RWE4Decisions Case Studies Workshops – June 2021

Generating Real-World Evidence in Outcomes-Based Managed Entry Agreements: Two Fictitious Case Studies

Report of Proceedings

Executive Summary

Coverage with Evidence Development (CED) is a form of Outcomes-Based Managed Entry Agreements (OBMEA) that can enable patient access to promising treatments whilst collecting additional data to enable re-appraisal. CED in clinical practice is complex and the ability of such schemes to deliver sufficient data to influence pricing and reimbursement renegotiations or alteration of treatment use is often questioned. However, with the increasing number of highly innovative treatments coming to market with limited clinical data, and advancements in digital health, there is renewed interest in use of CED. Alongside this, there is recognition that CED should only be instigated when "decision relevant" uncertainties can be resolved by data collection within a timeframe that will inform re-appraisal. Furthermore, they should be the "exception and not the norm".

With this context, RWE4Decisions held trans-national multi-stakeholder workshops to discuss CED plans for two fictitious highly innovative treatments for rare disorders. The nature of the fictitious treatments was contrasting as one treatment was life-long and the other once-in-a-lifetime. Each rare disease had no existing disease modifying treatments, and the new treatments had a high price and major uncertainties in the evidence base available to HTA/Payers.

Pros and cons of real-world data sources that might resolve the decision-relevant uncertainties were considered. Challenges in accessing the data arising due to the rarity of the condition, alignment of post marketing data collection requirements, publication of detailed data collection plans and data governance of data provided by highly specialised centres were discussed. Potential actions that could be taken by individual stakeholders or collaborative initiatives were agreed.

Action	Lead Stakeholder
1. To enable rapid implementation of an Outcomes-Based Managed Entry Agreements (OBMEA) using Coverage with Evidence Development (CED), the potential need for post reimbursement data collection should be discussed in advance. **National or collaborative horizon scanning processes should identify products that might require OBMEA and undertake iterative dialogues (scientific consultations) with the sponsor company, regulators, clinical experts and patient groups to discuss potential data sources (e.g., disease registries, health system data, patient reported outcomes, regulatory studies).** This should include initiation of governance processes to access data. This could be undertaken for a particular disease, or type of therapy, as well as individual treatments.	Horizon scanning collaboratives

Action	Lead Stakeholder
2. **CED should only be initiated when sufficient data can be collected to resolve decision relevant uncertainties and the re-appraisal will lead to a decision that can be enacted** (full reimbursement, disinvestment, alteration of eligible population/treatment regimen). This requires collaboration and alignment of all stakeholders in the process and clarity on how the evidence will be used in subsequent decision-making.	All stakeholders in a health system
3. **HTA/Payers need to clarify the decision-relevant uncertainties that arise from appraisal of the evidence to drive discussions with stakeholders about the data to be collected in CED**. Data collection needs to be kept as simple as possible, focusing on the most meaningful outcomes related to the decision-relevant uncertainties that can be reliably collected within the timeframe for re-appraisal. Identification of key clinical questions.	Individual HTA/Payers
4. **For rare diseases, collaboration across countries to align data collection requirements and access to datasets is needed**. This requires agreement on a minimum data set, the feasibility (or not) of collecting data of sufficient quality and methods for data amalgamation.	HTA collaboratives
5. Processes need to be developed for Payers to interact with regulators to be kept informed of their post marketing data collection requirements and avoid duplication of effort, and to use DARWIN.	HTA/Payers/ Regulators/ Industry
6. For CED to be successful a **proactive approach to data collection involving all relevant stakeholders needs to be enacted**. This includes clear responsibilities for data collection, processing, querying and analysis, to improve quality and monitor sufficiency for re-appraisal.	All stakeholders
7. **Data collection plans should be clearly documented in a publicly available report**, possibly via the IMPACT HTA template for OBMEA.	HTA bodies
8. **RWE4Decisions should collect relevant guidance relating to generation of RWE in a repository and help develop bespoke HTA/Payer guidance for transnational use**.	RWE4Decisions
9. Financial investment in data infrastructure, collection and analysis is needed to support enactment of CED schemes that can inform optimal of use of high-cost therapies, including reduction of treatment costs.	National Governments/ EU/ Industry
10. **A demonstration project of a OBMEA CED for a highly innovative technology enacting these recommendations should be undertaken by an HTA/Payer collaborative group** such as BENELUXAI or FINOSE. This could be a 2-step approach: 1° agreement on a minimal clinical data set for national data collection and 2° connect national data collection cross-border, and with larger networks.	HTA Collaboratives

Contents

Glossary

ATMP	Advanced Therapeutic Medicinal Product
CED	Coverage with Evidence Development
CIBMTR	Center for International Blood and Marrow Transplant Research
EBMT	European society for Blood and Marrow Transplantation
EHDEN	European Health Data and Evidence Network
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERN	Expert Reference Network
EU	European Union
EUnetHTA	European network for HTA
GDPR	General Data Protection Regulation
HTA	Health Technology Assessment
INAMI	National Institute of Health and Disability Insurance, Belgium (when translated)
ISCT	International Society for Cell and gene Therapy Europe
JACIE	Joint Accreditation Committee of ISCT and EBMT
MAH	Marketing Authorisation Holder
MEA	Managed Entry Agreements
MINERVA	Metadata for data dIscoverability aNd study rEplicability in obseRVational studies
NHS	National Health Service
OBMEA	Outcomes-Based Managed Entry Agreements
OECD	Organisation for Economic Cooperation and Development
OMOP	Observational Medical Outcomes Partnership
OPTIMAL	Operational, TechnIcal, MethodologicAL framework
PAES	Post Authorisation Efficacy Study
PASS	Post Authorisation Safety Study
PLEG	Post Licensing Evidence Generation
PRO	Patient Reported Outcomes
QOL	Quality of Life
RCT	Randomized Controlled Trial
RWD	Real World Data
RWE	Real World Evidence
SMA	Spinal Muscular Atrophy

About RWE4Decisions

RWE4Decisions is a multi-stakeholder initiative commissioned by the Belgian National Institute of Health and Disability Insurance (INAMI-RIZIV). It brings together HTA bodies, payers, regulatory agencies, policy makers, clinicians, patient groups, researchers, industry and academic experts to discuss challenges and potential solutions for generation of real-world evidence to inform decisions about highly innovative technologies. RWE4Decisions – Real World Evidence for Decisions

For further information contact the RWE4Decisions Secretariat on secretariat@rwe4decisions.com.

Status and citation of this report

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1. Background

Highly innovative technologies are often expedited through regulatory systems and come to market with limited, immature clinical trials, which results in uncertainties in the evidence base that are crucial to certain decision-makers. There is increasing interest in how this evidence from clinical research can be complemented with real-world data (RWD) to better inform challenging decisions made by health technology assessment (HTA) bodies, payers and other competent authorities for pricing and reimbursement (CAPRs) about the added value of these technologies.

In 2020, the RWE4Decisions initiative ran workshops with a light-touch scientific consultation process about real-world evidence (RWE) generation plans for three treatments in clinical development using the TRUST4RD taxonomy (Annemans and Makady 2020). Confidential feedback was given to the companies about the evidence generation plans for their treatment and general learnings were extracted. It was concluded that iterative multi-stakeholder dialogues/scientific consultations during the life cycle of an innovative technology could be helpful to discuss potential RWE approaches that might augment the evidence arising from clinical research. The importance of a transparent and robust approach to development of RWE was emphasized, including the need to publish protocols and analysis plans. Recommendations included:

1. Need to engage with other EU-wide collaborations – particularly the European Reference Networks (ERNs) and European Joint Project on Rare Diseases to ensure HTA/payer needs are understood when disease registries are developed and to ensure payers can have access to relevant data.
2. Payers need to be clear about what data are required post-HTA/reimbursement and collaborate to define a layered core dataset outlining data that identifies essential, important, or nice to have data.
3. International disease-based registries are recommended - but issues relating to content, funding, management and ownership need to be discussed.

In 2021, the focus has been on the requirements for RWD collection post-HTA.

Sometimes it is not possible for an HTA/payer/CAPR to recommend/reimburse use of a promising highly innovative technology because there are uncertainties about important aspects of the added clinical benefit or value for money compared to best standard of care ("decision-relevant uncertainties"). Conditional reimbursement/recommendations may be granted with an outcomes-based managed entry agreement (OBMEA) to try to resolve the decision-relevant uncertainties, with reimbursement based on the response of individual patients, or on a cohort of patients that will be analyzed at a future date. Individual-based OBMEA may apply eligibility criteria for treatment initiation and continuation, but a lower price is paid, no payment, or refund received for a patient that does not achieve a pre-specified response. Such agreements are administratively burdensome for reimbursement processes. Population-based schemes, which include Coverage with Evidence Development (CED) (KCE 2017) or Post-Licensing Evidence Generation (PLEG) (EUnetHTA 2020), can be used when the decision-relevant uncertainties may be resolved by data collection within a reasonable timeframe. However, CED schemes are complex and their ability to deliver

sufficient good quality prospective data within a limited timeframe to influence re-appraisal or subsequent pricing and reimbursement renegotiations is often questioned. Recent research interviewing CAPR experts discussed whether the EU regulatory post-authorization requirements for 15 newly authorized medicines could be sufficient for CAPR purposes (Eichler et al. 2021). Few OBMEAs were in place for these medicines, but it was felt that the regulatory post-authorization data could potentially have helped resolve some of the uncertainties faced in pricing and reimbursement. However, some CAPRs felt that the public information provided by the EMA was insufficient to support the implementation of payer OBMEA, but potential for collaboration across CAPRs was noted.

A review of the 25 CED schemes used with high-cost hospital medicines in the Netherlands between 2006 and 2012 (Makady et al. 2019) found numerous aspects relating to OBMEA design and implementation that negatively impacted their value to decision-makers. Only 12 CED schemes had been finalised and re-appraised at the time of publication. Eleven of these extended the data collection and reporting period beyond the standard of four years, to an average of six years. The assessment committee concluded that the evidence submitted at re-appraisal was sufficient to assess appropriate use in Dutch clinical practice in 9/12 cases, but only sufficient for cost effectiveness in 7/12 cases. Furthermore, insufficient evidence was generated for one-third of the research questions stipulated in the OBMEA. In 10 cases, continued reimbursement was recommended, with six of these requiring further additional data collection. In two cases, advice to discontinue reimbursement was not implemented at the time of publication.

Discussion by Makady et al (2019) provides learning points for RWE4Decisions of (❖):

- ❖ A range of factors may have negatively affected the ability to undertake OBMEA in the Dutch setting within the 4-year reporting period, including:
  - time needed to setup new registries required for data collection, to compile and analyse data, and to assess and appraise
  - insufficient study period to capture outcomes of interest in different conditions.
- ❖ Value of Information analysis could have been used to determine the feasibility and value of data collection for specific parameters in the OBMEA.
- ❖ Regular review of research progress could have informed decisions about continuation, adjustment or termination of the OBMEA.
- ❖ A strategy for implementation of decisions after an OBMEA is needed, which is agreed among all stakeholders.

Internationally, the Organisation for Economic Cooperation and Development (OECD) found that it is difficult to evaluate the success of OBMEA given a lack of transparency in reporting sufficiency of data and impact of analyses arising from OBMEA, but that CED schemes generally have a poor record of success and the administrative burden of collecting and analyzing data requires substantial financial investment (Wenzl and Chapman 2019) .

In 2021, the RWE4Decisions initiative decided to explore issues relating to RWD collection in a OBMEA with CED, using two fictitious highly innovative technologies. The two cases related to promising therapies with different types of uncertainty – a recurring treatment given in a rare chronic condition that occurred in children and a one-off cell therapy for a refractory cancer. The objective was to determine what RWE could effectively address decision-relevant uncertainties to enable re-appraisal/input to pricing and reimbursement negotiations at some future point. Discussion was to include the potential use of European and international real-world data sources, such as registries, and consider the potential to develop trans-national approaches to align processes for OBMEA constructs, data collection and analysis across different health system jurisdictions.

2. Methods

Individuals with relevant experience in HTA, OBMEA and the clinical condition were invited to the workshops, aiming to get representation from HTA bodies, payers, clinicians, HTA academics, patient representatives, registry holders, pharmaceutical industry, research bodies, regulators and policy makers. The workshops were primarily designed for EU stakeholders but included other countries with similar forms of HTA and pricing and reimbursement processes, including EU accession countries, the European Economic Area, United Kingdom and Canada. A full list of participants is presented in Appendix 1.

All meetings were virtual. Two preparatory meetings briefly reviewed RWE4Decisions work (Annemans and Makady 2020), (Facey et al. 2020), discussed recent OBMEA initiatives and agreed the Terms of Reference for the workshops and outlines of the case studies.

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Each case study workshop began with a clinical presentation of the case study and the design of clinical trials, clarifications about the case study and discussion of the decision-relevant uncertainties for HTA/payers.

Breakout groups then reviewed the decision-relevant uncertainties and chose a few uncertainties to consider. Four questions were discussed in each workshop, with slightly different questions in workshop 2, learning from the experience of workshop 1. Each group had a scribe and facilitator, who had volunteered from the participant group. The Nominal Group Technique was used for plenary feedback, where for each question, one item was shared by each group in rotation and clarified, until there was saturation of ideas. The notes from the breakout rooms were reviewed by the relevant facilitator and used to augment the documentation from the plenary session. This report was drafted by the facilitator and all participants were invited to review it.

3. Review of Other Initiatives

In the preparatory meetings other initiatives relating to OBMEA of highly innovative treatments were discussed.

Discussion of the EUnetHTA PLEG pilot for nusinersen in spinal muscular atrophy (SMA) (EUnetHTA Joint Action 3 2020b, 2020a) yielded the following key points and learnings (❖).

- A large number of evidence gaps were reported by various countries after the HTA. However, it does not appear that all of these are critical to HTA/payer decision-making. It is important to consider the feasibility of collecting sufficient, good quality, timely data for reappraisal and identify the truly decision-relevant uncertainties.
    - ❖ Seek to identify the truly decision-relevant uncertainties that are feasible for resolution by timely RWD collection.
- The EUnetHTA publications of the evidence gaps and minimum dataset for the OBMEA were issued approximately two years after the pricing and reimbursement decisions were agreed in most countries and more timely collaboration to create such reports is needed.
    - ❖ Enact processes that support timely agreement among HTA/payers on the minimum dataset for each OBMEA.

- In Finland, there is no national registry for SMA and so it was planned to collect the PLEG data from two university hospitals using electronic health records. This would have required a data request and a permit for secondary use of health data from the national authority, Findata. The data request and data permit application would have required more and different types of information than were available in the EUnetHTA reports and there was insufficient resource and time to develop the necessary documentation within the EUnetHTA pilot.
    - ❖ Develop protocols for OBMEA/PLEG data collection that are sufficiently detailed to enable development of the necessary documentation for permits to access national health and care data for secondary use.

- The PLEG pilot was unclear about how data would be used across borders. This was to be considered at a later stage but was not addressed due to delays that occurred due to the pandemic.
    - ❖ If it is intended to aggregate data across jurisdictions, trusted processes that safeguard the privacy of patient data are needed - The circumstances in which access to individual level data might be needed vs use of aggregated data should be clarified.
    - ❖ Improved processes for patient consent need to be developed.
    - ❖ It should be clarified that OBMEA are part of health service evaluation to inform decision making and not research per se, recognizing that for research ethical approval would be needed, but that appropriate governance is needed in either case.

The EU-funded IMPACT HTA project has undertaken a comprehensive review of the AIFA registries for MEA in Italy, showing the streamlined nature of a bespoke national web-based platform. This includes details of the data collection plans for each treatment/indication (Xoxi, Facey, and Cicchetti 2021). All of the 283 indication-based registries established since 2006, require outcomes to be collected to determine appropriate use of treatment in eligible patients, but only 60 (21%) use individual patient outcomes to determine refunds (so-called Payment by Results). In r2017 a new process to evaluate innovation was instigated and this has led to a reduction in the number of outcomes-based agreements. There is no CED, but the data collected in registries are used to inform pricing and reimbursement decisions in a confidential manner. The AIFA registries closely reflect the indication approved by the regulators, with eligibility criteria similar to those in the main clinical trials.

Learnings (❖) taken from the IMPACT HTA AIFA registry review were presented as:

- ❖ National web-based registry systems for data collection in MEAs can efficiently collect data with real-time quality checks and produce clear reports of status at regular intervals.
- ❖ National web-based MEA systems may result in duplicate data entry in addition to standard health data collection systems, thus placing burdens on physicians and pharmacists
- ❖ National web-based individual-based OBMEA could aggregate data to inform pricing and reimbursement re-negotiations and optimization of treatment delivery.

IMPACT HTA also worked with experts in the EU, Canada and Australia to determine how OBMEA were implemented for nusinersen in SMA and tisagenlecleucel in haematological cancers (Facey et al. 2021). This research identified that several countries reimbursed the products without data collection, whereas others implemented individual or population-based OBMEA. The formal documentation of the data being collected to resolve uncertainties was publicly available, but not always easily accessible (often in non-English in a specific area of a pricing and reimbursement website). There were many similarities in the data collected across the countries, but also some differences. Only a few countries included multi-stakeholder input in the development of the OBMEA. In the countries that undertook CED,

more purposeful approaches to data collection have recently been developed to take a proactive approach to ensure data quality and sufficiency for re-appraisal. For example, through a covenant of agreement among stakeholders to the Minister of Health (the Netherlands) or through regular multi-stakeholder monitoring meetings to resolve practical assessment and data collection issues in the real-world setting (England). This group recommended that plans, interim and final reports for OBMEA should be made publicly available in an international repository.

Learnings from the IMPACT HTA OBMEA case studies were presented as:

- For rare conditions, there is a particular imperative to align requirements for RWD collection (core/minimum dataset) across decision-makers (regulators, HTA, payers) and across health system jurisdictions.
- Carefully planned approaches for data collection and monitoring are needed to ensure there will be sufficient RWD to create RWE at the time of re-appraisal that could resolve the decision-relevant uncertainties.
- Information about the constructs of OBMEA, interim reports on progress and final reports after re-appraisal need to be brought together in an international, public repository.

IMPACT HTA took the legal template for pricing and reimbursement of medicines in Belgium and the documents outlining the data collection arrangements from the OBMEA case studies in Australia, England and Ireland to develop a standard template for data collection in OBMEA. This was consulted upon internationally and is now widely available for use.

- The IMPACT HTA template for data collection in an OBMEA could help align implementation of OBMEA across jurisdictions.

To address the practical and technical challenges faced by patients with rare diseases accessing advanced therapeutic medicinal products (ATMPs), EURORDIS established the RARE IMPACT collaboration in 2018, which is currently in its second phase. The aim of the initiative is to provide an efficient and predictable pathway to access ATMPs by aligning standards for evidence generation across decision-makers and coordinating registry infrastructures to improve the evidence base for ATMPs. This will be achieved in three workstreams. The consultancy Dolon is leading work on the pricing and economics of ATMPs, whilst EURORDIS is leading work on evidence generation for ATMPs, and criteria for accreditation of specialist centres. A key deliverable of phase I has been a series of reports reviewing the challenges and actionable solutions for improving patient access to ATMPs in 10 European countries considering four domains of assessment, affordability, availability and accessibility.

4. Workshops Scene Setting

Dr Diane Kleinermans, President of the Commission for Reimbursement of Medicines, on behalf of Mr Jo de Cock, Chief Executive at INAMI, reflected on the issues faced by payers and the rationale for the workshops.

In recent years, new, increasingly sophisticated health technologies have been developed that are often aimed at increasingly targeted populations. At the same time, the pressure of various stakeholders to speed up access to these promising therapies is growing. This means that marketing authorisations are often based on limited data in small populations covering a short time-period. For example, orphan medicinal products may obtain a marketing authorisation based on a single arm phase II study in a dozen patients or based on registry data. This does not provide robust answers about the entire scope of a medicine.

The health system budget is limited and 1€ can only be spent once. The added benefit and value for money of a new treatment must be determined. This challenges payers who have to make pricing and reimbursement decisions, which affect access to these new therapies, while many uncertainties persist about the real-life and long-term effectiveness, and optimal use of the treatment.

To address this problem, OBMEAs have been implemented by some payers to provide patients with early access to innovative drugs, whilst limiting budgetary risk and aiming to answer key uncertainties. Resolution of the uncertainties in the framework of an OBMEA is often based on the collection of RWD, with the aim of generating RWE, which can support the final decision of the payers, after a re-appraisal, at some time in the future. However, several payers have had frustrating experiences with OBMEA, with the answers to the most important, decision-relevant, uncertainties often not, or only partially, available at the end of the OBMEA timeframe. Reasons for this are multi-factorial, including insufficient time to collect the data, poor quality data and difficulties to interpret them, lack of data, lack of clarity about the decision-relevant uncertainties, lack of collaboration amongst stakeholders, etc.

Nevertheless, payers still believe that the use of RWE is one of the tools that can be used to reduce uncertainties and support pricing and reimbursement decisions. However, RWE cannot meet all the evidence needs and analytical methodologies are still in their infancy. More clarity is needed on what RWE can achieve, and what it cannot. Just as it has taken years in the previous century to regulate randomized controlled trials to ensure their robustness and quality, similar work is required for RWE, to ensure quality, interpretability and usefulness.

Belgians are recognized as pragmatic people and Jo de Cock, who leads the RWE4Decision initiative strongly believes in multi-stakeholder dialogues to air issues and discuss solutions using the concept of “learning by doing”. Hence to enable open discussion among stakeholders, with a public output, these workshops used fictitious cases that are a plausible representation of the types of diseases and treatments that have been most challenging to payers recently. The aim was to generate discussion about the challenges and potential solutions associated with collection of RWD to resolve the key uncertainties identified in pricing and reimbursement negotiations within the framework of an OBMEA.

Two very different highly innovative treatments and conditions were considered. Both have limited clinical evidence, but with advice from clinical experts there is a view that that the treatments may have high therapeutic value in areas of unmet need. However, there are a range of uncertainties crucial to HTA/payer decision-making and most of these could be resolved by data collection in an OBMEA. The workshops discussed the potential for data collection nationally and internationally to inform an OBMEA and how challenges may be resolved.

5. Workshop 1 – Therapy Given on an Ongoing Basis for a Chronic Rare Disease

5.1 Presentation of Fictitious Case

NeurMX is a degenerative rare disease that affects the motor neurones, causing muscle weakness leading to worsening physical disabilities. It has a prevalence of 1/10,000 in girls, generally aged 0-19 years. There are a range of symptoms associated with NeurMX that are heterogeneous among patients and include nutrition and developmental issues, mobility loss, orthopaedic problems (posture, standing, walking), fatigue, respiratory impairment. There is an unmet need for a disease modifying treatment to slow disease progression and limited clinical expertise. Consequently, the care pathway is uncoordinated and there are very limited natural history data. There is a global disease registry, which may include relevant patients, but coding of data is not consistent across the registry.

There are two phenotypes of disease.

Type A occurs in infants up to the age of 5 and is rapidly progressive. Type A leads to an inability to sit, stand or walk and impacts respiratory function. Most patients need a wheelchair by the age of 8 and will only survive to their mid-teens. Type B is less severe and occurs in children and adolescents.

Type B leads to developmental issues, inability to walk independently, impaired respiratory function and difficulty maintaining weight. Survival into adulthood is expected.

A highly innovative, disease modifying treatment called Fixit has received a marketing authorisation from EMA for “treatment of NeurMX disease”. Fixit is given by infusion every three months using a fixed dose. The price is confidential. The evidence available for Fixit is shown in Table 1.

Table 1. Clinical evidence to support Fixit

	THOR	THOR extension	OPPA
Design	Phase III randomised, single blind n=60, Fixit n=30, Best Standard of Care (BSC) provided consistently within trial	Phase III open label follow-up	Phase II open label, non-comparative n=30, Fixit
Inclusion	≥ 12 years old Type B NeurMX 3rd decile of body weight, Ambulatory (with/without aids)	Patients on BSC in THOR trial switched to Fixit	2-5 years old Type A NeurMX Adequate hydration and nutrition (with/without gastrostomy)
Efficacy Assessments	<u>Endpoints at 12 months</u>	<u>Follow-up until treatment discontinuation</u>	<u>Interim Analysis of quarterly assessments</u>
	Muscle strength test Respiratory function BMI Fatigue PRO Survival	All assessments	**Motor milestones** Tube feeding Permanent assisted ventilation Survival

5.2 Data Collection to Resolve the Decision-Relevant Uncertainties for Fixit

The uncertainties that might arise from this evidence base for HTA/payers were discussed in plenary in the workshop and prioritized in five breakout groups. Several groups considered these uncertainties (1-4) to be key:

1. Long term safety and efficacy (to validate assumptions in initial determination of added benefit/economic model)
2. Patient population

- Selection of patients for treatment as per clinical trial eligibility, or widely as per marketing authorisation?
- What about patients not studied? Especially those with phenotype A with impaired survival?
- When should treatment start?
- How big will the population be?

3. Other aspects of patients' quality of life beyond fatigue

- EQ5D for economic modelling
- Other validated "symptom" questionnaires, such as ACTIVLIM for upper limb impairment, which is validated in children and adults
- Other PROMs developed for young people with neuromuscular diseases?

4. Quality of life of caregivers

Two of the five groups felt that the following uncertainties (5-9) were important:

5. Poor understanding of disease progression, including questions about good diagnostic processes, newborn screening and determining outcomes that matter
6. Small numbers of patients studied, particularly in the area of highest unmet need in the younger population.
7. Other clinical outcomes, biomarkers or endpoints to measure functional ability Can a responder be defined?
8. Comparator - what is best standard of care in our health system? Would this treatment be used in combination with other treatments?
9. What restrictions are needed – specialist centre, specialist healthcare professionals?

Other potential uncertainties suggested were:

10. Duration of treatment, what treatment discontinuation rules should be used?
11. Health state utility values and transition probabilities to validate the economic model.
12. Health resource use along the pathway of care.

The breakout groups discussed four questions relating to data collection in an OBMEA to resolve the uncertainties they thought were key in the Fixit evidence base.

Question 1. What sources of RWD might be used for the OBMEA?

- Ongoing randomized controlled trials (RCTs) should be completed
- National and international disease registries/clinical audits (preferably approved by HTA/regulatory bodies) for natural history and evaluation of new treatment in clinical trial population and in sub-groups where there is minimal data (Type A)
- Administrative health system data – reimbursement/prescription datasets, healthcare resource utilisation, etc

- Electronic health records to review patient journeys since diagnosis
- Biobanks
- Apps for measuring quality of life (QoL), activities of daily living, symptoms, side effects etc particularly in this younger population, but patients must be involved in development of the apps
- Potential for use of wearables
- Regulatory sources – e.g., Post authorisation efficacy studies (PAES) and post authorisation safety studies (PASS).

Question 2. Who do we need to interact with to get those data?

- Clinicians and specialist centres to use their knowledge, design good research, ensure data collection fits in with standard clinical practice
    - relevant EU Expert Reference Network (ERN)
- Health systems as they roll out digital health strategies to encourage consideration of HTA needs
- Patients and patient groups having this particular disease, or more broadly suffering from neurodegenerative disorders, or patient platform organisations
- Regulators – European Medicines Agency (EMA), National Competent Authorities
- Registry holders (Clinical expert groups, patient groups, industry, payer)
- Commercial data analytics organisations
- HTA organisations
- Academia
- Marketing Authorisation Holders (MAH).

Question 3. What challenges might arise in accessing data for the OBMEA?

<u>The rare condition</u>

- This disease is heterogeneous, so some outcomes may be more important for patients than others, hence it is necessary to collect a range of outcomes
- This disease has high unmet need with no effective treatments, so care is not standardised, there are no good quality registries and optimal outcomes have not yet have been developed or validated
- Genotypic and phenotypic understanding of disease likely to evolve as this new treatment becomes available, relevant biomarkers may emerge during the data collection period
- The implications of a new treatment being authorised during the OBMEA.
- The need for interaction with ERNs, who are in different stages of implementing disease registries, and who have little contact with payers – need to encourage capture of data that will allow identification of NeurMX patients, their treatment and outcomes.

<u>Population and Treatment</u>

- Selection of patients for the OBMEA – as per clinical trial population, or wider as per authorised indication, or sub-group where there is less data?
- Are treatment continuation rules specified or is duration of treatment a question in the OBMEA?

Data collection

- Need to develop consensus among all stakeholders about the minimum dataset of outcomes that matters
- Is it feasible to establish a disease registry, or should it be a subset of another registry for a similar muscular disease – if so, is there sufficient granularity to identify NeurMX?
- Are registry/database holders willing to modify their data collection processes to accommodate the needs of payers?
- Is it feasible to collect data in clinical practice over the long term?
- No national infrastructure for good data collection in the health system
- How can we convince those who will have additional administrative burden of data collection that it is worthwhile? Incentives for good quality data? Is there sufficient resourcing for data collection and management (and training)?
- Challenges with bespoke data collection in a hospital setting – need for individual contracts, expensive, external support to resolve questions about data collections and monitor quality
- PROs are a burden to complete – is there a more direct way of getting the data – but privacy challenge
- Delays in recording and transmitting data to the repository
- If patients move outside the jurisdiction of the registry, how can they be followed (value of pan-European registry)?

Data governance

- Time taken to go through governance measures to access data or to establish new data collection mechanisms
- Data ownership and enactment of the General Data Protection Regulation (GDPR) – is consent assumed or can it be collected?
- Is it accepted in the health system that the data collection is for health service evaluation or individual treatment optimization purposes, not for research, and so no research ethical approval is required?
- Ensuring security of data storage and access
- Legal constraints to cross-border collaboration.

Data analysis

- May need to combine data sources within a health system and across countries for this rare disease
- Even within one health system, linkage and interoperability of different datasets may be challenging
    - can siloes be broken down to bring data together for analysis?
    - terminology – lack of harmonization of coding and standardization of data collection forms across institutions and datasets
- Lack of expertise in managing registries and undertaking analysis of RWD
- The outcomes collected and timing of assessments may not align with the ideal data collection specifications for the OBMEA
- Lack of good quality data and incomplete data to enable meaningful re-appraisal
- Funding for data collection and analysis – who pays for what, at what intervals, for what aspect (establishment vs ongoing data collection).

Question 4. What good practices could be shared to overcome these OBMEA challenges?

Individual stakeholders

- HTA/payer - Horizon scanning to identify when several innovative technologies are being developed in one disease, evaluate availability of disease registries and encourage establishment of a new EU/international registry if needed, including agreement of ownership, funding etc.
- HTA/payer – At appraisal, clarify the decision-relevant uncertainties that are critical to reassess value – then discuss potential data sources and trade-offs for additional data collection, contrasting data requirements with feasibility of collection in clinical practice
- HTA/payer - Cross-country collaboration more likely to be needed for such rare diseases in small countries, at least agree core outcomes to be collected
- HTA/payer - Use tools and methods developed for use of RWD in other fields to judge quality of potential data sources and analytical methods
- HTA/payer - Publish a protocol for the OBMEA data collection and analysis (with independent review?) that is sufficiently detailed to gain approvals from data controllers (and store in international repository)
- Industry – support development of disease registries early in a medicine's life cycle (in clinical research)
- Methodologies - Potential to combine data from RCTs and RWE, e.g., using observational single arm registry studies to fill gaps in existing networks of RCT evidence in network meta-analyses (Schmitz et al. 2018)
- Clinicians - Need increased collaboration between clinical societies/ERNs and those interested in patient access to innovative therapies
- Patient groups – advise on patient relevant outcomes, feasibility of data collection plans (apps/visit schedule etc) and processes for sharing personal data
- Patient groups - work with parents to show how assessments, particularly PROs can help them understand their child's experience
- EMA - collaborate with HTA/payers to define minimum dataset (e.g., expand what EMA has undertaken for CAR-T therapies)
- Legal – Create transparent legal and governance frameworks that support trans-national OBMEA.

Multi-stakeholder

- Scientific Consultations/Early Dialogues to discuss gaps in evidence base and what may be resolved by RWD collection (using TRUST4RD taxonomy) throughout the life cycle, so that OBMEA can be developed quickly at time of initial appraisal
- At the start of the OBMEA, agree what data is essential to all stakeholders for decision making during follow-up and at the end of the OBMEA.
- Fully transparent process with clear protocols, plans for monitoring data and resolving data queries, statistical analysis plan and trusted analytical team
- Develop digital solutions for data capture with patients
- Invest in data monitoring to improve data quality
- Annual meeting of all those involved in data collection (including clinicians, patients etc) to check status, quality, completeness, issues in data collection, with incentives for good practice

- Develop tools used by other decision-makers to create RWE for use in HTA, covering issues such as use and analysis of data from electronic health records
- Need pilots to test collaboration and pool data
- Build on learnings from good collaboration among stakeholders during the Covid-19 pandemic.
- Engage with the European Health Data Space to ensure that HTA/payer needs are understood.

6. Workshop 2 – One-off Cell Therapy for a Cancer Refractory to Other Treatments

For case study 2, further assumptions were made about the pricing and reimbursement context, building on the discussions in workshop 1. It was clarified that data collection is planned for three years in the OBMEA to inform understanding of real-life effectiveness in the health system and enable re-appraisal to inform revised pricing and reimbursement/access negotiations after four years. Annual reviews to monitor data sufficiency will be performed to check if an earlier analysis is possible or if data collection is too slow and the OBMEA is futile.

Data collection will be undertaken under the auspices of "health service evaluation" to optimize use of treatment, it is not research and does not require ethical approval. A formal data collection plan will be jointly developed by stakeholders and this and the statistical analysis plan will be published. Clinicians, patients and industry can be involved in data collection. The health system will fund the treatment. Industry will fund data analysis for their submission to the re-appraisal, but other stakeholders may also contribute to funding analyses.

6.1 Discussion of Fictitious Case

SofTissBone cancer is a cancer that develops in the soft tissue, bone and cartilage. It is generally diagnosed between 18 and 60 years old and is associated with certain genetic mutations. Symptoms include local swelling, large mass in affected site, pressure around tumour, changes in swallowing or hearing, pain that gradually increases (especially at night), fractures due to weakened bones and fatigue. SofTissBone cancer is very rare, occurring in approximately 1/200,000 people per year. Factors affecting prognosis are similar to other cancers, including aspects such as histological type, grade, tumour size, metastases and also include primary site, age and sex. Treatments used for other similar cancers are given including surgery, chemotherapy and radiotherapy. There is an unmet need for treatment of patients who are unresponsive or relapse on these therapies.

A new cell therapy, 1timetherapy, has received a marketing authorisation from EMA for personalised autologous cell therapy for the treatment of adults with progressive SofTissBone cancer that is refractory to other treatments. In such refractory end-stage cases, survival is expected to be short. 1timetherapy is a single, fixed-dose given intravenously. Leukapheresis must take place in a specialist centre (only available in larger countries) and takes approximately 25 days. The price is confidential. The clinical evidence available for 1timetherapy is presented in Table 2.

Some health systems have reimbursed 1timetherapy for this indication, but other countries are planning to collect additional data via CED in the OBMEA, but these plans are not yet finalized or published.

After ensuring all participants understood the case study, the uncertainties that might arise for this treatment were discussed considering a Population, Intervention, Outcome framework (no Comparator for this refractory group of patients). In addition to uncertainties related to the determination of value, *operational issues* relating to the administration of this complex therapy were also raised that are important to ensure quality and equity.

Table 2. Clinical evidence to support 1timetherapy

	EWOK trial	NatHist study
Design	Uncontrolled Study n=80, 1timetherapy	Retrospective Chart Review U.S.A centre over many years (during which time best standard of care has evolved) n=30 potential patients
Inclusion	Patients aged 18-40 years Stage III/IV SofTissBone cancer, Genetic mutations X or Y, Refractory to standard treatments	Matching on Age, Sex, Histology showing SofTissBone cancer, Stage III/IV, Failed chemotherapy and other treatments
Assessments	Data cut-off with minimum 6 months follow-up **Complete remission** Number receiving 1timetherapy Progression-Free Survival Duration of remission Health-related QoL Serious Adverse Effects (and treatments to resolve them) Survival	Progression-Free Survival (no standardised response assessments performed, so determined by proxy of stable disease) Survival

Potential questions about the evidence base at the time of pricing and reimbursement were put into a PICO framework:

Population:

- What is the place of 1timetherapy in the care pathway/population?
- Are there any sub-populations that might have a better outcome (e.g., in line with trial entry criteria, or other)?
- *Will all eligible patients have access given the limited number of specialist centres?*

Intervention:

- What are the service delivery issues for this complex treatment – time for leukapheresis, successful implantation etc
- Healthcare resource utilisation for the whole process related to the autologous transplantation
- *Criteria to agree accreditation of specialist centres in health system and educational requirements for physicians – how is access across the entire eligible population organised?*

Comparator:

- In the natural history control group from the retrospective chart review:
  - ❖ Did the clinical identification of patients evolve over time?
  - ❖ Did the definition of refractory status evolve over time?

Outcomes:

- Is 1timetherapy “potentially curative” as claimed by the company? – What are the longer-term effects from the full analysis of the clinical trial and in real-life - sustained remission, survival, QoL?
- What serious side effects might occur, are the treatments proposed in the clinical licensed in this health system? What is the resource use for these treatments?
- What rescue treatments might be needed if there is relapse after initial response to 1timetherapy?
- *What duration of follow-up is feasible (as this is a one-off therapy and patients do not need to return for treatment, they may not attend clinic regularly if they feel they are in remission)?*

6.2 Potential for Use of the European Blood and Marrow Transplant Registry for HTA Purposes[1]

In workshop 1, disease registries/clinical audits were highlighted as an important source for RWD in an OBMEA to determine natural history and to monitor new treatments. To set the scene, for this fictitious cell therapy case, Sofie Terwel, GoCART coordinator at the European society for Blood and Marrow Transplantation (EBMT) described the EBMT registry and the increasing opportunities for collaboration with regulatory/HTA decision makers (complete report of presentation in Appendix 2).

The EBMT was established by healthcare professionals in 1974. The EBMT registry holds data on more than 740,000 haematopoietic stem cell transplantations from 577 centres in 71 countries. It is now working on alignment with the Observational Medical Outcomes Partnership (OMOP) common data model, which will facilitate interoperability with other data sources and is aligning definitions and data collection forms with the US BMT registry, CIBMTR.

Examples of use of the EBMT registry outside the Society are provision of an external control arm for a regulatory submission and to support EMA PASS requirements for CAR-T treatments, with >1,900 in the registry as of May 2021. Research commissioned by external stakeholders must be approved and is undertaken according to a contract that ensures compliance with data governance. Recent work with EMA has resulted in an alteration to the patient informed consent form to provide consent for data to be used in regulatory and HTA analyses.

Some of the challenges faced by registry holders were discussed. Registries need to be appropriately resourced to provide good quality data within international governance mechanisms. RWD will not be of the same quality as those from RCTs. There is a gap between what decision-makers request and what clinicians feel is reasonable to collect in routine care, so data requests need to be realistic. Secondary use of registry data has challenges that need to be overcome, including the diverse regulatory landscape for non-interventional studies and implementation of GDPR legislation, which varies between Member States. More collaboration is needed to minimize fragmentation of efforts.

[1] Section approved by EBMT representatives

6.3 Data Collection to Resolve the Decision-Relevant Uncertainties for 1timetherapy

In plenary, the PICO framing of potential issues was discussed, and it was agreed that the decision-relevant uncertainties for 1timetherapy could be summarised as:

- place in care pathway and sub populations that may benefit most
- service delivery in standard practice (including management of serious side effects) and associated healthcare resource utilisation
- long-term effectiveness and need for rescue medication after relapse.

Three small groups discussed four questions relating to the feasibility of a 3-year data collection programme in an OBMEA to resolve these key uncertainties to inform a re-appraisal of 1timetherapy in four years' time.

All groups focussed on long-term effectiveness and safety and associated resource use. The third group also considered place in care pathway and whether sub populations could be defined.

Question 1. What sources of RWD might be used to resolve these uncertainties in the OBMEA of 1timetherapy?

- Ongoing trials should be completed, and regulatory reports (for PAES and PASS) shared
- Registries
    - Clinical registry such as EBMT
    - Payer MEA registry for the treatment/indication
- Electronic health records, claims and administrative data relating to cancer treatment
- Bespoke study within the health system using a data platform or templates to standardize data collection
- Cancer patient organisations – evidence from surveys, PROs, other sources
- PhD research studies. Participants saw a possibility of exploitation of registry data by academics, with the view of stimulating PhD research. This could be carried out on the clinical data set but also on data governance to launch a subsequent OBMEA.
- Given the rarity of SofTissBone cancer, transnational collaboration is recommended.

Question 2. Feasibility of using different data sources to collect this RWD for this OBMEA?

a) What are the pros and cons of different sources?
    - Prefer disease vs treatment registry, with multi-national engagement, leveraging what is already being collected, but if new elements are needed what is the mechanism/financial implications for those additions?
    - If data collection is not routine (or duplicated) this adds to the clinical burden and incorrect coding etc is more likely. So, ensure a minimum dataset is defined, which would probably align with what centres would routinely collect
    - Natural history studies are subject to selection bias in curation and so should be pre-planned and clearly presented with sensitivity analyses under different assumptions
    - QoL studies (to develop a new disease specific measure) are expensive and should be discouraged.

b) Barriers to accessing these data?
   - Health system - lack of unique patient identifiers that allow linkage across health system data
   - Clinicians - needing to contribute to different data collection processes and not being sufficiently resourced for the OBMEA
   - Clinicians – patients need to be tracked over 3 years, but they may not stay in same location and may move (but note that the HTA/payer requirement is for follow-up over a much shorter period than the EMA who are likely to ask for 15 years of data)
   - HTA/payers - lack of experience and resource to recognise potential of national RWD sources, engage in discussions about expansion of existing RWD sources, and access and analyse RWD
   - HTA/payers – no formal collaborative processes to share information about OBMEA being planned and in progress
   - Concerns about data sharing with stakeholders
   - Inconsistent terminology, different population characteristics or care pathways are barriers to cross-country approaches.

c) What is needed to overcome issues?
   - Start discussions about RWD collection needs early in the life cycle of the medicine and in an iterative manner with all stakeholders (ala TRUST4RD)
   - Consider a national infrastructure for registries/clinical audits to create consistency and efficiency
   - Develop collaborations with registry holders to discuss decision-maker needs (including regulators), potential for consolidation across different sources and additional resources required
   - Involve patients in registry design/requirements
   - Create a common protocol for data collection, clearly identifying patients eligible for treatment and collecting a range of baseline information
   - HTA/payers need to align across jurisdictions to agree with other stakeholders the details of a minimum dataset (assessments, timing etc) that is crucial for the re-appraisal vs what is nice to have, but this needs to be realistic taking account of what is feasible in clinical practice
   - Flexibility in data capture, particularly for safety, to enable capture of unexpected effects and as understanding of use of treatment may evolve
   - Develop processes for patients and patient groups to efficiently collect relevant information for the OBMEA, for example creating a platform for collection of PRO data or aligning national surveys or protocols to study patient experience to allow data amalgamation.
   - Clear governance framework that outlines plans to ensure data security and governance in relation to each stakeholder.
   - Commercial companies (such as google) are developing health data sources, but these are also contentious with the general public. Is there anything that can be learnt from these high-tech players?

Question 3. Considerations when developing the data collection protocol for this OBMEA?

- Include details of all clinical and patient assessments, data sources, analysis plans, monitoring process and how the resulting evidence will be analysed in the OBMEA.
- The protocol should specify how that data will be used in the re-appraisal (e.g., comparison to agreed clinically relevant benefit, comparison to estimated standard of care, input to economic model with judgements against certain ICER thresholds, etc)

- Consider whether a control arm is needed and how those data will be collected – e.g., as part of the OBMEA or in a separate study. If it is a separate study, challenge of collecting retrospective/prospective standard of care data must be addressed.
- Is collection of longer-term outcomes on the untreated population valuable to determine relative efficacy or are the populations different?
- If sub populations are defined by a biomarker that is not part of a natural history dataset, how can this group be assessed.
- Defining the minimum dataset will be difficult for such a very rare disease where knowledge is still evolving about the disease and natural history, so some flexibility is needed. However, try to keep it simple, focus on the most meaningful data (e.g., survival) that is driving the determination of value.
- For this refractory condition, patients have undergone challenging chemotherapy regimens and are facing end of life, this must be considered when assessments are considered. Also in this situation, survival may be considered as the most important quality of life consideration.
- What are the reasons for non-infusion of T-cells – clinical or administrative? Are there issues in a standard clinical setting that were not considered in the clinical trial that may impact re-appraisal?
- Milestones should be clearly defined – at what point is it reasonable to assume the treatment effect is durable?
- Processes for managing missing data will be needed, particularly in relation to the responder definition.
- Will there be sufficient survival data for re-appraisal after 3 years of data collection? If not, what outcomes will feature in the analysis? If progression-free survival, can it be reliably analysed?
- The monitoring process for data sufficiency and quality should be documented – frequency of monitoring, who is involved, aspects considered, authority of recommendations (e.g., advice to HTA/payer that timing of re-appraisal needs to be altered).

Question 4. How could we align data collection across stakeholders/health systems? Are there particular opportunities for collaboration given this is a cancer?

EU

- EC/EMA have an important role in bringing stakeholders together to develop European-wide data collection in disease registries or bringing existing health system data together, as planned in DARWIN and the European Health Data Space
- There are many cancer initiatives at national and European level and as Europe's Beating Cancer Plan develops how can HTA/payers engage to share their needs?

Member States

- IT systems need to be developed to meet clinical and decision-makers' needs to facilitate collection of high-quality data once and enable their use multiple times for bona fide purposes. This requires substantial investment and standardization to ensure interoperability.

HTA/payer

- Very early dialogue among stakeholders is needed to develop the OBMEA data collection protocol
- Can payers agree on a definition of "curative"?
- HTA/payers need to drive alignment of OBMEA data collection requirements across countries and this would be easier if data collection was really kept to a minimum – i.e., the key drivers of value.

- There are many existing registries/data sources for cancer and chemotherapy, need to review how HTA bodies use those (e.g., in Spain and England) and what could be done in other countries.
- Need to share good practices in relation to RWD use across HTA/payer bodies
- Consider mandating use of validated registries by regulator/HTA.

Patient groups

- Inform patient groups and patients about the purpose of OBMEA and the opportunities they provide to patients. Empower and resource patient groups to be involved in discussions about the construct and conduct of the OBMEA and to contribute to re-appraisal.

7. Discussion

7.1 Reflections from the Workshops

The aim of the workshops was to align understanding of data collection requirements in OBMEAs for two fictitious therapies, leading to "an evidence generation framework". The case studies were both highly innovative therapies for rare diseases, one was a repeat treatment given to children, the other, a one-off cell therapy given to adults. Learnings from workshop 1, particularly about stakeholders that needed to be engaged, were taken into workshop 2 and the format was changed to focus discussion more closely around the fictitious case.

Both treatments had important uncertainties related to the population to be treated and long-term safety and effectiveness. The treatment for the neuromuscular disease in children also had uncertainties about quality of life for patients and carers, whereas the one-off cell therapy had major questions about service delivery in clinical practice (including management of serious side effects) and associated healthcare resource utilisation.

Both workshops identified a wide range of potential RWD sources and stakeholders to engage with, but these were not clearly associated with the specific uncertainties to be addressed and a clear evidence generation framework was not developed, but useful discussions about RWE generation were undertaken.

In the first workshop, challenges were discussed relating to various aspects of the rare disease, the population to be treated (inclusion and continuation), data collection, governance and analysis. Solutions to these issues included horizon scanning, scientific consultation, HTA/Payer clarification of decision-relevant uncertainties, cross-country collaboration on data collection plans that are published, development of disease registries that take account of HTA/payer needs, use of RWE best practice methods from other fields (e.g. pharmacoepidemiology), investment in data monitoring, improved engagement with stakeholders, pilots to test collaborative processes and enact data governance.

In the second workshop, the pros and cons of a range of different data sources were discussed. To overcome challenges in accessing data it was proposed that discussions about RWD collection need to occur early in the life cycle of a highly innovative technology with all those involved in/affected by the data collection. A common data collection protocol that could be aligned across jurisdictions with appropriate information governance is needed and links need to be made with existing cancer or rare disease clinical networks. The data collection protocol needs to published and include information about planned assessments, data sources, monitoring and analysis plans and how the data will be used in future decision-making.

7.2 Wider Policy Reflections about Feasibility of OBMEA for Highly Innovative Technologies

Issues raised about the implementation of OBMEA by other initiatives, the Netherlands, Italy and across the EU featured in the two case studies. However, two elements identified before the workshops were not discussed:

- Value of Information analysis could have been used to determine the feasibility and value of data collection for specific parameters in the OBMEA
- The IMPACT HTA template for data collection in an OBMEA could help align implementation of OBMEA across jurisdictions.

It is clear that for OBMEA based on CED, it is first essential to document the truly critical decision-relevant uncertainties at the point of appraisal and then weigh the ideal data collection regime to resolve those uncertainties against one that is feasible. The workshops showed that this is a difficult task as with more stakeholders involved, the questions that might be answered with additional data collection grow. This is not unexpected in the arena of rare diseases where there is a paucity of knowledge about the condition. Hence data collection not only seeks to demonstrate added value but also to understand natural history and real-life effectiveness and thus optimize treatment. This could explain why formal Value of Information, focused on economic willingness to pay thresholds and not wider aspects of decision-making is not used. However, more must be done to compare the wish list of data requirements with the reality of constraints in standard clinical practice, the different data sources that may be required, the ease and cost of data access and timeliness of data collection. This requires expert discussion with data controllers and trade-offs to come to a feasible minimum and nice to have dataset.

OBMEA are resource intensive, but the workshop demonstrated that there is potential to focus them on high-cost treatments and if investment is made to support collection of good quality data this could optimize treatment use and create efficiency savings. Furthermore, if OBMEA can be operationalised within emerging digital health ecosystems (nationally or internationally) their use could be expanded.

Multi-stakeholder collaboration is essential – particularly with clinical networks to explain HTA processes and potential data collection requirements. Patient groups need capacity and capability development to be able to contribute to the design and monitoring of an OBMEA and delivery of patient collected RWD. Their views on issues relating to ownership of data, how information will be shared with them during and how they can use it after the OBMEA must be addressed.

For rare diseases, particularly in small countries, HTA/payers need to align OBMEA requirements across jurisdictions, then share protocols, analysis plans, progress reports and analyses in a public repository. Where possible transnational work should be considered in existing HTA/Payer collaboratives such as BENELUXA or FINOSE, potentially using the OBMEA data collection framework developed by IMPACT HTA.

Discussions about RWD requirements in OBMEA could start in collaborative horizon scanning or Early Dialogues/Scientific Consultations and may drive early collaborative projects, such as qualification of disease registries for HTA purposes.

RWD collection is increasingly seen as a continuum over the life cycle of a technology and so sources employed pre-launch may be appropriate for use in an OBMEA. Furthermore, comparable critical assessment approaches should be used in each phase.
Development of cross-border collaborations need to consider what level of alignment is required. A common minimum dataset does not ensure interoperability, should a common data model, such as OMOP be used by HTA bodies? Is it necessary to see data architecture

descriptions to understand how data from different counties are collected, integrated, arranged and used as outlined in IT frameworks? The requirements to run efficient OBMEA should inform and shape future data ecosystems, both nationally and internationally and align with developments in DARWIN, the EU Health Data Space and HTA/payer/NCAPR collaborative efforts.

There is a need to build capacity and capability for RWE development and assessment in the HTA community. Guidance exists in health systems to support use of health data for a range of purposes that may or may not include HTA, such as those from HIQA in Ireland providing information management standards and guidance on data quality . Other stakeholders such as academics, regulators and data analytics organisations have developed guidance relating to pharmacoepidemiology and pharmacovigilance that could be adapted to HTA. RWE4Decisions could collect relevant guidance in a repository and work with other networks/stakeholders to develop bespoke HTA/payer guidance.

8. Actions for stakeholders to support successful implementation of OBMEA for highly innovative technologies

Action	Lead Stakeholder
1. To enable rapid implementation of an Outcomes-Based Managed Entry Agreements (OBMEA) using Coverage with Evidence Development (CED), the potential need for post reimbursement data collection should be discussed in advance. **National or collaborative horizon scanning processes should identify products that might require OBMEA and undertake iterative dialogues (scientific consultations) with the sponsor company, regulators, clinical experts and patient groups to discuss potential data sources (e.g., disease registries, health system data, patient reported outcomes, regulatory studies).** This should include initiation of governance processes to access data. This could be undertaken for a particular disease, or type of therapy, as well as individual treatments.	Horizon scanning collaboratives
2. **CED should only be initiated when sufficient data can be collected to resolve decision relevant uncertainties and the re-appraisal will lead to a decision that can be enacted** (full reimbursement, disinvestment, alteration of eligible population/treatment regimen). This requires collaboration and alignment of all stakeholders in the process and clarity on how the evidence will be used in subsequent decision-making.	All stakeholders in a health system
3. **HTA/Payers need to clarify the decision-relevant uncertainties that arise from appraisal of the evidence to drive discussions with stakeholders about the data to be collected in CED**. Data collection needs to be kept as simple as possible, focusing on the most meaningful outcomes related to the decision-relevant uncertainties that can be reliably collected within the timeframe for re-appraisal. Identification of key clinical questions.	Individual HTA/Payers

Action	Lead Stakeholder
4. **For rare diseases, collaboration across countries to align data collection requirements and access to datasets is needed**. This requires agreement on a minimum data set, the feasibility (or not) of collecting data of sufficient quality and methods for data amalgamation.	HTA collaboratives
5. Processes need to be developed for Payers to interact with regulators to be kept informed of their post marketing data collection requirements and avoid duplication of effort, and to use DARWIN.	HTA/Payers/ Regulators/ Industry
6. For CED to be successful a **proactive approach to data collection involving all relevant stakeholders needs to be enacted**. This includes clear responsibilities for data collection, processing, querying and analysis, to improve quality and monitor sufficiency for re-appraisal.	All stakeholders
7. **Data collection plans should be clearly documented in a publicly available report**, possibly via the IMPACT HTA template for OBMEA.	HTA bodies
8. **RWE4Decisions should collect relevant guidance relating to generation of RWE in a repository and help develop bespoke HTA/Payer guidance for transnational use**.	RWE4Decisions
9. Financial investment in data infrastructure, collection and analysis is needed to support enactment of CED schemes that can inform optimal of use of high-cost therapies, including reduction of treatment costs.	National Governments/ EU/ Industry
10. **A demonstration project of a OBMEA CED for a highly innovative technology enacting these recommendations should be undertaken by an HTA/Payer collaborative group** such as BENELUXAI or FINOSE. This could be a 2-step approach: 1° agreement on a minimal clinical data set for national data collection and 2° connect national data collection cross-border, and with larger networks.	HTA Collaboratives

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Appendix 1. Participants

Participants in one or both workshops

HTA/Payers, Ministries of Health

Austria

Anna Nachtnebel, Senior HTA Expert, Department for Pharmaceutical Affairs, Dachverband der Sozialversicherungsträger
Claudia Wild, CEO, Austrian Institute for Health Technology Assessment

Belgium

Jo De Cock, CEO, National Institute for Health and Disability Insurance (INAMI-RIZIV)
Marc van de Casteele, Coordinator expertise pharmaceuticals, INAMI-RIZIV
Karen Facey, HTA Consultant, INAMI-RIZIV
Frank Hulstaert, Senior HTA Expert, Belgian Health Care Knowledge Centre
Diane Kleinermans, President of Commission of Drugs Reimbursement, INAMI-RIZIV

Canada

Laurie Lambert, Lead RWE, CADTH
Nicole Mittmann, VP of Evidence Generation, CADTH

Denmark

Trine Ann Behnk, Strategic Advisor – Business Development and Advisory, Amgros
Jette Rathe, RWE Clinical Expert, Amgros
Heidi Møller Johnsen, Chief Health Science Officer, Danish Medicines Council

Finland

Piia Rannanheimo, Pharmaeconomist, Finnish Medicines Agency

Germany

Christoph Rupprecht, Head of Department for Health Policy and Health Economics, AOK, Rheinland/Hamburg

Ireland

Aisling O'Leary, Chief Pharmacist, National Centre for Pharmacoeconomic Evaluations

Slovenia

Tit Albreht, Senior Health Services and Health Systems Researcher, Slovenian National Institute of Public Health
Marjan Suselj, General Director, Health Insurance Institute of Slovenia

Spain

Carlos Martín Saborido, Advisor at the National Health and Pharmacy General Directorate, Spanish Ministry of Health

The Netherlands

Rick Vreman, Advisor at the Dutch National Health Care Institute (ZIN)
Marijke de Vries, Advisor at ZIN

Norway

Helga Haugom Olsen, Senior Consultant, Norwegian Medicines Agency

Poland

Dominika Grzymala, Junior Specialist in Analysis and Medical Fund, Polish Agency for Health Technology Assessment and Tariff System (AOTMiT)
Anna Zaremba, Head of the Reimbursement Unit, AOTMiT

Portugal

Cláudia Furtado, Head of the HTA, Pricing and Reimbursement Division and Information and Strategic Planning Division National Authority of Medicines and Health Products

Romania

Felicia Cuilu-Costinescu, HTA Head of Department, National Agency for Medicines and Medical Devices of Romania

Sweden

Niklas Hedberg, Chief Pharmacist, Swedish Dental and Pharmaceuticals Benefits Agency

International organisations

Suzannah Chapman, Junior Health Policy Analyst, OECD
Martin Wenzl, Health Policy Analyst, OECD

Clinicians

Cinzia Bellettato, Project Manager, MetabERN, Italy
Denis Lacombe, Chief Executive Officer, European Organisation for Research and Treatment for Cancer
Roberto Salgado, Coordinator of Pathology Network Antwerpen, UZ Antwerp, Belgium
Maurizio Scarpa, Coordinator MetabERN, Regional Coordinating Centre for Rare Diseases, Udine University Hospital, Italy

Registry/research institute

Eoin McGrath, Advocacy & Quality of Care Director, European Society for Blood and Marrow Transplantation (EBMT)
Sofie Terwel, GoCART Project Coordinator, EBMT

Patient representatives

Matti Aapro, President-elect, European Cancer Organisation
Hervé Nabarette, Deputy Director for Public Affairs, AfM Telethon
Liz Ryburn, Support Services Manager, SMA UK
Chris Sotirelis, EMA Patient Expert & Patient Advocate
Elizabeth Vroom, Chair, World Duchenne Organization

Academics

Entela Xoxi, Pharmacologist, Università Cattolica del Sacro Cuore, Italy

Industry

Astra Zeneca: **Karen Coulton**, Head of Payer Engagement**;**
Alison Horsfield, Global Strategy & Innovation Director - Oncology Market Access;
Michael Seewald, Vice President of Medical Evidence;
Muriel Licour, Europe Director Epidemiology, RWE, Oncology portfolio

Gilead Sciences: **Simon Butler**, Associate Director, Government Affairs;
Gab Castaigne, Director HEOR;
Martin Brown, ACE HEOR Director

Novartis: **Ivana Cattaneo**, Executive Director, Oncology Policy & Healthcare Systems;
Gorana Capkun, Global Head RWE Enablement, Oncology;
Yanni Hao, Expert in RWE for Cell & Gene Therapies;
Simona Paratore, Head of Medical for Cell & Gene Therapy in Europe

Roche: **Ansgar Hebborn**, Head of European Access Policy Affairs;
Gomathi Kaliappan, Health Systems Strategy Lead
Sreeram Ramagopalan, Global Head, Real World Evidence (Market Access)

Takeda: **Toon Digneffe**, Head of Public Affairs and Public Policy;
Mercedes Echauri, Vice-President Market Access Europe and Canada;
Ipek Ozer Stillman, Lead, Global Health Economics

RWE4Decisions Secretariat

Laura Batchelor
Marine Borchardt
Lydia Shotton

Attended Preparatory Meetings

HTA/Payers/Policy Makers
Suzanne McGurn, CEO, CADTH, Canada
Liisa Maria Voipio-Pulkki, Senior Advisor Specialist, Finnish Ministry of Social Affairs and Health, Finland
Tom Lawrence, Data Scientist, Senior Advisor Specialist, National Institute for Health and Care Excellence (NICE), UK

Regulator
Xavier Kurz, Senior Advisor Specialist, Head of the Surveillance and Epidemiology Service, European Medicines Agency (EMA)

European Commission
Flora Giorgio, HTA – Team leader, Unit Medical Devices, DG SANTE

Clinician
Patrick Neven, Specialist in gynecology/oncology, UZ Leuven

Patient representative
Simone Boselli, Public Affairs Director, EURORDIS

Apologies were sent from a range of other individuals from expert clinical centres, HTA bodies, patient groups, payers, policy makers and regulators across Europe.

Appendix 2: Presentation on Potential for use of the European Blood and Marrow Transplantation registry for HTA purposes[2]

Sofie Terwel, GoCART coordinator at the European society for Blood and Marrow Transplantation (EBMT) described the EBMT registry and the increasing opportunities for collaboration with regulatory/HTA decision makers.

The EBMT is a not-for-profit international collaboration of healthcare professionals established in 1974. It has 5,454 members across 577 centres in 71 countries. Centres contribute data voluntarily to the EBMT registry. Forty thousand new transplants are recorded annually in the registry and up to 2020 it included more than 740,000 haematopoietic stem cell transplantations (HSCT) in more than 600,000 patients. Following the authorisation of CAR T-cell therapies for some haematological cancers, >1,900 treatments have been recorded up to May 2021.

The EBMT registry aims to collect data from routine clinical practice once and use it often for bona fide purposes related to science and education. The data collected relates to a patient's disease, treatment and outcomes. Centres have access to all their own data. National bodies in a country can request access to data for their country subject to approval by centres in their country. EBMT has access to all data reported to the registry across all centres and countries. EBMT and the centres are data controllers. The data can be used by members who participate in working groups that undertake retrospective analyses of the data, or prospective studies that often involve international collaboration.

The Joint Accreditation Committee of the International Society for Cell and Gene Therapy (ISCT) Europe and the EBMT (JACIE) develop and maintain global standards for the provision of quality and medical laboratory practice in the field of HSCT and cell therapy. JACIE is the only official accreditation body for transplant programmes in Europe. In terms of standards, EBMT statisticians are supporting development of a benchmarking programme, which was first published in 2020 and rolled out early in 2021.

Another main function of the EBMT registry is to provide data for safety surveillance, which is of interest to clinicians, regulators and pharmaceutical companies. Furthermore, data from the registry can be used to demonstrate effectiveness, for example by creating an external control arm in a regulatory submission, as was undertaken for Zalmoxis in treatment of high-risk malignancies .

The potential value of the data in registries to support regulatory decision-making was outlined by McGettigan et al. (2019), but it was recognised that registries are underused due to heterogeneity in registry design, the data collected and its quality, and data sharing impediments. The challenges EMA regulators faced with RWE have been summarized in the OPTIMAL framework, covering data infrastructure and the potential for data sharing, the technical aspects associated with the data and lack of standardisation and the reliability and validity of the data, as outlined in Table A1. (The solutions presented by the authors are shown in Appendix 3).

[2] Section approved by EBMT representatives

Table A1. OPTIMAL Framework for regulatory use of RWE – Challenges (Cave et al, 2019)

OPerational	TechnIcal	MethodologicAL
Feasibility Governance Sustainability	Extent and completeness of data collected Collection of adequate time elements Consistent use of appropriate terminologies and data formats Potential for data linkage Consistent, accurate, and timely data collection, recording and management	Variability in results from multi-data source studies Understanding the data source environment Adequate data collection on potential confounders and effect modifiers Identifying potential for selection and information bias Management of missing data Sound data analysis and interpretation

The EBMT has identified the potential utility of its registry for other stakeholders and has built new relationships with EMA, DG Sante, the pharmaceutical industry and HTA bodies. This has required EBMT to become familiar with new terminology and concepts such as HTA and PLEG.

To accommodate these collaborations and comply with GDPR legislation, new processes have been put in place to enable source data verification and sharing of pseudonymized data, for example with Marketing Authorization Holders (MAHs) in support of EMA PASS requirements. EBMT is also involved in the work EMA is undertaking on Metadata for data dIscoverability aNd study rEplicability in obseRVAtional studies **(**MINERVA**).** They are also part of the European Health Data and Evidence Network (EHDEN) and as a result of this are making improvements to the interoperability of the registry, using the OMOP common data model. Internationally, activities are underway to harmonize data collection forms with other similar registries, such as the Center for International Blood and Marrow Transplant Research (CIBMTR) in the USA.

To ensure patient-centred processes a Patient Advocacy Committee and Patient Engagement Taskforce has been established and the multi-stakeholder GoCART Coalition has been launched to maximize the potential of cell therapies.

EBMT's vision is that the future is not about RCTs vs RWE, but RCTs AND RWE as proposed by Eichler et al. (2020). However, challenges still exist.

- It is not realistic to expect that data collected from different centres as part of standard clinical practice, or for reimbursement processes, will be of the same quality as that seen in clinical trials. There is a gap between the information regulators and industry want and what centres can reasonably collect and report in routine clinical care.
- For cell therapies that have a curative intent, regulators have required 15 years of follow-up and although patients will have been treated in a specialist centre, they may not stay connected to that centre for a 15-year period. This creates patient follow-up and consequently data collection challenges.
- There are questions about study design – is primary data collection required with specially designed forms in the registry, or is secondary use of data available as a standard in the registry appropriate? This study design has implications e.g., for safety reporting requirements and GDPR.

- There are challenges working across Europe and the manner in which GDPR legislation is interpreted as the frameworks for approval of non-interventional or registry studies are not standardized across countries.
- Registry development and maintenance requires financial resources and so payment is required for any data access.

A major step forward in collaborative efforts was a result of EBMT's early engagement in the EMA registries initiative that began in 2015. This resulted in definition of the "must-have" EBMT datasets for EMA and industry in February 2018, in anticipation of the approval of two CAR T-cell therapies that used EBMT registry data in August of that year. In 2019, EMA issued a positive qualification of the cell therapy module in the EBMT registry and in 2020 EBMT contracted with two MAHs to support their PASS obligations (McGrath et al 2020). This process was observed by the EU network for HTA (EUnetHTA) who have established their own process for registry qualification for HTA purposes via the REQueST tool. EUnetHTA has used this tool on the EBMT registry and results are expected in summer 2021.

The GoCART coalition is a new initiative developed by EBMT that aims to include healthcare professionals, medical societies, patient representatives, health authorities, pharmaceutical companies and HTA bodies and payers. Its vision to be a trusted partner and leading force in the field of cellular therapies at national and international levels. The mission is to promote patient access to novel cellular therapies and to contribute health and well-being through multi-stakeholder collaboration. Six work packages are addressing data harmonisation, standards of care, HTA, education, policy and advocacy and scientific excellence. GoCART is particularly keen to involve HTA bodies and payers and would develop the HTA workstream with them to consider how the EBMT registry data could be leveraged for HTA.

In conclusion, registries are evolving and want to contribute to data-based regulatory and HTA decision-making. However, it is important that decision-makers are realistic in their requests for data and take account of registry infrastructures that often have long-established and high quality processes developed by leading medical societies. Registries should not be considered as "cost-free" data as they need to be appropriately resourced to provide good quality data within international governance mechanisms. Challenges with the use of registry data include GDPR limitations and a wide lack of familiarity in using registry data to support decisions, particularly in relation to ethics committee reviews. There is an important need to harmonize interpretation of data protection and Network and Information Systems regulations across countries in Europe and to continue to collaborate to minimize fragmentation of efforts.

Discussion

Who can access data in the EBMT registry, who can ask questions of the registry and who decides whether a registry can be adapted to include additional items relevant for decision makers?

The EBMT registry was traditionally limited to clinicians, but since the EMA registries initiative, contracts have been set up with industry to support collection of data to meet post marketing regulatory requirements. Organisations can request data from the registry via a formal process that ensures research, ethical and legal compliance based on a clear contract. Care is taken to ensure strict governance of how access is given, to whom and to what, given that the patient owns the data, with the centre having a stewardship role for information governance. For example, following approval of relevant centres, a contract was

set up with a French regulatory body to follow individual French patients who had received a specific treatment.

There is potential for increased collaboration with regulators and HTA bodies in future, as the work on the cell therapies has led to a change to informed consent forms for the entire registry that seeks consent to share data with regulators and HTA bodies.

Can EBMT and CIBMTR in the USA collaborate?

EBMT and CIBMTR meet monthly for information sharing and to coordinate joint activities. Data collection forms have been harmonized for cell therapies and a similar exercise is being undertaken for the data capture about the underlying haematological cancers. Other activities are planned that should enable comparison of data collected in Europe and the USA.

Appendix 3. OPTIMAL Framework - EU solutions to RWE generation (Cave et al. 2019).

1. Operational
    a) Early and repeated consideration of the need for RWD during drug development
    b) Landscaping of potential data resources
    c) Long-term funding for data infrastructures
    d) Published documentation of data source characteristics and policy for collaboration and data sharing
    e) Management of access in line with GDPR and national legislation
    f) Data anonymization processes where required
    g) Data sharing agreements at study inception
    h) Use of the ENCePP *Code of Conduct for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies*

2. Technical
    a) Use of common data elements, data formats and terminologies, or mapping to international system
    b) Partial or full data mapping to common data model, including routine validation process
    c) Quality assurance and control procedures—indicators of data quality
    d) Internal or external data audit
    e) Benchmarking to external data source
    f) EMA qualification procedure for data source.

3. Methodological
    a) Detailed description of study design and data collected in data sources
    b) Documentation of feasibility analyses
    c) Registration of study in public database, with study protocols and results
    d) Use of best methodological standards in statistics and epidemiology
    e) Use of EMA Scientific Advice procedures for study protocols.