unfavorable cost-effectiveness and) exists, the minister of health decides to reimburse after price negotiation, (still in the beginning, so not that much experience yet) The goal of these arrangements: improve (cost)effectiveness by adjust starting and stopping criteria when possible and change dose schemes			
OBMEAs in use	**Rationale implementing/design OBMEA**	No information	Primarily financial goal (replacement of discounting)	No information	No information	No information	Lack of evidence from existing studies	Simplification of the system	No information	-Rationale for design: reducing the burden of data collection: >Ultra-orphan pathway: reduce the burden of data collections for clinicians, putting the responsibility for the data collection on MAH >Interim accepted decision option: reduce the burden of	-Development of the centralized registry for pharmaceuticals out of necessity (not looking at registries in other countries): >silo working of health care providers >aimed for homogenizing treatment of patients >benchmarking of	Primarily financial goal

		Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
										data collection not only for NHS but also for the MAH since the company is already collecting data for the submission to EMA	hospitals >observe if the predefined outcomes agreed in the risk-sharing contract can be achieved with the therapy	
Transparency	**Publicly available study protocol/registration**	Not in place (confidential)	Not in place yet (intentions to change it in the future)	Not in place	Not in place	Intention to make it public (considering views of industry, payer)	-Study protocol and statistical analysis plan (SAP) will be developed by MAH (in collaboration with the registry operator) and sent to G-BA for approval -No decision yet if study protocol and SAP will be made publicly available -Registration of study in public study registries	Not in place since no prospective observational study, but administrative data is used	-Publicly available study protocol -Potential registration in place	No involvement of SMC	Not in place	No formalized process probably depends on the type of study conducted

		Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
	Standardization/SOPs	Not in place (just legal basis describing how MEAs (not specifically OBMEAs) should be set up)	-Not in place -Pragmatic approach developed during negotiations on an individual basis -pCPA uses internal benchmark agreements for other drugs (not publicly available)	Not in place (rigorous evaluation process with different predefined steps)	-Not in place -Pragmatic approach based on experience from former negotiations rather than a policy-related process	Currently developed within the different working groups	-SOPs of registries are part of evaluating the appropriateness for the generation of routine practice data for benefit assessments -Registry operators are responsible for SOPs on the level of data generation -General procedure of evaluation described in the "Verfahrensordnung" of the G-BA	General SOPs for registries and MEAs (not specifically for OBMEAs)	Publicly available report on the conditional inclusion of procedure of orphan drugs, conditionals, and exceptionals	-Standardization of the initial assessment process (SOPs in place) -MAH is responsible for data collection, no involvement of SMC	Good practice guideline [available only in Catalan] specifies: contract duration, clinical criteria, economic conditions, eligibility criteria	No information
Transparency	**Dissemination of results**	-Confidential: study protocol, type of MEA, etc. -No publication of results (only if MAH mentions them in the HTA reports which are publicly available)	-Confidential: results, price, agreement structures, type of agreement -No publication of results -Nothing public, only the existence of an agreement for a drug and the	-Confidential: price, some clinical data, results, etc. -Results are shared only between the members part of the process (sign confidentiality consent) -Legally obliged to publish all assessment reports, some data	-Confidential: all details, conditions of agreements, products with MEAs -HTA report will be publicly available, but the conditions of the agreement are confidential -Ideally:	Time lag until reports are published--> aiming for early reports, briefing notes, etc.	-Dossier and benefit assessment are publicly available -Aiming for publication of study protocol and SAP -Data collection may include the integration of international registries if the registries can provide data in accordance	Confidential agreements (contains, i.e., information on outcome measures, results) -Public: inclusion criteria for each indication and registry, the timing of evaluations of disease status, etc. -Physicians/clinicians need to know criteria to make sure the right patients get the right treatment, and the	-Orphan drugs, exceptionals, and conditionals: negotiated price should be made public (not sure if the price for Nusinersen is, in fact, public, MAH will probably not cooperate then) -"everything will be public as long as [...] there is [are] no privacy issues".	-Patient access schemes are entirely confidential (nature of schemes, type, etc.) -Data collection completely confidential (responsibility of MAH) -Re-assessment process: publication of detailed advice document	-Confidential agreements (name of the drugs, contract, conditions, data, etc.) -Results are not published -Difficult to share information, MAH disagrees -Interface with Valtermed registry --->"sharing"	-MAH owns data, publication not possible (reconsider that in the future) -TLV publishes the evidence the MAH needs to submit -Results are not published

		Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
			clinical indication	are redacted for reasons of confidentiality -Publicly accessible only if generated from public databases -Data exchange with CADTH but limited to information allowed by MAH	conditions, clinical data, different outcomes of the scheme should be public		with the protocols-->aiming for a standardized assessment of registry data across different registries ("Master protocol and Master SAP")	right data is included in the registry for reimbursement purposes -No dissemination of results		(information on the evidence considered) but the level of transparency depends on the MAH -MAH redact (substantial) parts of it as Commercial-in-Confidence or Academic-in-Confidence -Public: principles for assessment, very brief summary of the critical appraisal	clinical data (mandatory by law)	
Strengths	**Value for money**	-Not paying for non-responders -"We're really paying for the gain in health."	-	-	-	-	-	-	More information available to decide on cost-effectiveness	-	Price is adapted to the value observed	-
	Centralized registry	-	-		-	-	-	-	-	-	Centralized registry, an overview of data	-
	Earlier patient access		-	-	-	-	-	-	Earlier patient access to new therapies	-	-	-
	Independent institution for data privacy	Privacy committee ("watchdog in what we are doing with the data of the social security")	-	-	-	-	-	-	-	-	-	-
	Addressing uncertainties	-	-	-	-	-	Specifically collecting data to address open questions,	-	-	-	Reducing uncertainties around clinical outcomes and	-

		Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
							uncertainties (which is not possible with every routine data collection)				economic impact	
Limitations	**Intransparency/ confidentiality**	"Cannot talk" about agreements	HTA assessment needs to rely on list prices which have considerable confidential discounts; HTA work is impeded by the confidential nature of these negotiations and final agreements	-	-	-	-	System owned by AIFA, challenging to have access to the system, share data, analysis	-	Publication of re-assessment is limited by the MAH who marks large parts of the reports as confidential	-	-
	Data outcomes (incomplete/ time lag)	-Data is incomplete, not timely -->time lag in the system, since MAH use data from sick funds, they blame them for collecting incomplete data, but end responsibility for answering uncertainties lies with the MAH -therefore, favor more theoretical schemes than schemes based on RWD -Clinical relevance of an outcome is not always given	"Major issue" to ensure sufficient quality of data to address identified uncertainties	-	-	-	-	-Often long duration of schemes that cause a change in the drug's clinical value affects the re-negotiations (different percentage of non-responders, survival data, etc.) -Often delayed launch of the registry leaves too little time for setting up the IT-System. -"Parallel data sourcing" - issues	-	-	-	-

		Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
								with having timely data				
Limitations	**Data collection issues**	Facing considerable delay in the collection of data	Difficult to consistently collect data because of different healthcare systems within Canada, different local laws regarding patient data protection, difficult to reach an agreement/consensus with different governments	-	-	-	-	Duplication of data: national AIFA registry + regional registries--> national data and regional data are not the same	-	Burden of data collection is perceived as one of the biggest barriers to expanding these schemes:	-	-
	Workload	Cumbersome organization of setting up these agreements, collecting data, agreeing on outcome measures, etc.	-	Implementation requires resources, creates work, not easy to implement	One barrier for implementing OBMEA: workforce needed for collecting, analyzing, and reporting data	-	-	-	-	-	Costs (follow-up of patients, etc.)	-
	Defining clinical outcomes	-	-	-	-Initial discussion about implementing OBMEA for CAR-T cell therapies: could	-	-	-	-	-	-	-

		Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
					not agree on specific clinical outcomes or continuous monitoring rules							
Limitations	**Mistrust**	-	Skepticism of payers with proposed schemes, how to ensure the quality of data, how to handle non-responders and incomplete data	-	Provinces and territories are skeptical when data collected by the MHA is used for OBMEA	-	-	-	-	-	-	-
	Interoperability	Data coupling currently not possible yet	-	-	-	-	-	No interactive data interoperability or integration of other data sources	-	-	-	-
	Political pressure disinvestments	-	-	-	-	-	-	-	Difficult to remove coverage	-	-	-
	Methodological issues	-	-	-	-	-	-Limited to the use of non-randomized data -->deprive yourself of an important methodological tool, difficult to identify small effects in non-	-	-	-	-	-

		Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
							randomized data					
Recommendations	**Critical success factors**	-Raising public awareness and better communication to patients: public education about the high costs of treatment, conditional nature of funding, possible disinvestment (proposed that bigger organizations like WHO, OECD, European Commission should be involved in that) -Create systems for collecting the type of data you are looking for, timely data	-Early involvement and engagement of stakeholders (patients, clinicians, MAH) in drafting the scheme to ensure broad acceptance (currently not possible in Canada because of confidentiality of agreements) -Great level of prespecification	Choose the right health technology before starting an OBMEA since the burden of data collection should be worth it	-Public transparency -High level of patient and clinical engagement -Find alignment between healthcare systems, making sure that consistent terms of an OBMEA can be created which are valid throughout the country	-	-Only start data collection if you can follow a well-conceived methodology -Early involvement and discussion on data sources with registry operators	-OBMEAs are only feasibly if you agree on the right data to collect, plan where you will get your data from (national, regional, local level) -Connect with people that share the same goal -Establish partnerships (public-private, academia) -Establish legislation, regulation to "justify" your work -Get support from people to manage the administrative burden (i.e., involvement of pharmacists, clinicians to enter data) -Not necessarily create new data but use what is already in place -Determine a minimum dataset -Determine data sources that produce high-quality data	-	-	-Establish a data record -Align with all stakeholders (hospitals, HTA body, payers, company) on the scheme	-Not reimbursing MAH in advance, only when specific endpoints are reached -->higher incentive to collect evidence -Finding the right balance between defining the well-targeted towards cost-effectiveness but complicated to measure outcomes and easier but less exact endpoints -Think about the rationale of implementing OBMEA: reduce the risk or reduce the price tag?

		Belgium (RIZIV-INAMI)	Canada (pCPA)	Canada (INESSS)	Canada (CADTH)	Canada (CanRE Value)	Germany (IQWiG)	Italy (AIFA)	Netherlands (ZIN)	Scotland (SMC)	Spain (CatSalut)	Sweden (TLV)
								-Develop a data platform to implement OBMEAs -Share results, enable participation of stakeholders				
Recommendations	**Cross-country collaboration**	-Perception that sharing data between countries will be possible/feasible in the future -Example: Set up international registries with Benelux countries on MSA and Multiple Sclerosis -International registry is the aim, but maybe far-fetched -->more realistically: exchanging registry protocols, etc.	-	-	-	-	Possible inclusion of international registries (see above)	-	-	-	-	-Joint assessments in the Nordic countries on some products but no joint approach for MEAs yet -Assumed those things might be discussed in the future
	European initiatives	RWE4Decision chaired by CEO of RIZIV-INAMI: increasing transparency, early dialogue between stakeholders to agree on the data to be collected, outcome parameters, aiming for an international registry, etc.	-	-	-	-	-	-	-	-	-	-

Abbreviations: AIFA – Agenzia Italiana del Farmaco, ATMP - Advanced Therapies Medicinal Product, CADTH - Canadian Agency for Drugs and Technologies in Health, CanREValue - Canadian Real-world Evidence for Value of Cancer Drugs, CAR-T-cell - Chimeric antigen receptor T-cell, CatSalut - Catalan healthcare service, CED - Coverage with Evidence Development, CEO – Chief Executive Officer, EMA – European Medicines Agency, G-BA – Gemeinsamer Bundesausschuss (Federal Joint Committee), HTA – Health Technology Assessment, RIZIV-INAMI - Rijksinstituut voor ziekte en invaliditeitsverzekering/ Institut national d'assurance maladie-invalidité (National Institute for Health and Disability Insurance), INESSS - Institut National d'Excellence en Santé et en Services Sociaux (Canadian HTA – Québec), IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), IT – Information Technology, MAH – Marketing Authorization Holder, MCDA – Multi-Criteria Decision Analysis, MEA – Managed-entry agreement, MSA - Multiple system atrophy, NHS – National Health System, OBMEA – outcome-based Managed-entry agreement, OECD - Organisation for Economic Co-operation and Development, pCPA - Pan-Canadian Pharmaceutical Alliance, SAP – Statistical Analysis Plan, SHI – Statutory Health Insurance, SMA – Spinal Muscular Atrophy, SMC - Scottish Medicines Consortium, SOP - Standard Operating Procedure, TLV - Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency), WHO – World Health Organization, ZIN - Zorginstituut Nederland (National Healthcare Institute)

7.9 Recommendations

7.9.1 Guidance for planning routine practice data collection

Prozessschritt	Arzneimitteltherapie	Nicht-medikamentöse Verfahren	Komplexe Interventionen
Fragstellung	• Identifikation einer offenen Fragestellung aus der Versorgung (Evidenzlücke) • Formulierung der Fragestellung gemäß PICO-Schema		
Planung	• Auswahl des Studiendesigns unter Berücksichtigung der erwarteten Therapieeffekte, der Machbarkeit und bereits vorliegender Evidenz – Primär: Durchführbarkeit einer versorgungsnahen RCT (z.B. registerbasierte RCT) prüfen – Bei Studien mit oder ohne Randomisierung: Studienplanung gemäß Behandlungsalltag (Ein- und Ausschlusskriterien, Interventionen, Endpunkte, Visiten); Ausnahmen sind Festlegungen, die sich aus der PICO-Fragestellung ergeben (z.B. genaue Definition der Intervention, Erhebung der relevanten Endpunkte) – Bei Studien ohne Randomisierung • Strukturierte Planung einer wünschenswerten, fiktiven RCT (z.B. mit Hilfe des Target Trial Konzepts) • Systematische Identifikation und Präspezifikation möglicher Confounder • Durchführung der Studie ohne Randomisierung nur bei grundsätzlicher Eignung der Datenquelle (Validität der Daten: Basisdaten, Verlaufsdaten, Erhebungszeitpunkte, Endpunkte, Confounder usw.) • Vor Beginn der Datenerhebung finalisiertes Studienprotokoll (bei retrospektiven Analysen: vor Beginn der Auswertung)		
	• Prüfen, ob aufgrund der Fragestellung die Arzneimitteltherapie gemäß Zulassung erfolgen muss (bei interventionellen Studien: Vorgabe im Studienprotokoll; bei nicht interventionellen Studien: Beschränkung auf entsprechende Datensätze)	• Bei Verfahren, die nicht häufig angewendet werden, exakte Definition dieser Verfahren (bei interventionellen Studien: Vorgabe im Studienprotokoll; bei nicht interventionellen Studien: Beschränkung auf entsprechende Datensätze) • Prüfen, ob die Zuordnung zum Verfahren an „Schulen" und nicht an prognostische Merkmale gebunden ist (instrumental variable [35])	• Intervention, Setting und Populationen genau definieren („System, auf das die Intervention wirken soll") • Partizipative Elemente sind konstitutiv (Patienten, Leistungserbringer, Aufsichtsbehörden, weitere Stakeholder) • Pilotierung von Designelementen i.d.R. unverzichtbar (Präzisierung der Intervention, Rekrutierung und Endpunkterhebung) • Prozessevaluation und -monitoring berücksichtigen (u.a. Rekrutierungserfolg, Reaktion des Systems auf Intervention, Ermittlung förderlicher und hindernder Faktoren, Identifikation von Determinanten der Effekte auf die Endpunkte) • RCT: Häufig Cluster-Randomisierung (i.d.R. auf Ebene der Institution), aber auch individuelle Randomisierung möglich • Es kann überlegt werden, auf eine detaillierte Baseline-Erhebung zu verzichten (weil bereits das i.d.R. eine Intervention darstellt) • Studien ohne Randomisierung: Bei Wahl der Kontrolle auf Ähnlichkeit möglichst vieler Randbedingungen achten (eher globale Auswahl, z.B. vergleichbarer Landkreis o.ä.) • Basiserhebung wichtiger als bei RCT
Datenerhebung	• Gewähltes Instrument zur Datenerhebung / spezifische Datenstruktur (z.B. Register) muss Daten in der notwendigen Qualität zur Verfügung stellen können (inkl. Daten zu Begleit- und Folgeinterventionen, bei Studien ohne Randomisierung auch inkl. Daten für Confounderkontrolle) • Möglichst kontinuierlicher Datenfluss – insbesondere bei geplanten Zwischenauswertungen • Möglichst Onlinedatenerhebung und Plausibilitätsregeln hinterlegen sowie Datenübermittlung / Speicherung nur bei vollständigen (Teil)Datensätzen zulassen • Bei interventionellen Studien mit oder ohne Randomisierung: Nutzung bestehender Strukturen zur Erhebung der VeDa prüfen (z.B. Indikationsregister)		
			Generell: • Kombination aus systembezogenen und individuellen Endpunkten bevorzugen (vorab sowohl präzise als auch unmittelbar umsetzbar definieren) • i.a.R. sind Mixed-Methods-Ansätze mit qualitativen und quantitativen Methoden erforderlich, jedoch in ausgewogenem Maß • Berücksichtigen, dass sowohl Datenerhebung als auch Prozessmonitoring einen Einfluss auf die Durchführung und den Effekt der Intervention haben kann • Erhebung der Endpunkte nicht durch Interventionspersonal • RCT: Bei Cluster-Randomisierung Start der Intervention erst nach Baseline-Erhebung
Auswertung	• Vor Datenbankschluss und vor Beginn der Auswertung finalisierter statistischer Analyseplan (SAP); Auswertung gemäß des präspezifizierten SAPs • Bei Studien ohne Randomisierung: präspezifizierter Algorithmus zur Confounderkontrolle und Adjustierung in der Analyse; Definition von Abbruchkriterien (z.B. keine ausreichende Balanciertheit der Daten trotz Adjustierung zu erreichen) • etwaige geplante Zwischenanalysen in der Methodik berücksichtigen (z.B. p-Wert anpassen)		

Prozessschritt	Arzneimitteltherapie	Nicht-medikamentöse Verfahren	Komplexe Interventionen
Interpretation und Bewertung	• Berücksichtigung der Aussagekraft der unterschiedlichen Studiendesigns und der konkreten Datenqualität bei der Interpretation der Ergebnisse • Bei Studien ohne Randomisierung: Ableitung von Aussagen zum Nutzen oder Schaden in Abhängigkeit von der Effektstärke und den Confoundern – in der Regel nur bei ausreichend großen Therapieeffekten (z. B. RR < 0,5) – ggf. bei Übertragbarkeitsfragestellungen unter Verwendung bereits vorhandener RCTs auch bei kleineren Effekten – wenn alle plausiblen Confounder und anderen Effektverzerrer eine entgegengesetzte Aussage vorschlagen • Kritische Interpretation etwaig genutzter Sekundärdaten • Kritische Diskussion der Übertragbarkeit auf ähnliche Settings, Regionen, Patientengruppen usw.		
Publikation	• Erstellung eines Ergebnisberichts gemäß ICH E3 • Erstellung einer wissenschaftlichen Publikation mit begleitender Veröffentlichung des vollständigen Ergebnisberichts inklusive Studienprotokoll und SAP		
Ableitung von Empfehlungen und Umsetzung	• Beurteilung im Gesamtkontext der Evidenz • Sicherstellung der Durchdringung der Ergebnisse in der Fachwelt / bei den Versorgern • Berücksichtigung des Einflusses relevanter Kontextfaktoren • Nutzung der identifizierten hindernden und förderlichen Faktoren • Rekrutierungsprobleme berücksichtigen		

Figure 7-5: Process steps employing routine practice data for assessing treatment effects (Hoffmann et al., 2021, p.473) [131]

7.9.2 Feasibility criteria

IMPACT HTA

Improved methods and actionable tools for enhancing HTA

Checklist for a Rare Disease Treatment
Is an Outcomes-Based Managed Entry Agreement Feasible?

Criteria for use by a Health Technology Assessment (HTA) body or Marketing Authorisation Holder (MAH) to determine whether an Outcomes-Based Managed Entry Agreement (OBMEA) with mandatory data collection for re-appraisal (Coverage with Evidence Development) is feasible for a rare disease treatment (RDT):

Answer "yes" to all statements.

1. A price has been agreed for the RDT that has been developed responsibly to support sustainability of the health system (as stated in the pricing and reimbursement/ commercial agreement).
2. High therapeutic benefit is predicted, but there are major uncertainties that affect internal or external validity of the clinical effectiveness, or the economic evaluation, such that the treatment would not be recommended by the appraisal process.
3. Decision-relevant uncertainties in clinical effectiveness that drive determination of therapeutic benefit and/or cost-effectiveness can be resolved or substantially reduced with additional data collection within a reasonable timeframe.
4. Planned or ongoing studies, or post-licensing data collection activities will not resolve all the decision-relevant uncertainties for this RDT at the time of re-appraisal.
5. Additional data collection is feasible and of value:
   - 5.1 A data collection plan/protocol can be developed with stakeholders that includes clear research questions related to the decision-relevant uncertainties and outlines the study design, data sources and analytical plans.
     (This should be approved by the HTA/Payer to ensure it is likely to provide data of sufficient quality to resolve the uncertainties whilst limiting the clinical and administrative burden placed on all stakeholders.)
   - 5.2 If needed, ethical approval can be obtained timeously.
   - 5.3 Patients, clinicians and the MAH will commit to participation in the OBMEA for the required timeline (recognizing that if a new treatment becomes available, clinicians/patients may wish to alter treatment).
   - 5.4 Data of sufficient quality and quantity can be collected within the timeframe of the OBMEA (and combined with other data generated internationally since the initial HTA) to inform re-appraisal or future reimbursement decisions, recognizing that some rare diseases may have small, heterogeneous populations and study durations may need to be longer.

IMPACT HTA Checklist for initiation of an OBMEA
March 2021

IMPACT HTA

Improved methods and actionable tools for enhancing HTA

Checklist for a Rare Disease Treatment
Is an Outcomes-Based Managed Entry Agreement Feasible?

Criteria for use by a Health Technology Assessment (HTA) body or Marketing Authorisation Holder (MAH) to determine whether an Outcomes-Based Managed Entry Agreement (OBMEA) with mandatory data collection for re-appraisal (Coverage with Evidence Development) is feasible for a rare disease treatment (RDT):

Answer "yes" to all statements.

1. A price has been agreed for the RDT that has been developed responsibly to support sustainability of the health system (as stated in the pricing and reimbursement/ commercial agreement).

2. High therapeutic benefit is predicted, but there are major uncertainties that affect internal or external validity of the clinical effectiveness, or the economic evaluation, such that the treatment would not be recommended by the appraisal process.

3. Decision-relevant uncertainties in clinical effectiveness that drive determination of therapeutic benefit and/or cost-effectiveness can be resolved or substantially reduced with additional data collection within a reasonable timeframe.

4. Planned or ongoing studies, or post-licensing data collection activities will not resolve all the decision-relevant uncertainties for this RDT at the time of re-appraisal.

5. Additional data collection is feasible and of value:

   5.1 A data collection plan/protocol can be developed with stakeholders that includes clear research questions related to the decision-relevant uncertainties and outlines the study design, data sources and analytical plans.
   (This should be approved by the HTA/Payer to ensure it is likely to provide data of sufficient quality to resolve the uncertainties whilst limiting the clinical and administrative burden placed on all stakeholders.)

   5.2 If needed, ethical approval can be obtained timeously.

   5.3 Patients, clinicians and the MAH will commit to participation in the OBMEA for the required timeline (recognizing that if a new treatment becomes available, clinicians/patients may wish to alter treatment).

   5.4 Data of sufficient quality and quantity can be collected within the timeframe of the OBMEA (and combined with other data generated internationally since the initial HTA) to inform re-appraisal or future reimbursement decisions, recognizing that some rare diseases may have small, heterogeneous populations and study durations may need to be longer.

IMPACT HTA Checklist for initiation of an OBMEA
March 2021

Figure 7-6: IMPACT OBMEA tool: Feasibility checklist [91]

Feasibility Considerations for RWE studies

- An adequate number of patients have received the drug of interest
- An appropriate comparator cohort can be identified
- The outcome being studied is relevant, measureable and obtainable from existing administrative sources
- There is an adequate follow-up time to ascertain the outcome of interest in the observation window
- Financial support and knowledge expertise to conduct analysis in a timely manner either at the provincial or national level exists.

Figure 7-7: Feasibility considerations conducting RWE research (Chan et al., 2019, p.15) [89]

7.9.3 Categories of uncertainty according to ISPOR-SMDM Taskforce

Preferred term	Concept	Other terms sometimes employed	Analogous concept in regression
Stochastic uncertainty	Random variability in outcomes between identical patients	Variability Monte Carlo error First-order uncertainty	Error term
Parameter uncertainty	The uncertainty in estimation of the parameter of interest	Second-order uncertainty	Standard error of the estimate
Heterogeneity	The variability between patients that can be attributed to characteristics of those patients	Variability Observed or explained heterogeneity	Beta coefficients (or the extent to which the dependent variable varies by patient characteristics)
Structural uncertainty	The assumptions inherent in the decision model	Model uncertainty	The form of the regression model (e.g., linear, log-linear)

Figure 7-8: Differentiation of different categories of uncertainty (Briggs et al., 2012, p.836) [135]

7.9.4 Data collection

Data collection agreement

Improved methods and actionable tools for enhancing HTA

Template for Adaptation by HTA Bodies

Outcomes-Based Managed Entry Agreement of a Rare Disease Treatment

March 2021

This template provides an outline for the agreement between stakeholders, which documents the details of data collection for an Outcomes-Based Managed Entry Agreement (OBMEA) of a rare disease treatment.

It uses terminology that comes from the IMPACT HTA Template for OBMEA and should be adapted to suit the healthcare system.

It is recommended that the completed document be shared publicly at the same time as the final appraisal report/reimbursement decision, to enable alignment of data collection activities post appraisal in other health systems.

Although this was developed for rare disease treatments, it could also be used with medicines for higher prevalence conditions.

This template has been developed as part of the EU Horizon 2020 funded project IMPACT HTA Work Package 10 on Appraisal of Orphan Medicinal Products. It arises from mixed methods research with stakeholders about implementation of OBMEA for rare disease treatments and draws on OBMEA templates from

- *Pharmaceutical Benefit Scheme, Australia*
- *National Institute of Health and Disability Insurance, Belgium*
- *National Institute for Health and Care Excellence, England*
- *Health Service Executive, Ireland.*

It incorporates comments from a wide range of stakeholders in the international HTA community.

For any queries contact Karen Facey: karen.facey@ed.ac.uk .

Red text – details to be completed
Green text - alter or delete as appropriate
Black text in yellow highlights – explanatory text in the template to be deleted

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The results presented reflect the author's views and not those of the European Commission.

Contents

1. Purpose of this Agreement

This public document outlines the data collection plans for the Outcomes-Based Managed Entry Agreement (OBMEA) for rare disease treatment (RDT) in indication and the responsibilities of those involved.

After rigorous appraisal of all the available evidence for RDT in indication to determine its added benefit/value for money, it has not been possible to recommended RDT for use/reimbursement in health system.

The HTA body appraisal <link to report> identified uncertainties in the clinical evidence/economic modelling that could be reduced/resolved by additional data collection on XXX patients receiving the RDT for indication over a period of duration of data collection.

Therefore, it has been agreed that access can be provided to patients to RDT for indication in health system via an OBMEA. This decision has been made in accordance with the IMPACT HTA OBMEA checklist/is documented in Appraisal report.

The aim of this OBMEA is to enhance the quality and strength of evidence provided to decision-makers for future appraisal determinations of added benefit/value for money to determine whether it can be routinely used/listed for use in the health system.

2. Basis for this Outcomes-Based Managed Entry Agreement

When high therapeutic benefit is predicted in an appraisal but this effect is associated with major uncertainties, or when there are questions about important assumptions in the economic evaluation, it may not be possible to recommend or reimburse a rare disease treatment. In this situation an OBMEA may be used if additional data can be collected within a reasonable timeframe to resolve/reduce the key (decision-relevant) uncertainties to better elucidate added benefit, optimize treatment use and patient outcomes, and demonstrate value for money.

In accordance with this premise and legislation/policy, this OBMEA has been developed by the signatories (front cover) for RDT in indication.

The purpose of data collection in the OBMEA is to optimize the treatment of individual patients and only use anonymized or pseudo-anonymized patient data for health system purposes, this Agreement is covered by XXX legislation relating to informed consent, data governance and ethics approval[3].

The treatment is funded by the health system. Data collection costs will be funded by the MAH/Expert Centre/Registry Holder/Payer/HTA body.

A separate, confidential, pricing and reimbursement agreement outlines the conditions in place to ensure an appropriate price has been negotiated for the RDT, which is in accordance with national pricing/reimbursement policies.

2.1 Uncertainties to be Resolved in the OBMEA

In the appraisal of RDT in indication, it was estimated that the prevalent population in the indication in country/region is PPP and the incident population is III/year.

Key uncertainties to drive outcomes-based reimbursement/continuation of treatment for individual patients are:

- V (e.g. successful infusion of treatment)
- W (e.g. patient-reported outcome)
- X (e.g. outcome indicating disease progression/treatment response)
- Y (e.g. 6-month or 12-month survival)
- Z (e.g. early discontinuation due to Serious Adverse Event).

Key uncertainties in the aggregated clinical/economic evidence were identified as:

- A (e.g. disease progression)
- B (e.g. Patient reported outcomes – generic and disease-specific)
- C (e.g. response)
- C (e.g. survival)
- D (e.g. time on treatment)
- E (e.g. maintenance of response after treatment discontinuation).

It has been identified that regulatory post authorisation efficacy/safety studies <link to study proposals> and other ongoing clinical studies <link> should resolve….
The remaining uncertainties are expected to be…….

The appraisal decision-relevant uncertainties that are expected to be outstanding lead to the following key research questions for the OBMEA:

- 1…
- 2…

The number of patients expected to receive treatment under the OBMEA is XX with XXX[4] included in the analysis, with minimum follow-up of YY. These data will be combined with pertinent data from other international sources for re-appraisal.
If an external comparator arm is required to answer the research questions, this should be addressed in the statistical analysis plan outlining methods for case matching, or in a separate protocol.

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[3] *Most health systems have exemptions for secondary use of patient data to improve individual patient care, but if a formal clinical trial is established, ethical approval will be required.*
[4] Include a sample size determination if possible

3. Patient Entry Process

Before considering entry of a patient into the OBMEA, the treating clinician should discuss treatment options and the requirements of the OBMEA with the patient or their carer/informal care-giver to ensure shared decision-making. This may include discussion of elements such as the benefits and risks of the treatment, how their eligibility will be determined, the expectations of the patient in the OBMEA beyond usual clinical practice (e.g. treatment adherence for the duration of the Agreement, prohibited medications, travel to clinic for regular assessments, treatment continuation according to specific criteria, restrictions on entering other clinical studies, willingness to record/electronically capture patient-reported data).

If data collection is not within a standardized health system structure which is an "opt-out" setting, patients or their carer/informal care-giver may be asked to sign a Patient Agreement/ Consent Form to indicate they understand the OBMEA and their role in it including collection of patient-reported data, adherence to treatment, attendance for clinic visits and consent for use and appropriate sharing of data[5].

Patients will be given a plain-language leaflet about the entire OBMEA process, what is expected of them and how their data will be used[6].

[Describe the system by which patients are approved for entry – a few simple explanations are suggested.]

Baseline patient data are entered into an electronic system that automatically checks patient eligibility according to the pre-specified criteria. Dispensing notification is sent to the relevant pharmacist.

Baseline patient data are entered by a physician and reviewed by the local prescribing committee or a national expert panel.

All patients who transfer from a clinical trial or expanded access programme or who have been paying for private treatment will be deemed eligible for treatment in the OBMEA and will be subject to the continuation criteria. If relevant data have been collected on the patients and the data are accessible, they will be analyzed as a separate sub-group.

4. Patient Eligibility

4.1 Inclusion Criteria

List clinical criteria for inclusion….

4.2 Exclusion Criteria

List clinical criteria for exclusion….

If it is not possible to measure an outcome in a group of patients, such as patients in a specific state (walk test in non-ambulant patients) or with a co-morbidity (cognitive impairment), then a joint clinical decision will be made about an alternative measure for all such patients (e.g. via the Monitoring Committee, section 6).

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[5] See NICE Example, page 16 onwards https://www.nice.org.uk/guidance/hst12/resources/managed-access-agreement-pdf-6968825245

[6] see example from the MPS Society – this should be developed with the patient groups, but funded by the MAH/Payer

Patient eligibility will be judged by a central panel.

If a patient or carer/informal care-giver feels the assessments to determine eligibility for the OBMEA have been performed incorrectly, the patient may have the assessments repeated at another treatment centre within the health system jurisdiction.

4.3 Continuation Criteria

The need for continuing treatment will be assessed at <x-monthly> intervals.

List clinical criteria for continuation of treatment
Note how dose adjustments, adverse events, allowance of short drug holidays etc will be managed.

A patient may withdraw consent to treatment and data collection at any time without prejudice to other treatment choices. This will stop their access to RDT and they may not be permitted to re-enter the OBMEA.

5. Data Management

Ensure this section addresses details about the
- research design
- outcomes to be collected
- source(s) of data/data platform
- data analysis plan
- ownership of data
- publication rights.

All data will be managed in accordance with signatories' governance processes (reference data management processes).

Data will be collected on XXX patients in the OBMEA until the end of the data collection period (including after treatment discontinuation) or until patient consent is withdrawn. Baseline data will be collected on all patients who are considered for the OBMEA but are deemed ineligible or decide not to participate.

Table X presents the required assessments and their frequency of measurement. This is a minimum dataset that is expected to resolve/reduce the decision-relevant uncertainties, but seeks to avoid unnecessary administrative burden on clinics and patients. This includes patient identification, baseline characteristics, treatment (Tx) information, eligibility criteria, key efficacy and safety outcomes and resource utilisation.

Table X. Data Collection Plan

Uncertainty/ Research Question	Data Item (Data Source)	Baseline	Follow-up 1	...	Follow-up X	End of TX (EoT)	EoT +1	..	EoT +Y

Table Y presents more details about the data sources.

Table Y. Data Sources

Data Source	Data Owner	Sufficiency
Bespoke national (treatment) registry	Health Provider/ Expert Centre	Comment on purpose of each data source, its relevancy to the OBMEA, whether it is quality assured, is linkage possible, timeliness, etc
National or international disease registry	Registry Holder[7]	
Health system (prescribing, mortality, administrative, laboratory test, resource utilisation etc)	Health Provider/ Payer	
Clinic specific data, e.g. collected via eCase Report Form	Clinician/ Expert Centre	
Patient reported outcomes (paper-based)	Patient	
Electronic patient reported information	Patient/ App Server/Host	
Patients receiving treatment outside the OBMEA	MAH/ Expert Centre/ Clinician	

Clinicians are expected to report adverse events according to regulatory requirements.

If data entry is not a pre-requisite for dispensing, treating clinicians will be required to enter all data within one month of treatment commencement and each clinic visit.

When data collection is substantially different from routine practice, training will be provided. This should occur before a centre starts entering patients into the Agreement, and after a few patients, to resolve queries.

Data will be subject to electronic verification where possible and quality checks to improve accuracy and completeness. Given the real-world nature of clinic visits, data rules will need to be applied to the data (e.g. windows around treatment visits).

All data will be collected in accordance with EU General Data Protection Regulation/National Data Protection Legislation. Treating clinicians will have access to de-anonymized data of their own patients for the purposes of optimizing individual patient care. Data processors (e.g. registry staff) may also have access to individual patient data and will work under strict confidentiality agreements. For all other purposes data will be (pseudo)anonymized using national procedures or presented in aggregate to ensure good data governance.

Data owners have responsibility for data protection within their own organisations and robust processes must be established to enable appropriate data sharing with the MAH/ Payer/ Expert Centre who is responsible for analysis. XXX procedures ensure safe data storage and access. Responsibilities are delineated further in the data processing agreement.

[7] E.g. European Reference Network, Specialist Society

Data transferred to the HTA body/MAH will be stored for no more than five years following the end date of this OBMEA, or no more than 10 years after initiation, whichever is shorter.

The plan for management of the real-world data and statistical analysis will be finalized in the early stages of data collection and published.

A report or publication summarising the data collected in the OBMEA will be published after the OBMEA is complete. Publications are not permitted by any party during the OBMEA.

6. Reviews

A multi-stakeholder Monitoring Committee[8] will be established to review progress and recommend actions to support successful conduct and completion of the OBMEA.
The MAH will provide information about any major alterations imposed by the regulator that may impact treatment[9].

Rare diseases are often heterogeneous in their disease course and so non-standard cases may arise. These will be discussed by the Monitoring Committee.

The MAH/Payer/Expert Centre/Registry Holder will provide standardized six-monthly/annual reports summarizing the number of patients treated under this Agreement in each participating clinic. Information about data quality and quantity for the outcomes will be scrutinized according to the planned patient entry numbers.

For an RDT, it is often difficult to predict the number of patients who may be eligible for treatment. Therefore, the Monitoring Committee will review the progress of recruitment carefully to review contribution of all centres and seek to ensure that all patients in the jurisdiction have equal access to treatment.

Clinical monitoring activities will be undertaken to improve recruitment and quality of data collection in individual centres. Issues arising in several centres, for example in relation to patient treatment or data collection, will be addressed in a Frequently Asked Questions document sent to all centres. This will be a living document throughout the lifetime of this Agreement.

The plan for data management and statistical analysis, and any revisions to address data issues, will be approved by the Monitoring Committee.

A review may trigger revision of the end date – to lengthen due to limited data or to expedite. The Monitoring Committee will report progress to the appraisal committee about half-way through the data collection period and produce a final report for input to the re-appraisal.

7. Re-appraisal/Pricing and Reimbursement Decisions

At the initiation of the re-appraisal, the MAH will make an evidence submission presenting analyses based on data from this Agreement and other relevant international sources, to address the uncertainties outlined in the appraisal. This could include (but is not limited to) new epidemiological studies (such as natural history), new trials, long-term follow-up information (including the latest EMA Periodic Safety Update Report), analyses relating to the clinical uncertainties, a revised economic model (showing how assumptions have been changed in light of new evidence).

[8] See IMPACT HTA Monitoring Committee ToR
[9] E.g. eligibility criteria, safety issues to be considered at discontinuation, dosing

Signatories to this Agreement will be given the opportunity to contribute to the re-appraisal process. Patient groups will be supported to prepare an IMPACT HTA patient group submission for re-appraisal to capture insights additional to those in the formal data collection.

It is expected that the OBMEA will terminate after re-appraisal resulting in the RDT being fully reimbursed/recommended for routine use, or not being listed/withdrawn from use. (If the monitoring process has been able to extend the period of data collection to be sufficient and modified the Agreement to address emerging issues, it is unlikely that there will be a need to extend the OBMEA after re-appraisal, but this is also this possibility.)

8. Responsibilities

This Agreement has been entered into with the approval of the "signatories", for action by them and *[list any stakeholders who are not signatories but who will be expected to act in accordance with this agreement]* clinicians and pharmacists.

Signatories to the Agreement have agreed (made a covenant) to do all they can to ensure the best possible data are collected for the OBMEA.

Signatories are given the right to contribute to any review of the Agreement.

The Payer agrees to pay the agreed price for appropriate use of the RDT (eligible patients, in accordance with continuation criteria) and in accordance with any individual patient outcomes-based agreement (e.g. based on early response or refund due to lack of response).

The MAH/Payer/Expert Centre/Registry Holder is responsible for the cost of collecting, monitoring, cleaning and analyzing the data.

The MAH commits to the planned re-appraisal review/pricing and reimbursement decision process, bearing any costs and in accordance with processes at the time of the review (which may be different from the initial appraisal).

Clinicians are responsible for entering the necessary data on their patients within 4 weeks and responding to data queries within 2 weeks.

Patients agree to collect patient reported data manually within the agreed timeframes/to use electronic devices.

Any party wishing to publish data from the OBMEA (after completion) must obtain approval of the data owner and for this case of rare diseases take particular care that no patient can be re-identified. All publications should acknowledge the OBMEA signatories and share a final copy with them.

If the MAH does not respect this Agreement, the Payer is entitled to revise it in consultation with the other signatories.

Figure 7-9: IMPACT OBMEA tool: Public documentation template [91]

Evaluation criteria for data quality

Category	Quality criteria
Mandatory criteria to ensure data quality	▪ Detailed registry description (aim, registry protocol) ▪ Exact definition / operationalization of exposures, clinical events, outcomes and confounders ▪ Current data plan / coding manual ▪ Training on data collection and recording ▪ Clearly defined inclusion and exclusion criteria for registry patients ▪ SOP system for data collection ▪ Package of measures to ensure the accuracy of data and to provide information on error rates (e.g. source data verification, internal and external audits, IT-supported checks [e.g. cross-reference checks]) ▪ Documentation trail - documentation of process and definition changes in the registry ▪ Scientific independence of the registry ▪ Sustainable financing
General criteria that are regularly relevant for registry studies for benefit assessments	▪ Use of exact dates for patients, disease and events ▪ Detailed information on the drug therapy (active substance, dose, dose change, including dates) ▪ Timeliness (including rapid availability and punctuality of the required results)
General criteria that may be relevant for registry studies for benefit assessments, depending on the research question	▪ Use of standard classifications (e.g. ICD-10) and terminology (e.g. MedDRA) ▪ Use of valid standard survey tools (questionnaires, scales, tests) ▪ Flexibility and adaptability (e.g. for embedding studies, for further data collection, in the event of changes in the health care situation) ▪ Linkability with other data sources
Criteria whose degree of fulfilment is to be assessed with regard to components of the research questions[a]	▪ Representativeness of the sample / selection of the sample ▪ Completeness of data per data collection time point (lost-to-follow-up, drop-outs) ▪ Completeness of data collection time points ▪ Correctness of data ▪ Collection of data on all confounders relevant for the research question ▪ Data consistency over time
a: The criteria mentioned are important criteria of data quality, but can only be assessed in relation to specific questions. On the one hand, for example, "accuracy of data" and "consistency of data over time" only refer to data that are relevant to the respective question. On the other hand, "representativeness of the sample" refers only to the population relevant to the research question, but not to the entire registry population. ICD: International Statistical Classification of Diseases and Related Health Problems; IT: information technology; MedDRA: Medical Dictionary for Drug Regulatory Affairs Activities; SOP: standard operating procedure	

Figure 7-10: Criteria data quality(Institute for Quality and Efficency in Health Care, p.8) [119]

7.9.5 Monitoring

Governance structure

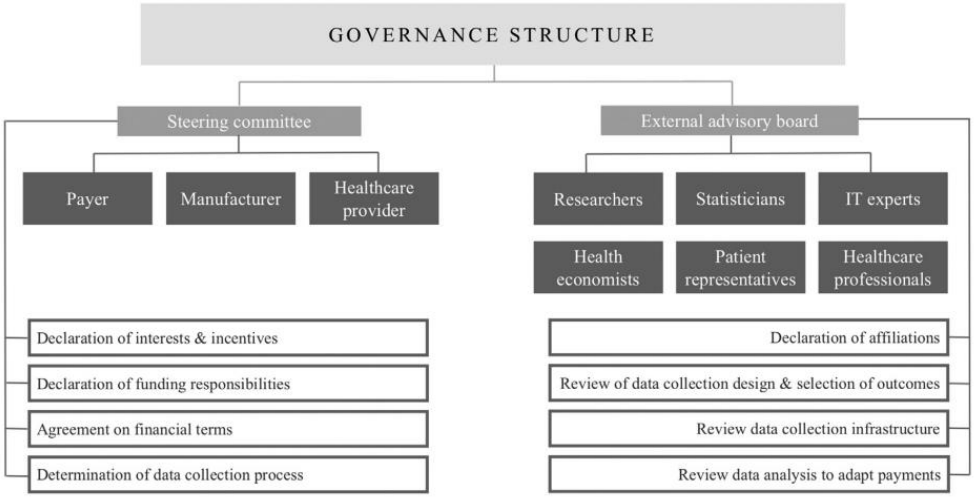

Figure 7-11: Governance structure for OBMEAs (Michelsen et al., 2020, p.12) [7]

Monitoring committee

IMPACT HTA

Improved methods and actionable tools for enhancing HTA

Template for Adaptation by HTA Bodies

MONITORING COMMITTEE TERMS OF REFERENCE FOR AN OUTCOMES-BASED MANAGED ENTRY AGREEMENT OF A RARE DISEASE TREATMENT

March 2021

This template provides an outline terms of reference for the "Monitoring Committee" of an Outcomes-Based Managed Entry Agreement (OBMEA) of a rare disease treatment.

It uses terminology that comes from the IMPACT HTA Template for OBMEA and should be adapted to suit the healthcare system.

It has been developed from a document used by the National Institute for Health and Care Excellence taking account of knowledge gained in IMPACT HTA Work Package 10 and revised after consultation with the international HTA community.

For any queries contact Karen Facey: karen.facey@ed.ac.uk .

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The results presented reflect the author's views and not those of the European Commission.

OUTCOMES-BASED MANAGED ENTRY AGREEMENT

MONITORING COMMITTEE TERMS OF REFERENCE FOR RARE DISEASE TREATMENT IN REIMBUSED INDICATION

REMIT OF MONITORING COMMITTEE

This is not intended to be a "Data Monitoring Committee" as used in a clinical trial (with responsibility for reviewing accruing data to monitor safety and decide termination according to an interim analysis plan). This RDT has been authorised by regulators and is being used within its licensed indication in clinical practice, so usual safety reporting and local clinical governance measures apply.

The purpose of an "OBMEA Monitoring Committee" is to bring together all stakeholders involved in a specific OBMEA to ensure that the real-world data being collected, perhaps from various sources, are of as good quality as they can be. The Committee may also advise on remedial activities to improve data quality, for example if they see issues in a particular centre, or common challenges in obtaining a particular assessment.

The Monitoring Committee is an advisory committee, responsible for ensuring the Outcomes-Based Managed Entry Agreement (OBMEA) of rare disease treatment (RDT) in reimbursed indication is implemented in line with the arrangements agreed. The Monitoring Committee oversees the implementation of the OBMEA and provides guidance on issues that arise with collecting the data in clinical practice.

This document describes the composition of the OBMEA Monitoring Committee (the "Committee") and its functions including proposed membership, responsibilities of the members and meeting arrangements.

BACKGROUND TO THE OBMEA

Summarize appraisal recommendation or pricing and reimbursement decision about the RDT and why the OBMEA was established. Refer to the HTA or reimbursement report and published OBMEA documents.

Refer to details about responsibilities for data collection, management and reporting in the OBMEA, clearly explaining how data will be shared to ensure patient confidentiality.

PURPOSE

Describe remit of the Committee. Consider including elements such as:

The Committee will meet quarterly and shall be responsible for monitoring the implementation of the OBMEA and recommending actions to support its operation.

This includes:

i. Monitoring progress of data collection as described in the OBMEA to ensure data quality and completeness, considering issues such as:
   a. patient enrolment
      i. in each centre
      ii. checking prescribing figures vs entries in the data collection system
      iii. checking recruitment rate and if slower than anticipated exploring reasons for this
   b. checking relevant assessments are being undertaken at appropriate timepoints (even after treatment discontinuation) and data is of good quality and any challenges in clinical practice are resolved (e.g. accessing genetic tests)
   c. agreeing reasonable adjustments for patients unable to perform assessments
   d. agreeing data management rules (e.g. increasing time windows around visits, managing missed visits etc)

ii. Reviewing 6-monthly/annual status updates on the sufficiency of the data with regards to the anticipated re-appraisal date and any treatment issues (e.g. as identified in adverse events or reasons for discontinuations)

iii. Addressing feedback from clinicians and patients about any issues

iv. Discussing proposed amendments to the OBMEA (which would be subject to renegotiation by with signatories).

v. Agreeing information leaflets and project updates to be shared with stakeholders (patients, carers, clinicians, health service).

vi. Providing a mid-term report to the appraisal/pricing and reimbursement committee about progress.

vii. Presenting a final report on the OBMEA to the HTA/Payer staff and appraisal/pricing and reimbursement committee at the outset of the re-appraisal. This should document any challenges faced in data collection for consideration in the critical assessment and re-appraisal deliberations.

The Committee will not:

i. Discuss or negotiate the commercial/pricing arrangement.

ii. Consider any new data with a view to requesting to expand the existing recommendation from the appraisal committee.

iii. Make other major amendments to the OBMEA

iv. Discuss or review individual patient cases.

MEMBERSHIP

The membership of the Committee is as follows:

- *Describe membership, this should include representatives of all the signatories to the OBMEA and may include others such as HTA/Healthcare Payer staff, treating clinicians, patient group representatives, Marketing Authorisation Holder.*
- *Indicate if there are sections of the meeting that can only be attended by certain members due to confidentiality.*

Members are expected to serve for the duration of the OBMEA.

Quoracy is reached when the following members are in attendance:

- *Define essential bodies to be represented and minimum number/percentage of members to be in attendance.*

If a Committee member is unable to attend a meeting, they may send their views to the chair/co-chair to be considered by the committee or send a nominated deputy. The deputy must abide by the rules of the committee, including confidentiality agreements.

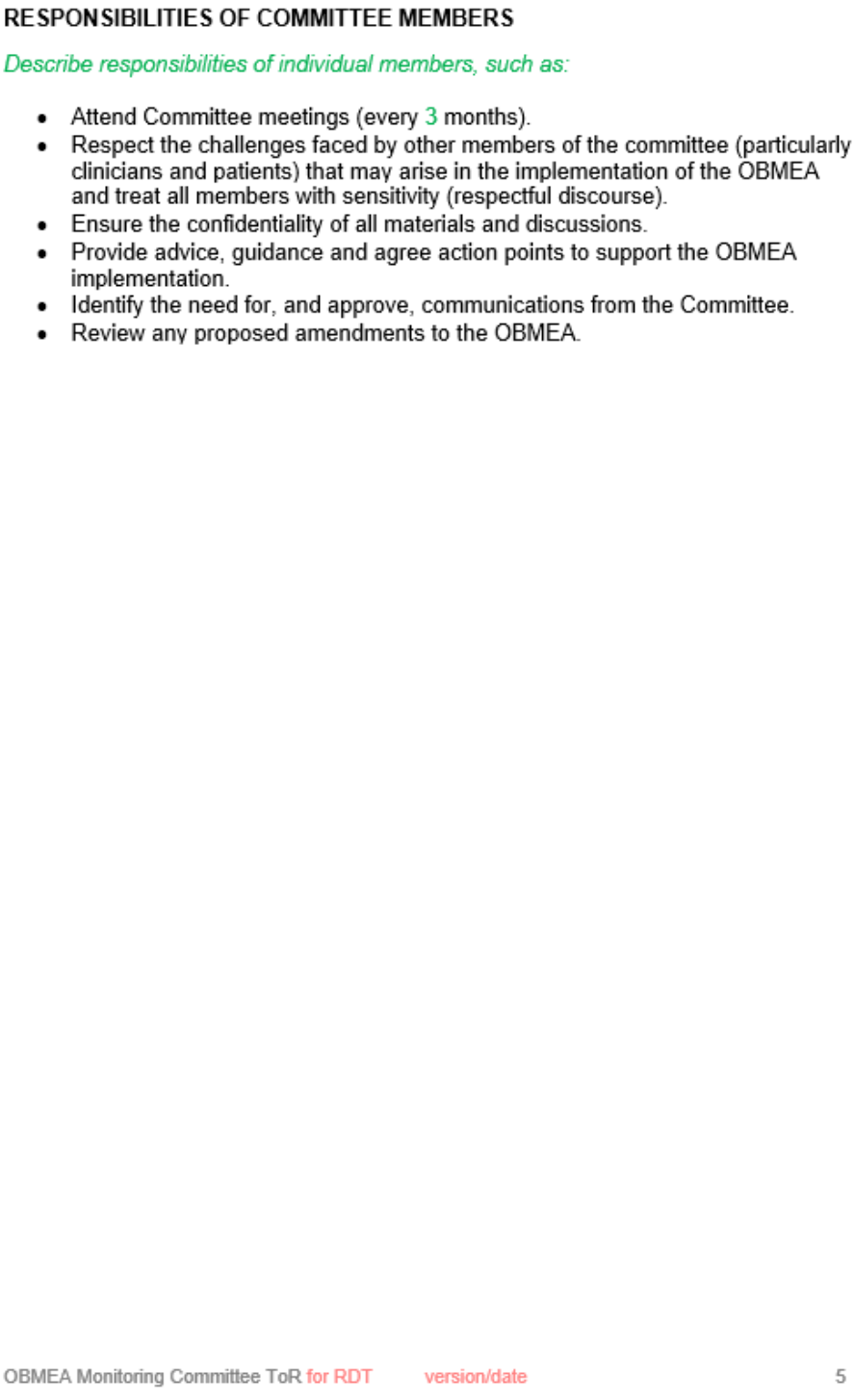
Decisions will be made via consensus, wherever practicable.

GOVERNANCE

The HTA body/Expert Centre/Registry Holder will act as Secretariat to the Committee: issuing meeting papers, chairing the meeting, preparing minutes.

Describe governance measures such as:

- All members of the Committee will be required to complete a Confidentiality Agreement form and Declaration of Interests form before attending any meetings involving discussion of the OBMEA.
- The data reports and information disclosed during the Committee meetings are strictly confidential and must not be shared or discussed with anyone outside of the Committee.
- Any confidential information will only be shared with the Committee via *<describe secure system>*.
- Any issues relating to the conduct of the Committee meetings will be escalated to the OBMEA signatories.
- Any breach of the confidentiality agreement could result in the member(s) concerned and their organisation being removed from the Committee.



RESPONSIBILITIES OF COMMITTEE MEMBERS

Describe responsibilities of individual members, such as:

- Attend Committee meetings (every 3 months).
- Respect the challenges faced by other members of the committee (particularly clinicians and patients) that may arise in the implementation of the OBMEA and treat all members with sensitivity (respectful discourse).
- Ensure the confidentiality of all materials and discussions.
- Provide advice, guidance and agree action points to support the OBMEA implementation.
- Identify the need for, and approve, communications from the Committee.
- Review any proposed amendments to the OBMEA.

OBMEA Monitoring Committee ToR for RDT version/date 5

Figure 7-12: IMPACT OBMEA tool: Monitoring Committee [91]

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Health Technology Assessment
GmbH