Improved methods and actionable tools for enhancing HTA

WP10 Guidance to Support Consistent HTA Appraisal for Orphan Medicinal Products

D10.3 Guidance on Use and Implementation of Outcome-Based Managed Entry Agreements for Orphan Medicinal Products (Rare Disease Treatments)

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EXECUTIVE SUMMARY

Background

When an appraisal process does not recommend a treatment with predicted high therapeutic/patient benefit for use/reimbursement within a health system due to uncertainties in the clinical and/or cost effectiveness evidence, an Outcomes-Based Managed Entry Agreement (OBMEA) could be proposed to resolve or reduce uncertainties. OBMEA may be based on the outcomes achieved by individual patients, only paying for achievement of a certain outcome, or providing a full or partial refund if response is not achieved, or stopping treatment if there is a decline in response. OBMEA may also aggregate data across patients to create population-based analyses, so-called Coverage with Evidence Development.

For the case of rare disease treatments (RDT), it is known that uncertainties will exist at the time of appraisal due to limited patient numbers, disease heterogeneity and evolving clinical knowledge, so OBMEA would seem a promising solution to patient access. However, many papers in recent years have shown the challenge in implementing OBMEA for more common conditions, without the added complexities that arise in RDTs. Even for individual-based OBMEA the administration of financial payments that differ by patient can be too complex for many systems. Whereas for the population-based systems, there are heavy burdens of data collection placed on clinicians and expectations of patients to undertake assessments that go beyond usual clinical practice.

This IMPACT HTA Work Package 10, workstream 4, sought to explore the issues related to use of OBMEA for RDTs and to develop tools to support their implementation.

Methods

This workstream used a mixed methods policy research approach. We

- reviewed published literature and the work of the COMED project
- undertook an international workshop to discuss implementation of OBMEA
- ran workshops with stakeholders involved in OBMEA for RDTs in England that used data from a variety of health service resources
- reviewed the extensive OBMEA undertaken in Italy on their national-web based registry platform
- observed a NICE committee responsible for monitoring an OBMEA and undertook follow-up interviews
- supported work to explore the use of RWE over the life cycle of an RDT, with a particular focus on cell and gene therapies
- in collaboration with HTA/Payer experts explored issues related to the implementation of OBMEA for two RDTs
- developed tools as a result of all our work, in collaboration with the HTA/Payer experts
- consulted on the draft tools with all individuals involved in our work over the three-year research period and publicly.

Results

The OECD identified four good practice elements for OBMEA that include defining a strategy to guide use of OBMEA, clear identification of uncertainties, a governance framework and transparency. We have sought to address all these issues and the many other challenges identified in our research in the OBMEA Checklist and Template. To support a purposive approach to developing sufficient high-quality data for an OBMEA, we outline the operating conditions of a monitoring committee, and to ensure patients' experiences are fully captured, we provide a patient group submission form for re-appraisal.

Tool	***Issue* and Resolution**
Checklist to determine feasibility of an OBMEA	*OBMEA should be the "exception not the norm" given the burden to the system (even in web-based platforms like those of AIFA).* Clear criteria are presented that seek to ensure the OBMEA will be able collect sufficient good quality data to reduce the uncertainties in HTA.
Template for an OBMEA	*The data collection elements of an OBMEA need to be separated from confidential pricing agreements into public documents. Data collection needs to be more purposeful to address decision-relevant uncertainties.* A template for adaptation by HTA bodies and use by all stakeholders involved that outlines the key elements of an OBMEA to be presented in a public document. This includes • purpose of the OBMEA - linking to the appraisal and uncertainties to be resolved • the legislative or policy basis for the OBMEA • patient entry and approval process • data sources, data management and information governance • reviews to monitor data quality and sufficiency • re-appraisal • responsibilities of all involved.
Terms of Reference for an OBMEA Monitoring Committee	*When data are not collected in a national registry system and come from a variety of sources, careful oversight is needed to ensure the data collected in clinical practice are of high quality and that clinical centres undertake clinical assessment of patients appropriately.* To ensure purposeful monitoring of the progress of the OBMEA a "Monitoring Committee" is proposed that includes all signatories and key stakeholders (such as clinicians). A Terms of Reference for this committee is presented for adaptation by HTA bodies that presents issues the committee should keep under careful review and so be able to take remedial action if any issues arise. The governance of the committee is also outlined.
Patient Group Submission Form for Re-Appraisal after an OBMEA	*OBMEA data collection is often shaped by the construct of the original clinical trial and may miss other benefits or disadvantages of a treatment as perceived by patients and their carers and families.* A patient group submission form is provided for adaptation by HTA bodies. This draws out experiences of patients, carers and families about what life was like before and after treatment in the OBMEA and any practical issues in the OBMEA.

Conclusions

There are many HTA initiatives emerging to address the appraisal challenges presented by RDTs with use of OBMEA. We hope that these IMPACT HTA WP10 tools will not only support successful implementation of OBMEA in individual countries, but also promote transparency, alignment of requirements and collaboration across countries in terms of data collection and ultimately optimization of patient care. We strongly propose that a public international portal (such as a the HTA database) be established as a repository for OBMEA documents (including the Agreement, analysis plans and reports).

List of Abbreviations

AIFA	Agenzia Italiana del Farmaco
ATU	Temporary Authorisation Scheme (France)
CED	Coverage with Evidence Development
COMED	Pushing the boundaries of Cost and Outcomes analysis of MEDical Technologies (EC H2020 project)
EC	European Commission
EMA	European Medicines Agency
ERN	Expert Reference Network
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
EVIDENT	Evidence Database on New Technologies
FDA	Food and Drug Administration
HST	Highly Specialised Technology
HTA	Health technology Assessment
HTAi	Health Technology Assessment International
I	Individual
INAMI	Institut National d'Assurance Maladi-Invalidité
JA	Joint Action
MAA	Managed Access Agreement
MAH	Marketing Authorisation Holder
MEA	Managed Entry Agreement(s)
MS	Member State
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OBMEA	Outcome-Based Managed Entry Agreement(s)
OECD	Organisation for Economic Co-operation and Development
OMP	Orphan Medicinal Product
P	Population
PAES	Post-Authorisation Efficacy Study
PaR	Payment at Results
PAS	Patient Access Scheme
PASS	Post-Authorisation Safety Study
PbR	Payment by Results
PBRSA	Population-Based Risk-Sharing Agreement
PICO	Population Intervention Control Outcome
PLEG	Post-Licensing Evidence Generation

PRO	Patient-Reported Outcome
PSA	Probabilistic Sensitivity Analysis
PROM	Patient-Reported Outcome Measure
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
RD	Rare Disease
RDT	Rare Disease Treatment
REQueST	Registry Evaluation and Quality Standards Tool
RS	Risk Sharing
RWD	Real World Data
RWE	Real World Evidence
SMC	Scottish Medicines Consortium
TRUST4RD	Tool for Reducing Uncertainties in the evidence generation for Specialised Treatments for Rare Diseases
UB	Università Commerciale Luigi Bocconi
UCSC	Università Cattolica del Sacro Cuore
UEDIN	University of Edinburgh
WP	Work Package
WS	Workstream
WTP	Willingness To Pay
ZIN	Zorg Instituut Nederland

1. Overview of Work Package 10

The overall objectives of the IMPACT HTA Project are:

- through methodological improvements, to contribute to the understanding of variations in costs and health outcomes within and across countries in the state of the art (best practices) of economic evaluation of new technologies;
- to develop and disseminate a number of innovative methodologies, toolkits and processes in areas such as extrapolation from randomized controlled trial (RCT) data, costing, outcomes measurement, value assessment of medical technologies, technology coverage determinants, and real-world evidence; aiming to inform value assessment processes, aid decision-making and, ultimately, improve efficiency in resource allocation; and
- to develop and disseminate tools facilitating European Union (EU)-wide cross-country collaboration across Member State governments, health technology assessment (HTA) agencies, professionals and the broader stakeholder community.

Work Package 10 (WP10) has addressed an area where use of economic evaluation in HTA is most contentious, that is to inform decisions about access and reimbursement of orphan medicinal products (OMPs) in the EU.

1.1 Rare Disease Terminology

The European Medicines Agency (EMA) can grant an OMP (sometimes called “orphan”) designation to a medicine that treats a rare disease that occurs in less than 1/2,000 people, is life-threatening or chronically debilitating and where there is no satisfactory treatment. This attracts additional regulatory support for clinical development of an OMP and regulatory review by a specialist committee. OMPs may obtain an accelerated regulatory evaluation and receive a marketing authorization that requires mandatory data collection of safety and efficacy post authorization.

At the outset of our research, we recognised that as our work had an international scope and went beyond medicines (e.g., to consider cell therapies) a more general term than OMP was needed. So, we have used the term rare disease treatment (RDT). RDTs include medicines designated as OMPs, but may also include treatments for rare diseases (RDs) for which the company has not sought an OMP designation in the EU. It can also be applied in countries outside the EU that each have their own definition of a rare disease. It should also be noted that in some countries there is a differentiation within the rare disease sector to identify ultra-rare. In some European countries this relates to diseases with a prevalence of less than 1/50,000 people. Henceforth we use the term RDT instead of OMP, unless a process is based on the OMP definition in legislation.

1.2 Challenges in Evaluating RDTs

RDTs often come to market via expedited regulatory approvals resulting in a small evidence base, often with uncontrolled or small confirmatory trials of short duration. This results in challenges for appraisal of clinical and cost effectiveness. Furthermore, given the challenges of medicines development in complex, heterogeneous rare diseases with sparsely located patients and few clinical experts, the costs of development can be large in relation to the total treatment population and often lead to high prices. Given the regulatory incentives for development of RDTs, treatments are often authorised with a limited clinical evidence base. Alongside poor understanding about the natural history of a rare disease, this can result in major uncertainties in the economic modelling. However, as these products treat rare diseases where there is often major disease burden and high unmet need, there is often stakeholder pressure for early access despite the uncertainties.

Countries handle these challenges in different ways. Some apply separate reimbursement mechanisms, others have special features that allow flexibility in the appraisal processes for RDTs (Nicod et al. 2020). All countries agree on the challenge of appraising these treatments and are seeking guidance to understand good practices and support fair decision-making. Hence, WP10 has developed guidance on novel approaches to appraise RDTs that will support robust, accountable decision-making across Europe.

The stated objectives of WP10 were threefold:

1. to develop guidance on novel approaches to appraising RDTs beyond conventional economic evaluation (e.g., cost-utility models).
2. to identify how evidence and knowledge obtained from a range of sources (including economic evaluation) can be integrated into an HTA appraisal to inform robust and accountable decisions.
3. to bring together existing initiatives and different stakeholder perspectives to advance the understanding on the appropriate ways forward for RDT appraisals.

Objectives 2 and 3 outline the manner in which objective 1, the key deliverables of this work package, are being developed.

Existing approaches and developments in appraisal of RDTs have been identified and explored through desktop research, case study analysis and partnership work with key stakeholders across the EU, Canada and New Zealand (workstream 1 (WS1, Milestone 40)). This work has been complemented by ethnographic observation and interviews of English-speaking appraisal committees to reflect on the evidence and inputs that influence decisions about RDTs (WS2, Milestone 41).

Two workstreams have explored issues and developed tools in two areas that are particularly challenging for appraisal of RDTs – namely use of Patient-Reported Outcome Measures (PROMs) (WS3, Deliverable 10.2) and use and implementation of Outcome-Based Managed Entry Agreements (OBMEA) (WS4). All this work is being brought together in an adaptable and reflective appraisal framework for RDTs that could be used within a country or across EU MSs (Deliverable 10.1).

This Deliverable 10.3 report presents the work of WS4 – use (establishment) and implementation of OBMEA for RDTs.

2. Background to work of WS4 Use and Establishment of OBMEA for RDTs

2.1 Introduction to OBMEA

As WS1 shows, there is increasing recognition that standard appraisal processes may not be suitable for RDTs due to the small patient populations studied, lack of information about natural history and heterogeneity of disease that can lead to major uncertainties. In addition, high prices lead to cost per Quality Adjusted Life Year (cost/QALY) values that are higher than traditional willingness to pay thresholds. This latter issue has become much more of a challenge in 2019 as cell and gene therapies have come to market with very high prices for one-off treatments that claim a curative effect, but with only short-term evidence, often from uncontrolled trials.

Appraisal processes can be adapted to account for some of these challenges (as outlined in WS1), but for some RDTs, particularly the ultra-RDTs, these adapted processes struggle to deal with important uncertainties and innovative reimbursement processes are needed (Morel et al. 2013).

MEA (also called managed entry schemes, patient access schemes, risk sharing schemes/agreements, managed access agreements) are one solution to enable access to treatments where traditional appraisal processes would not lead to their use/reimbursement.

According to Klemp, Frønsdal, and Facey (2011) an MEA is an arrangement between a company and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specific conditions to manage

- budget impact (total budget cap, discount, limited number of doses, free first cycles etc.)
- utilization to optimize performance (targeted patients, specialist delivery, etc)
- uncertainty relating to clinical and or cost effectiveness, such as long-term effects, real world effectiveness (known by a range of names including coverage/access with evidence/data development/generation/collection, performance-based schemes, outcomes-based agreements).

Klemp et al. (2011) noted that MEA may be difficult to negotiate, require legal input and increase bureaucracy. Furthermore, although they defined the MEA as being between the company and payer/provider, they recommended a formal written agreement among all stakeholders; identifying the rationale, aspects to be assessed, methods of review and criteria for ending the agreement. This applies even for most financially-based agreements, but for the OBMEA to optimize performance or resolve uncertainties, detailed governance procedures addressing independence, data ownership, audit, transparency and appeal is also needed (MacLeod and Mitton 2010).

Unlike medicines' regulation, there is no EU-wide process for pricing and reimbursement negotiations of a treatment. This can only be considered within the jurisdiction responsible for paying for health care, such as a National Health System or Health Insurance Fund. So, a company may have different agreements in different health systems or a health system may have different data collection/reimbursement rules for similar treatments. As a result of all these issues, Klemp et al. (2011) questioned the sustainability and effectiveness of MEA and suggested that they should be the exception and not the norm.

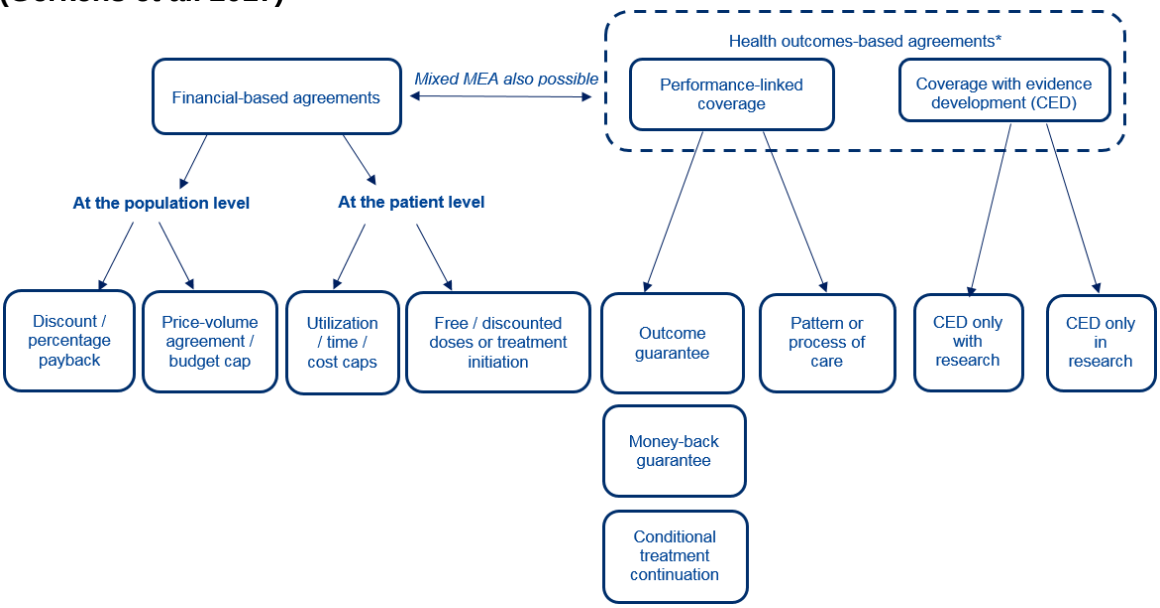
Over the past decade, use of simpler financial-based MEA has in fact become common-place with application of a confidential discount to the published list price of the treatment to bring the cost/QALY below a willingness to pay threshold, or application of a budget cap to the total amount of money that can be spent on the treatment within the healthcare system. However, for high cost RDTs, with major uncertainties in the evidence base, this is not sufficient and there is interest in the potential of OBMEA, not only to provide data to resolve uncertainties, but also to test the real-world effectiveness of complex treatments within a health care setting and optimize treatment use.

OBMEA may occur at two levels (individual/patient and/or population) and are likely to be combined with a financial agreement such as a confidential discount.

- Individual (I) – ensuring only eligible patients receive treatment, sometimes with assessment of outcomes to determine treatment continuation (appropriate use) or linked to payment schemes (paying only if response achieved or refund if response not achieved)
- Population (P) – using Coverage with Evidence Development (CED)/Post Licensing Evidence Generation (PLEG) as a conditional coverage mechanism post health technology assessment (HTA)/reimbursement that requires evidence collection to inform re-appraisal or pricing and reimbursement (P&R) re-negotiations.

ISPOR depicted these processes (Garrison et al. 2013) and they have also been considered for the specific case of RDTs (Morel et al. 2013). More recently, the Belgian HTA body, KCE, has created the following description.

How to improve the Belgian process for Managed Entry Agreements?, KCE Report 288 (Gerkens et al. 2017)



Descriptions of MEA (reproduced from KCE report, Gherkens 2017)

Financial-based MEA

Population

- Discount on the price / percentage payback: percentage reduction of the price /percentage of the real turnover that must be refunded.
- Price-volume agreement/ budget cap: the unit price is linked to the expenditure (volume). One or various thresholds of expenditure (volume) can be defined (i.e., preset budget(s)). A compensation mechanism is given once a threshold is passed (payback/refund, discount). A variant of these MEA are budget caps, i.e., no refund until a predefined level of turnover and 100% of refund after.

Individual patient

- Utilisation or time or cost capping schemes: maximum doses, time, or cumulative cost of treatment per patient after which the manufacturer pays (at least partly) for any additional doses required.
- Free (or discounted) doses / Free (or discounted) treatment initiation: the therapy is free (discounted) up to a certain number of doses or treatment cycles.

Health Outcomes-Based MEA (OBMEA)

Performance-linked coverage: link clinical outcomes to payment or reimbursement

(Individual)

- Outcomes guarantee: payment for responders only, i.e., the manufacturer is only paid if the product meets an agreed outcome target.
- Money-back guarantee: refund for non-responders, i.e., the manufacturer provides refunds if the product does not meet an agreed outcome target.
- Conditional treatment continuation: payment / reimbursement for continued use only for patients reaching a pre-defined intermediate treatment milestone.
- Pattern or process of care: payment / reimbursement is linked to practice patterns (e.g., adherence of the patient to the treatment), is granted only for patients that satisfy eligibility criteria for example as a result of a genetic test, or is limited to reference centre.

Coverage with Evidence Development (CED): the coverage decision is temporary and is conditioned upon the collection of evidence
(Population)

- Only with research: evidence collection only for a sample of patients, i.e., only a sample of patients must be involved in the study while all patients are covered.
- Only in research: evidence collection for all patients, i.e., only patients participating in the study are covered.

CED has been defined as "any plan by which the performance of the product is tracked in a defined patient population over a specified period of time and the level or continuation of reimbursement is based on the health and economic outcomes achieved" (Garrison et al. 2013). More recently EUnetHTA Joint Action (JA) 3 has created the term Post Licensing Evidence Generation (PLEG) that complements evidence already generated for HTA appraisal, to address remaining uncertainties and potentially cover wider questions of disease management and healthcare delivery in the post marketing authorisation (licensing) phase[1].

Literature shows that implementation of CED is challenging with questions about who should fund treatments, data collection and analysis, what and how data should be collected in a timely manner in standard clinical practice, confidentiality issues, the ability to obtain sufficient data to allow reassessment and enact the result of the reassessment, particularly if this means disinvestment. In addition, for rare diseases, issues such as paucity of data and the need to collaborate across jurisdictions arise (Morel et al. 2013), (Balvanos J 2019).

Even for individual OBMEA (such as only paying for a certain response or receiving a refund if an outcome is not achieved), the administrative burden of having to collect outcomes to determine the price paid for each patient and manage the financial flow is so challenging that these seems have been rarely used for medicines in most countries, with Italy being an exception.

2.2 Methods in WS4

The aim of WS4 has been to develop guidance and tools to support the use and implementation of OBMEA (particularly CED/PLEG) to support re-appraisal of RDTs taking account of the four good practices identified by Wenzl and Chapman (2019). To achieve this a policy analytic approach has been taken, building on expertise of IMPACT HTA partners, expert engagement and public consultation.

We have used multi-methods research (desk top reviews, workshops, literature reviews, case studies, consultation) to explore issues related to the use and implementation of OBMEA in RDTs. This began by a review of responses to questionnaires in our first workstream. We then worked to understand implementation issues related to use of OBMEA for RDTs in two very different systems, namely NICE's Highly Specialized Technologies (HST) Programme in England and the Agenzia Italiana del Farmaco (AIFA) in Italy. We have connected with other EC funded research – EUnetHTA PLEG (WP5B) and the Cost and Outcomes of Medical Devices (COMED) project to share learnings, avoid duplication of effort (particularly in relation to literature searches) and align on direction. On this foundation, we worked with HTA experts internationally to review the implementation of OBMEA for two different RDT cases and participated in multi-stakeholder initiatives to explore real-world data issues in OBMEA for cell and gene therapies. This work has culminated in tools to support use of OBMEA in RDTs that have been consulted on internationally. Details of the methods for each activity are outlined in the following sections.

[1] https://eunethta.eu/pleg/ Accessed 20 April 2020.

3. WS1 FINDINGS

The survey, desktop research and expert consultation undertaken in WS1 about appraisal processes for RDTs included a question about OBMEA as follows:

3.3 Does the process allow any form of Managed Entry Agreement/Patient Access Scheme/Access with Evidence Generation? (state name of each process and tick all that are possible, for each process)
Name of process:

- Confidential discount
- Budget cap
- Outcome based scheme to collect additional evidence for later reassessment
- Outcome based scheme for individual patients, only paying for certain performance
- Other, not specified
- Unsure
- No.

Appendix 1 displays the questionnaire responses for this question. This provided a helpful insight into the use of OBMEA in a range of countries and whether they were specific for RDTs. However, knowledge of the researchers and details in other published papers indicates that since the data collection in 2018-2019 not all the entries are up-to-date. Furthermore, experts in several countries clarified that although these OBMEA mechanisms were available, they were rarely used due to the complexities of administration and implementation. So, we took Appendix 1 as a starting point for further exploration of issues related to OBMEA.

Taking Appendix 1 at face value it indicates that most countries that could employ OBMEA do so within their standard appraisal processes and only Lithuania and UK-Scotland limit these processes to RDTs or ultra-RDTs. Furthermore, different forms of OBMEA are potentially available for use in different countries, as summarized in Table 1.

TABLE 1. INITIAL DELINEATION OF FORM OF OBMEA BY COUNTRY

Form of OBMEA	Country
Individual only (no CED elements)	Estonia Lithuania (RDTs only) Sweden
Population only (including individual elements for eligibility and continuation of treatment)	Canada Czech Republic Latvia Netherlands Portugal *(unclear response)* UK – England UK – Scotland (ultra-RDTs)
Individual or Population Agreements possible	Belgium Italy Poland Slovakia
Form unknown/unclear	Austria (different processes for RDTs) Bulgaria Ireland Slovenia Switzerland

Hence given the rather imprecise picture of the implementation of OBMEA for RDTs in European countries from the WS1 work, it was decided to explore their actual use in WS4 by undertaking case studies described in Section 7.

4. LEARNING FROM OTHER EC FUNDED HTA PROJECTS – EUNETHTA AND COMED

4.1 EUnetHTA PLEG

EUnetHTA Joint Action (JA) 3 is undertaking a product-specific PLEG pilot on the OMP Spinraza (nusinersen) for spinal muscular atrophy. This was led by HTA bodies in Italy, Norway, Croatia, Finland, Netherlands and Portugal. The first phase studied evidence gaps, minimum datasets, quality requirements etc. This work was reported in Spring 2020 (EUnetHTA Joint Action 3 2020a) (EUnetHTA Joint Action 3 2020b). It is stated that, where possible, a second report compiling and analysing the data from different jurisdictions will be reported, but it is unclear that this will happen given delays that arose in defining the data requirements.

We also chose nusinersen as one of our case studies as outlined in section 7 and reflect on the comparisons in the discussion.

EUnetHTA JA3 has also undertaken two pilots that assess the suitability of existing disease-specific registries for PLEG purposes, reviewing outcomes collected and quality of data via the EUnetHTA REQueST tool. Both registry qualification pilots relate to RDs - namely cystic fibrosis and specific forms of haematological cancers treated by cell-therapies. As obtaining sufficient real-world data of good quality is a major problem in an OBMEA and the European Reference Networks (ERNs) must each establish a registry, this is an important tool to ensure that these clinical registries consider the needs of HTA.

EUnetHTA may also have other relevant information in the EVIDENT database that enables sharing and storage of information relating to PLEG activities by individual partners, but this is restricted to EUnetHTA partners and we have not been able to obtain information about it.

4.2 COMED

WP7 of the COMED project was established to assist policy makers with the design and implementation of CED for medical devices. Carlo Federici and MD at UB have shared emerging work in confidence with the IMPACT HTA WP10 team to enable discussion of findings, avoid duplication of work and ensure complementarity of approaches.

COMED D7.1 (June 2019) reported a systematic review of the challenges associated with the design and implementation of CED MEA for all types of health technologies. The systematic review included 62 articles and categorised the challenges of CED MEA. A paper summarizing the 27 papers relating to medical devices was then published (Reckers-Droog et al. 2020). In the second paper, a taxonomy was slightly altered to define phases of CED as:

- desirability (whether a CED scheme should be undertaken)
- design
- implementation
- evaluation of the scheme

with underpinning ethical issues.

KF developed elements from D7.1 and the published paper into considerations relevant for CED of RDTs as outlined in Table 2.

TABLE 2. CHALLENGES WITH CED MEA RELEVANT FOR RDTS - DEVELOPED FROM COMED

Phase of CED	Considerations
Desirability (deciding whether a CED scheme is required)	• Lack of explicit criteria about appropriateness of a CED MEA can lead to stakeholder pressures for its use to enable access • Diverse qualitative approaches, principles and checklists have been published to establish whether a CED MEA is appropriate and feasible including issues such as: ➢ treatment is expected to be beneficial, but would not be recommended by the current HTA ➢ relevant evidence can be generated following reimbursement in a timely manner and will impact re-appraisal ➢ the subsequent reimbursement decision can be enacted and the costs of that are justified • Lack of clarity about the clinical and economic uncertainties in the HTA may hamper evaluation of the appropriateness of a potential CED MEA
Research Design	• The purpose of the Agreement should be clearly communicated including a statement of the decision problem (HTA uncertainties to be resolved) • The design of study for data collection should be clearly justified (RCT, uncontrolled data collection, protocol or use of existing data collection arrangements) • The relationship between all stakeholders (company, HTA/payer, clinicians, patients, researchers) should be documented with a process to align expectations of the scheme and manage conflicts of interest • Outcomes to reduce uncertainties identified in HTA should be chosen that are measurable within the timeframe of the CED MEA • The intended sample size should be defined and justified • Length of data collection period ➢ sufficient data to resolve uncertainties, but not so long that data are not relevant for the clinical context at the time of re-appraisal ➢ fixed timeline or dependent on interim results • Data collection is challenging in the real-world and should consider issues such as: ➢ routine (health system data or clinical registries) or bespoke ➢ balancing simplicity (taking what's available) with need to generate relevant evidence for decision-making ➢ adequacy of IT infrastructures ➢ ensuring sources are valid, reliable and accurate to provide comprehensive and relevant data ➢ lack of standardization of registries ➢ challenges in linking different datasets ➢ responsibilities for data collection ➢ processes to maintain patient confidentiality ➢ development of data collection forms and processes to query and validate data ➢ independent (robust) analysis • Negotiations to reach a contractual agreement can be lengthy and complex

Phase of CED	Considerations
Implementation	• Execution challenges include: ➢ Lack of experience with CED ➢ Staff turnover ➢ Complexity of billing requirements ➢ Inconsistency of research and non-research elements ➢ Identifying and counselling potential participants ➢ Burden of the data collection ➢ Substantial administrative burden that is often not funded • A clear process is needed to obtain informed consent (and reconsent if the MEA changes) that may be bespoke for the research or within existing processes (e.g., such as registries) • Resources and training may be needed to ensure stakeholders collect good quality data • Costs for CED can be substantial, so funding arrangements must be agreed (company, payer, HTA, clinician)
Evaluation (and translation into policy)	• Clear decision rules are needed for re-appraisal based on the new evidence (e.g., linking specific outcomes with particular pricing and reimbursement decisions, delisting) • There is a risk that the CED research does not answer the initial HTA questions or is of insufficient quality (accuracy, reliability, completeness) • Need to ensure that the Agreement yields data of sufficient quality to provide new information on the uncertainties identified in the original HTA • Timely compilation and analysis of the data from the CED Agreement is needed to input to the decision-making process • Interpretation of the new evidence needs to be aligned among all stakeholders given the confounding factors and biases that are likely to exist in this RWD • Need to be able to implement the revised reimbursement decision based on the additional evidence (particularly if disinvestment is recommended) • Evaluate how the additional evidence impacts the re-appraisal and decisions about future use of the health technology considering key questions such as: ➢ Was there integrity in the design and analysis? ➢ Have the intended outcomes been collected? ➢ Was uncertainty in estimates of these outcomes reduced? ➢ Has the additional evidence informed the re-appraisal? ➢ Does each stakeholder consider the CED Agreement has been of value? • Payers could benefit from knowledge of CED MEA, but there is a lack of transparency about Agreements due to commercial confidentiality but not all elements (such as objectives, design and evaluation of impact) are subject to confidentiality
Ethical Issues (underpinning)	• *As the treatment is expected to be beneficial, is uncontrolled data collection more acceptable because there is lack of equipoise?* • *Which CED schemes count as research? (If registries are already in place, is that research?)* • *As the CED Agreement will only be available to certain centres are geographical inequalities introduced?* • *Is ethical approval needed?* • *Does participation in research as a condition of treatment amount to coercion, and if so, can it be ethical?* • *What consent process is appropriate?* • *Is it ethical to withhold treatments from patients who won't consent?* • *Who owns the data?*

Understanding these challenges is essential to improve a CED MEA's chance of success, but it is also recognised that given most CED MEA are confidential there may be other challenges (Reckers-Droog et al 2020). Public sharing of information about CED MEA could not only identify other challenges, but also help develop shared learnings.

Reckers-Droog et al (2020) suggest that future research should seek to validate and deepen understanding about the intensity of the challenges for different health technologies and go beyond this focus on challenges for the payer/company to consider impacts for other stakeholders such as clinicians and patients. This proposal influenced the work of WP10 WS4 as outlined in the following sections – with a focus on evaluating stakeholder challenges and exploring challenges in different health systems, even those where OBMEA are not made fully public.

5. Stakeholder Workshops to Explore Implementation Issues

5.1 Public multi-stakeholder workshop at HTAi 2019

Fifty-two people from different HTA stakeholder groups attended a one-day pre-conference workshop at HTAi 2019 in Cologne. Half of the workshop was devoted to discussing challenges in implementing OBMEA for RDTs. The workshop was a mix of presentations from experts, small group work and plenary discussions. All presentations are available for HTAi members at link. A full report is available on file. A summary is provided here with additional interpretations given our current knowledge.

Opening presentations from IMPACT HTA partners - KF, EX and SU outlined the issues with RDT appraisal, described OBMEA, explained the registry system used by AIFA in Italy and the Managed Access Agreement (MAA) system used by NICE in England. Additional presentations gave an overview of challenges experienced by ZiN in the Netherlands and real-world data issues. A patient group representative (who had previously worked at the HTA body in France) noted that OBMEA exacerbate issues relating to lack of transparency about price (as it is difficult to calculate what the average cost per patient is with complicated individual schemes).

A panel discussion with the audience raised the following key points:

- HTA agencies may not have knowledge of EMA requirements for post licensing studies (Post Authorisation Efficacy/Safety Studies – PASS/PAES).
- Industry wants predictability in HTA/payer decision-making processes, but this predictability could be at odds with best outcomes for patients (allowing flexibility in decision-making).
- NICE tries to select technologies for OBMEA that are clearly "winners", i.e., with large QALY gains.
- OBMEA should involve true risk sharing.
- Uncertainty can evolve over time and new information about RDs can sometimes bring more uncertainty (we know better what we don't know).
- Agreement needed among all stakeholders about the data to be collected.
- In the NICE process, patients/guardians receiving treatment in an OBMEA have to sign an agreement, which indicates they understand their individual role in adhering to treatment and attending all clinic visits to provide good data.
- Three years is not long enough for an OBMEA, at least five years is needed to capture data. How long is reasonable?
- How are patients in the OBMEA managed if the re-appraisal does not recommend the treatment?

Small groups then discussed five questions.

1. When should OBMEA be used for RDTs?
   - Need early engagement with HTA, government, payers.
   - To establish value where this is still unclear
   - When there are uncertainties that can be reduced in a reasonable time scale
   - Consider incidence/prevalence and feasibility of MEA
   - Cell and gene therapies, which are a high price, one-off treatment with purported long-term effects, need outcomes-based process.

2. What OBMEAs have worked well?
   - NICE Cancer Drugs Fund
   - Italy has substantial experience with OBMEA through use of company funded registries that are integrated within the healthcare system and are the responsibility of the payer – but there is a move away from individual outcomes-based agreements to simpler financial-based schemes.
   - OBMEA based on completion of a phase III study or undertaking a phase IV (post-marketing) study organised by the company (funded by the company and well conducted)
   - Those aligned with regulatory post authorisation requirements such as PAES/PASS
   - Those that have involved patients in their design
   - Those where there is transparency
   - Those with a clear entry AND exit strategy.

3. What is the best process for data collection?
   - Collaborate early in development to collect evidence earlier - map gaps so strategies to address these can be developed
   - Clarify data collection requirements at the outset, what's in it for each party and establish resources
   - Use observational studies
   - Use good designs with follow-up
   - Engage with ERNs to obtain natural history data
   - Use a condition-specific registry if there is one, but check the quality and completeness of its data for the purposes of OBMEA
   - Consider Pan-European (or worldwide) approach to data collection to secure meaningful data, taking account of interoperability requirements but recognizing differences in care that might limit amalgamation of data
   - All stakeholders (and HTA/Payers across countries) agree a minimum dataset of outcomes to be collected that is patient-centred and includes clear information about treatment starting and stopping (and restarting).
   - Could collect PROMs via digital tools – but need to encourage patient honesty to get good quality data in unblinded data collection settings.
   - USE RWD within an appropriate legal framework
   - Use predictive modelling
   - Work with stakeholders to ensure generation of good data.

4. Can information about constructs of OBMEA, and data, be shared across borders?
    - Need consistency in definition of RDT internationally, and ultra-RDT
    - Could share the following information about OBMEA, but currently this is NOT generally shared:
        - key research questions
        - principles for use of OBMEA
        - data to collect
        - framework
        - timeframe
        - who to involve?
    - Need to explore ethical issues – particularly those related to patients.

5. How should stakeholders be involved?
    - Early and continuous (iterative) multi-stakeholder dialogue
    - Open and stable, multi-stakeholder communication platform
    - Need to align stakeholders, but recognise they don't have the same interests
        - HTA/payer/health system – needs to set boundaries
        - clinicians
        - patients and patient groups
        - industry (should they provide some resources?)
    - Shared ownership – need to consider weight/priorities, governance, monitoring
    - Agree roles and responsibilities to find who can support what aspect.
    - Consider data collection responsibilities across the key parties (industry, clinician, health system) to gather data that is sufficiently robust for assessment
        - Who is responsible for the study design?
        - Ethics
        - Who owns the data?
    - Provide support processes for all
    - Resources – what aspects can be coordinated at EU level?

5.2 Workshops for those involved in NICE OBMEA for RDTs

5.2.1 OBMEA in the NICE HST programme

The NICE HST programme evaluates treatments for ultra-rare and complex conditions that require specialised services. Of the nine appraisals undertaken in the HST programme up to May 2019, three included MAA (Managed Access Agreements), which in our terminology are CED OBMEA with individual elements to ensure appropriate use and conditional continuation. These were all uncontrolled observational studies that were undertaken as service evaluation within the NHS and thus did not need ethical approval.

Each HST OBMEA is a combination of individual-based and population-based outcome schemes – with strict entry criteria and annual reassessment to determine continuation of treatment up to the point of re-appraisal at the end of five years. Each uses a different data collection mechanism – the first originally relied on clinicians to manage the data collection, the second uses an established clinical registry, the third is managed by the company using a bespoke registry added to a company global registry. The first re-appraisal was planned for summer 2020 but it was suspended in February because the MAH had not provided an evidence submission that was adequate for the appraisal committee to make a decision. However, in spring 2021, the appraisal has now restarted and we look with interest on the outcome.

NICE OBMEA (in any appraisal programme) comprise two components - the Commercial Agreement (reimbursement negotiation) with the Payer (NHS England) and the Data

Collection Agreement with NICE. The separation of these means that the Data Collection Agreement can be shared with all stakeholders and made publicly available.

The Data Collection Agreement has a standard template that includes:

- key areas of clinical uncertainty
- the eligible population and rules for continuing treatments
- the specification for data collections (including data sources and transfer processes to ensure confidentiality)
- the timeline of the agreement.

These are among the most transparent of processes, with the agreements and responsibilities published on the NICE website.

5.2.2 Multi-stakeholder workshop

Experience of implementation challenges is emerging and so in May 2019, a workshop was undertaken with all stakeholders including NICE staff, pharmaceutical companies, patient groups, clinicians, the Payer (NHS England) and the group responsible for critical assessment (Evidence Review Group). The workshop used small group work across and within stakeholder groups to explore OBMEA establishment and implementation issues. The questions drew on the COMED findings and the COMED WP7 lead reviewed the workshop plan.

A confidential workshop report was prepared for UEDIN and UB team members that included the detail of each small group discussion and is available on file. A summary report was prepared and shared with participants. Key findings were:

- OBMEA should be the exception, not the rule, and may be used for promising HSTs, which have uncertainties that could not be resolved during the appraisal but could be resolved by data collection.
- OBMEA include clinical endpoints that are used to determine eligibility of patients to enter, for annual decisions about continuation of treatment and to develop evidence to resolve uncertainties.
- In addition to appraisal experts and industry, clinicians and patient representatives need to be involved in agreeing the data to be collected to ensure the data collection is realistic in clinical practice. (However, to avoid delays OBMEA should be developed rapidly and getting agreement of all relevant parties to the data collection agreement is challenging.)
- All parties need education at the outset of the agreement to understand the process, their responsibilities and resource requirements.
- Close working with patient groups is essential to ensure that the implications of the OBMEA for patients are appropriately considered, including the mandatory agreement about treatment adherence, data collection requirements, the process for the HST re-appraisal and understanding of the consequences for access to treatment at the end of the OBMEA.
- The form of data collection – via clinic records and transfer to a central database, add-on to existing registry, bespoke registry, data linkage etc needs to be carefully considered, planned and monitored to ensure that there are sufficient resources in clinic to deliver and clean data to ensure it is of sufficient quality and quantity for the HST re-appraisal.

- A range of issues has arisen in the conduct of the OBMEA such as identification of eligible patients across the country in an equitable way, process for assessments given a range of challenges in the real-world, application of continuation criteria, enforcement of treatment regimen, completeness, quality and timeliness of data. The discussion of these in regular multi-stakeholder oversight meetings has been valuable.
- The data collected in the OBMEA will not be of the same quality as a clinical trial, clarity is needed on how the data will be assessed.
- NICE HST methods have altered since the establishment of these OBMEA to include reference to cost/QALY thresholds, but as these OBMEA were based on clinical uncertainties the data being collected in the OBMEA may not be adequate to support economic modelling.
- Patient groups need resources to support individual patients in their participation in the OBMEA and clinicians need more resources to enact the OBMEA if it is to produce high quality data.
- Going forward, a clearer process for OBMEA is needed, akin to the clarity that accompanies all NICE appraisal processes.
- There is interest in the new “ultra-orphan pathway” in Scotland, which requires negotiation of a “fair price” and three years’ of data collection organised and funded by the company. Any patient within the licensed indication will be eligible to enter the scheme and data can be collected from electronic health records in NHS Scotland.

5.2.3 Patient group workshop

NICE encourages patient groups to be involved in every stage of the HST OBMEA from establishment through to re-evaluation by:

- helping to develop the data collection agreement for the OBMEA, identifying that outcomes that matter to patients are studied and commenting on eligibility criteria
- acting as the link to the patient community to provide feedback to NICE about real-life experience of accessing treatment in the OBMEA
- producing tools to help explain the OBMEA to patients/carers
- providing input to the RDT-specific Managed Access Oversight Committees (MAOC), which discuss issues arising in the OBMEA (eligibility, treatment, patient assessments) and agreeing a consistent way forward, which will in future help standardise processes
- providing input to re-appraisal.

From the multi-stakeholder workshop, it was clear that patient groups involved in NICE OBMEA for RDTs would value more support. A teleconference was held with patient group leaders involved in the HST programme (and nusinersen in the Technology Appraisal programme). The material they had developed to support patients in their OBMEA was gathered and a patient group specific workshop was developed with them and held in January 2020, including the lay representatives from the NICE HST appraisal committee.

A summary of key issues raised in the NICE patient group workshop were:

- It can take a long time to agree the commercial and data collection agreements and this can lead to delays, but it can also feel like important decisions such as the eligibility criteria are too rushed.
- Patient groups have been signatories to the OBMEA and may have responsibilities for some data collection.
- Throughout the conduct of the OBMEA patient groups act as the representative for patients, feeding in questions and concerns from patients to other stakeholders and ensuring that other stakeholders are taking account of patients’ needs. This is a major burden given they are not funded for this work.

- In some cases, appropriate PROMs were not used in the original HTA and so new PROMs are being sought for the OBMEA. However, it has not been possible to develop these rapidly and so many patients have entered without baseline PROM assessments. (Post-Meeting note – work done with patients at the outset identified that no existing PROMs were sufficient to address their key quality of life issues, but there was insufficient time to develop a new PROM, so existing measures are now being used.)
- The stakeholder involvement processes for reappraisal have been similar to those in the original appraisal process and not focused on the key uncertainties that are to be addressed by the OBMEA.
- The OBMEA should resolve the major uncertainties identified in the initial HTA, but the company could also commission analysis of health system data to demonstrate unexpected clinical benefits that may not have been studied (such as reduction in hospitalisations).
- Patient group (and clinician) submissions to the reappraisal process should focus on the "real-life" benefits and disbenefits of the treatment that are not collected in other evidence. This may be obtained in a variety of ways, but is ideally undertaken with robust qualitative research methodology, for example using interviews or focus groups to gain input from a wide range of patients eligible for the OBMEA.
  Questions such as the following, may be helpful:
  - Why did patients choose NOT to go on treatment in the OBMEA?
  - Why did patients discontinue treatment?
  - What are the experiences of those still on treatment?
  - Have patients or carers seen benefits that are more holistic, such as better participation at school
- When the company submission is critically assessed, outstanding questions about the uncertainties should be presented to the patient groups (and clinicians) to allow them to check their sources and enable them to be better participate in the deliberative discussion.
- Sharing of experiences across patient groups is valuable and will be particularly important after the first re-appraisal.

As a result of these discussions, we agreed to develop a patient group submission form for re-appraisal as outlined in section 0.

In this workshop discussion about the OBMEA process, it was agreed that for RDTs there should be a slight alteration to the COMED taxonomy presented in Table 2 to consider the following three phases of OBMEA.

TABLE 3. PHASES OF AN OBMEA FOR AN RDT

Phase	Activities
Establishment	purpose, stakeholder responsibilities, research plans, agreement on eligibility and continuation criteria, outcomes to be studied
Implementation	data collection infrastructure, monitoring to improve data quality and completeness, amendment processes, feedback mechanisms for clinicians and patients, resourcing, ethical issues
Re-appraisal	process for re-appraisal and inclusion of stakeholder inputs, ability to implement a revised reimbursement decision

5.3 Issues arising in follow-up of NICE workshops

After the workshops, we worked with EK to document in more detail the most challenging or common issues that have arisen in NICE OBMEA as presented in Table 4. These provide additional insight into some of the implementation issues raised in Table 2.

TABLE 4. ISSUES ARISING IN CONDUCT OF NICE OBMEA FOR HSTS

Issue	Example
Establishment	
Patient consent	In some cases, patients and/or their carers sign a form at the outset indicating that they have read and understood the terms of the OBMEA. This includes for example, confirmation of understanding the assessment schedule, data collection and sharing principles, and treatment continuation arrangements following the expiry of the OBMEA. These arrangements can be complex to describe and there is a need for careful counselling during the consent process and in some cases additional support and guidance from patient groups to ensure that patients and/or their carers fully understand the terms at the outset, and continue to confirm their understanding.
Research on children	There are potentially complex scenarios that can arise when treatment is delivered in the real-world setting compared to a clinical trial, which must often be considered by clinical experts on a case-by-case basis. For example, a guardian may decide to discontinue treatment, but when a child reaches age of consent they may wish to go back on treatment. Careful counselling is key to ensure there is clear understanding of the terms for re-joining the OBMEA.
Use of PROs in continuation criteria	If PROs are used as one of the continuation criteria, there is a risk that patients could manipulate responses to ensure continuation. This could be mitigated by a trained interviewer gathering PROM responses in an interview.
Implementation	
Reasonable adjustments to planned assessments	In the real-world, clinical setting of the OBMEA, some eligible patients may not be able to undertake planned assessments to determine treatment continuation (e.g., not possible to assess ambulation if in wheelchair). It would be helpful to document how this is handled to ensure consistency of approach with all patients in the OBMEA. Ideally, this should be published in an Addendum to the OBMEA.
Repeated missed treatments lead to discontinuation	If several treatment administrations are missed, this may be labelled as non-compliance and lead to discontinuation according to the OBMEA criteria. However, some treatments require hospital visits and it can be envisaged that family circumstances may preclude clinic attendance (particularly if disease is genetic and other family members need substantial care – e.g., Duchenne Muscular Dystrophy and families of boys). Hence careful communication with patients and carers is important to determine cases of non-compliance that would have been avoidable.
Emergence of new treatments	Clear policies concerning treatment switching, handling of data for patients who have switched, and mechanisms to adapt the OBMEA in response to changes in the treatment path are important measures.
Stakeholder burden	The burden on patients, patient groups and clinicians in an OBMEA is extremely large and so it is imperative to ensure that they are only undertaken when they can collect sufficient data to impact the re-appraisal.
Duration of data collection	There needs to be clarity about the quantity of data needed to resolve the key uncertainties (for example with a sample size calculation) and clear monitoring strategies to address arising issues with data collection. If the OBMEA is not gathering data of sufficient quality or quantity to inform the re-appraisal at the planned time, flexibility to amend the OBMEA may be needed.

To explore these further, we observed a NICE Managed Access Oversight Committee, where the progress of a specific OBMEA was discussed by a multi-stakeholder group. This confirmed the issues and identified the requirement to take a proactive approach with all stakeholders to ensure data quality and sufficiency for re-appraisal.

6. AIFA REGISTRIES FOR RDTS

Since 2006, the Agenzia Italiana del Farmaco (Italian Medicines' Agency - AIFA) has used MEA with mandatory data collection when there is uncertainty about the clinical benefit, appropriate use or budget impact of an authorized medicine that will be used in the hospital setting.

MEA are implemented on a national web-based registries platform owned by AIFA and co-managed by the health system regions who are responsible for assigning centres to provide treatment. Following the appraisal of a medicine, a construct for the data collection is created by an AIFA member of staff to capture essential information about the patient, treatment and address the uncertainties. The system includes automatic validation checks and standardised reporting. The MAH pays approximately €30,000/year for the first three years for the construct, updates on data collection and data reports. Thereafter the annual cost is €10,000.

At a minimum, for each medicine/indication, a discount is in place and an individual "appropriateness" OBMEA to track the eligibility of patients (clinical data, diagnosis and patient characteristics), treatment (drug dosage, administration, end of treatment) clinical outcomes, adverse events. These constructs are publicly available on the AIFA website for each medicine, an example for Nusinersen prepared in English by EX is presented in Figure 1.

All database entries, apart from dispensing are entered by treating physicians who are unable to prescribe the next cycle of treatment unless they enter data and the patient is eligible to continue.

Some registries have more complex performance-based arrangements:

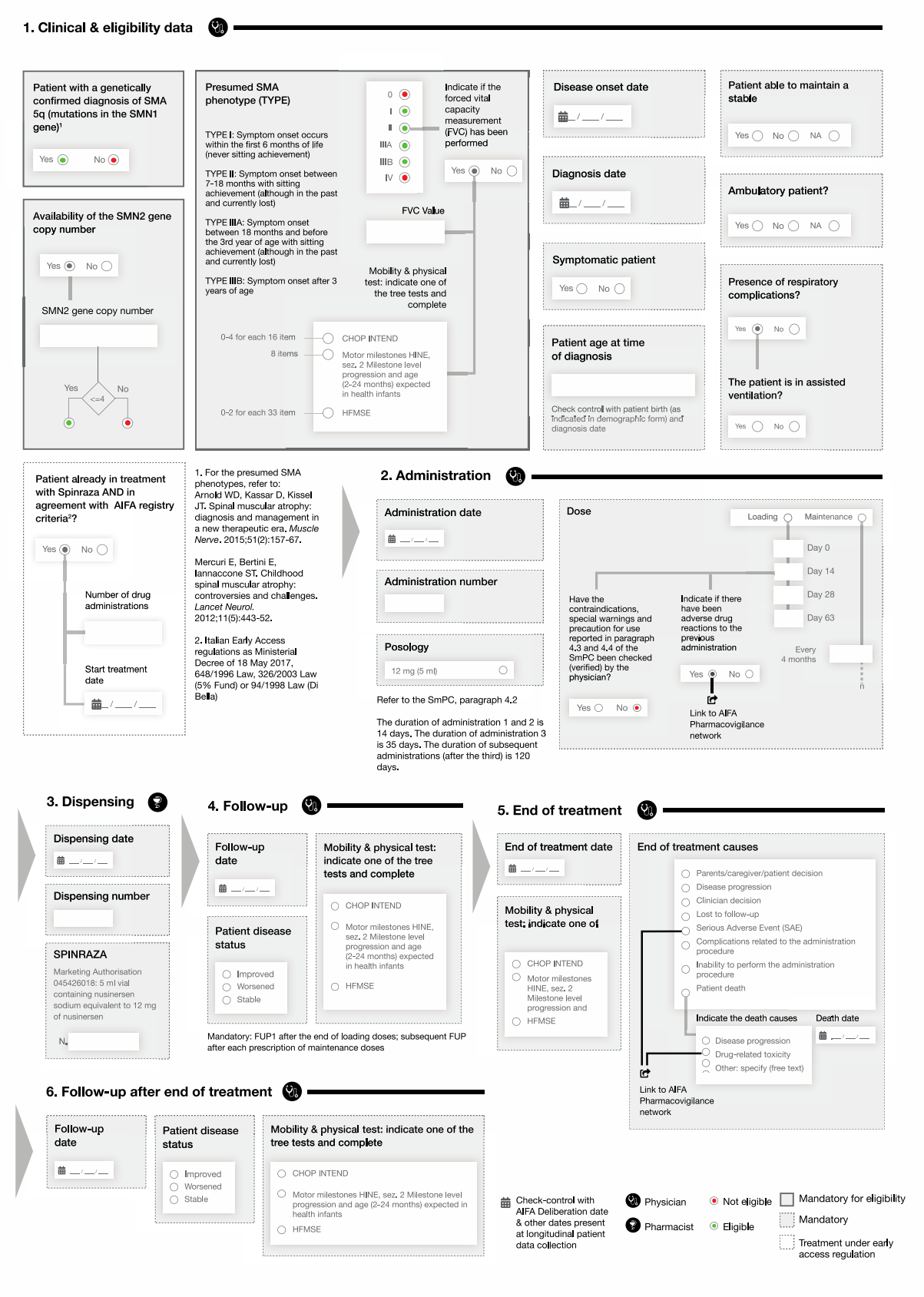
- Risk sharing (RS) - discount for non-responders
- Payment by results (PbR) - refund full cost of therapy (money-back guarantee)
- Payment at Result (PaR) – payment only if treatment successful (outcomes guarantee).

EX developed a comprehensive database of all MEA implemented by AIFA. Information from a range of sources including EMA data and AIFA published documents have been used to explore the different forms of registries used for OMPs vs other medicines. Analyses show that since inception of the AIFA registries in 2006 up to the end of 2019, there have been MEA for 283 treatment-indications. Many registries run for many years. Only 77 of the 283 that have been initiated since 2006 have been closed.

Eighty-eight registries have been established for OMP indications. Seven of these were financial-based MEA. The remaining were OBMEA. The vast majority (64) were appropriateness registries. Ten OMP indications required PbR registries. The PaR registries are the newest form of registry, introduced in 2019 to handle the CAR-T therapies (2 treatments, 3 indications).

The data collected in these registries is used for pricing and reimbursement re-negotiations, but despite this impressive data collection effort, there have been few publications arising from the AIFA registries. However, reports are now being produced for the new PaR schemes and will be valuable for the international community when translated.

Figure 1. AIFA Registry Construct for Nusinersen (Xoxi et al, 2021)



We identified that although AIFA is identified internationally as having the most efficient system for running OBMEA, the use of more complex PbR has declined over the years due to the administrative burden. Alongside this decline, a new appraisal consideration of the innovation status has been introduced (based on a categorization of unmet need, added value and evidence GRADE). The majority of OMP indications have been found to have conditional or full innovation status and been accompanied with an appropriateness OBMEA.

More detailed analysis and discussion is presented in the manuscript in the D10.3 portfolio that was submitted to Health Policy in September 2020. After five months and despite several enquiries, it was still in the review process. Hence it was withdrawn and has now been submitted to *Pharmacoeconomics*.

7. CASE STUDIES

Background
Concerns have been raised that many countries and regions are not transparent about their use of OBMEA (Wenzl and Chapman 2019), with England and Italy being obvious exceptions. Therefore, it was decided to learn more about implementation of OBMEA in other countries using two different RDTs as case studies. A standard template (Appendix 2) was developed by EX to document the operational basis for OBMEA, eligibility and continuation criteria, outcomes to be collected, responsibilities for funding, data collection etc

The case studies selected were an RDT and ultra-RDT in the non-cancer and cancer fields that have generated discussion in the HTA community about their OBMEA:

- nusinersen (Spinraza) for 5q spinal muscular atrophy
- tisagenlecleucel (Kymriah)
    - for paediatric and young adult patients up to 25 years of age with refractory or relapsing B-cell acute lymphoblastic leukaemia
    - for adult patients with relapsed or refractory diffuse large B-cell lymphoma.

The template was issued by EN to our HTA/Payer contacts in all countries in the EU, Australia, Canada and New Zealand in April 2020. Responses had to be chased during the following months, as many of the HTA expert contacts became involved in Covid-19 issues. To focus our call for responses, we also contacted the MAH's to ascertain the countries they knew to have OBMEA. Information from the templates was extracted by KF in a more succinct format and validated with the respondent.

Nusinersen
Templates were returned from Austria, Portugal and Spain that provided general responses about OBMEA construction and limited information about the data collection plans because the agreements are confidential. Belgium, England and the Netherlands showed CED OBMEA. Bulgaria, Italy, and Lithuania showed individual-based OBMEA to determine eligibility, continuation and in some cases total budget cap. An initial response was received from Latvia that documented an individual-based scheme, but due to health system pressures, it was not possible to validate the data summary. A detailed national treatment protocol was also proposed for Ireland but it was not executed. In Poland, it is unclear if the scheme proposed by the HTA body was implemented due to confidentiality issues. See Tables 1 and 2 in the embedded paper.

Tisagenlecleucel
Templates were returned showing CED schemes in Australia, Belgium and England and an individual-based scheme in Italy. Publications described CED in France and an individual-based scheme in Spain. In Austria, it is known that the national specialist group of haematologists organised data collection via the European Society for Blood and Marrow

Transplantation, but the reimbursement decisions (including any OBMEA) were agreed in regions and are confidential. In Canada, CADTH recommended that tisagenlecleucel be provided via interprovincial agreements and that standardized outcomes data be collected in a pan-Canadian registry to generate real-world evidence for consideration in future assessments to assess longer-term effectiveness, safety and cost-effectiveness[2]. No further details of this are published. See Table 3 in the embedded paper.

Findings

We ran two workshops for the HTA/Payer experts that had completed the template to discuss the background to, and construct of, the OBMEA within their health system context. These workshops generated valuable discussion among the experts as they were keen to hear others' experiences. One important insight was that the OBMEA are not just used for re-appraisal or pricing and reimbursement decisions, but have been used to optimize use of treatments. One example was use of the OBMEA to test restricting eculizumab treatment to three months duration in the Netherlands, and when this was found to have no detrimental effects, the change was accepted by clinicians and patients. Workshop participants wished to stress that OBMEA were burdensome and they did not wish to be seen as promoting them for every medicine – they should be the exception, not the norm.

As many have indicated that OBMEA are confidential, we were surprised to find that the detailed construction of these Agreements was publicly available. This proves that these data collection elements can be disentangled from confidential pricing/commercial agreements but may not be published in English or published in as obvious a place as HTA reports.

We found commonalities in approach across countries in that OBMEA are used to resolve uncertainties, decided on a case-by-case basis and may be limited to specific types of treatments (like OMPs in the Netherlands). Not surprisingly there was commonality across the uncertainties, but also some slight variations in the data collected and marked differences in the duration of the agreements. Data collection methods were very varied – ranging from the Italian approach of a national web-based system, to bespoke systems accessing administrative data within the health system and other information such as clinical registries. Some countries commissioned formal research for the CED, others considered this as health service evaluation (without ethical approval).

We concluded that for the case of RDTs OBMEAs need to be more purposeful about their data collection activities.

This requires clarification of the research questions to be answered in relation to the decision-relevant uncertainties in the appraisal and a consideration of sample size. This should determine the sample size required statistically and also the potential number of patients that might be eligible and opt for treatment (considering both prevalent and incident populations and how that will affect recruitment and any prioritization necessary). This would help determine if cross country collaboration is just desirable, or if in fact, it is essential to have any meaningful data from the OBMEA for re-appraisal.

Then every effort must be taken to ensure data quality and completeness, particularly when a range of data sources is used. We particularly liked the "covenant" used in the Netherlands that is signed by all parties to commit to do all they can to collect high quality data for the OBMEA. This assurance is needed before ministerial sign-off for the funding of the OBMEA.

To enable collaboration, we suggested that all OBMEA are published, preferably in a central international portal, like the INAHTA HTA database. Furthermore, we see enthusiasm among

[2] Tisagenlecleucel (Kymriah) for Pediatric Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma | CADTH.ca

HTA/Payers to discuss uncertainties at an earlier stage to align data requirements. This would be of benefit to all stakeholders.

A manuscript presenting this research was submitted to *Pharmacoeconomics* in March 2021 and is available in the D10.3 portfolio.

8. Real-World Data

8.1 Use of Real-World Data to Determine value of RDTs

As WS4 began, interest grew in the HTA community about the use of RWD. There was recognition that robust RWE could be particularly important for RDTs where there is a paucity of evidence in traditional clinical development. Furthermore, the NICE workshops highlighted the challenges faced in the first three OBMEA for HST products with data collection from a variety of sources and different responsibilities across the three examples for data collection and data clarifications. The workshop concluded that much more guidance was needed on use of RWD.

As a result of their work in IMPACT HTA, KF, EX and SU were invited to be part of two multi-stakeholder initiatives commissioned by the Belgian Payer (INAMI) about use of RWD in the appraisal of RDTs, including OBMEA. KF took on a co-facilitation role in the first initiative, TRUST4RD and has presented internationally on the work. TRUST4RD developed a taxonomy for characterization of the uncertainties that might arise in HTA/Payer appraisal of an RDT relating to:

- size and characteristics of the population
- natural history of the disease and its current management
- the new treatment
- the health eco-system.

The TRUST4RD approach proposed use of this taxonomy in iterative (scientific advice sessions) dialogues with all stakeholders to identify uncertainties that are of most concern to decision-makers, so that potential approaches to resolution, perhaps via generation of RWE could be discussed. In this iterative approach (during the clinical development program up to HTA and into OBMEA if required), as evidence is generated, uncertainties could be reviewed and prioritised, and evidence-generation plans revised. This would help discussion of evidence-generation trade-offs. Importantly, it would allow early identification of the potential need for an OBMEA. The paper was published in Orphanet and is available here.

KF led work on the second initiative, which focused on the use of RWE in the appraisal of highly innovative technologies (such as cell and gene therapies). These complex one-off treatments are high cost given their complexity of development and the purported high value they deliver. However, there are major uncertainties in the determination of benefit, often in the longer-term.

This RWE4Decisions initiative involved a workshop with presentations from HTA bodies and MAHs about their experience of use of RWD for these technologies after the HTA appraisal. Two interesting findings emerged.

One HTA body had commissioned external research to determine the real-life effectiveness of the CAR-T therapies (Schulthess et al. 2019) using US data. This publication has generated interest because it showed smaller effects in clinical practice than in the clinical studies, but there were concerns raised by others that the patients treated were sicker than intended in the marketing authorisation.

MAHs described how they are being increasingly requested to undertake bespoke RWE studies for different jurisdictions about similar issues after HTA but with slightly different data requirements.

A range of other interactive work was undertaken with stakeholders to develop actions that each stakeholder group could undertake to improve the development of RWE for HTA/Payer decisions. The proposed actions were amended after public consultation.

The paper identified that there is growing interest in HTA bodies about better use of RWE to inform determination of value for RDTs both during appraisal and in OBMEA. Key findings relating to OBMEA were:

- HTA bodies need to be more explicit about the research questions they think can be answered by RWE – clearly defining the decision-relevant uncertainties to be addressed in an OBMEA
- There needs to be discussion about the value of different RWD sources and determination of their quality and completeness for HTA purposes e.g., via the EUnetHTA REQuEST tool
- Collaboration across stakeholder groups is needed for the generation of robust RWE with processes for management of interests
- Plans for RWD collection need to be shared publicly
- RWD requirements need to be aligned across jurisdictions.
- RWD analytics organisations that have academic links are important stakeholders in terms of sharing data analytics knowledge, which is very limited in HTA and Payer bodies.
- Policy developments such as the development of the EU Health Data Space and the creation of the “Data Analysis and Real-World Interrogation Network” (DARWIN) by EMA and the Member States will help develop RWD infrastructure across the EU and support capacity building in terms of RWE assessment methodologies.
- The HTA community is not fully equipped to evaluate RWD. More clarity is needed on methods for assessment and processes to align data collection across countries.
- RWE4Decisions proposes a learning network involving all stakeholders to enable cross-fertilization of ideas. This requires an agile approach with trialing of innovative approaches and “learning by doing” similar to that used in quality improvement processes. This would enable knowledge sharing, dialogue and innovation.

This paper is published in the *International Journal of Technology Assessment in Health Care* and is available here.

After this paper was published, multi-stakeholder workshops were undertaken in September 2020 to provide advice to MAH’s about RWE generation plans for highly innovative technologies. This resulted in the following findings that are relevant to OBMEA of RDTs.

- Need to focus on RWE generation plans, even if tentative, with honesty and openness, discussing
  - challenges
  - pros and cons of different RWE designs/data sources
  - propositions for long-term evidence generation post-launch
  - practicalities of data collection including who should be responsible and approaches to reduce duplication/maximize use of all data collected
  - need for clarity that RWE may not resolve important uncertainties
- International disease-based registries are recommended to overcome duplication of data collection, but the practicalities of their use for an individual RDT is complex given issues relating to content, funding, management, ownership etc and this issue needs further joint discussion.

- Payers need to be clear about what data they require post HTA/reimbursement and collaborate to define a layered core dataset that identifies the essential (for all countries/decision makers), important and nice-to-have data (for local diseases)
- Registries should be disease based and coordinated across countries collecting data that is relevant for and can be accessed by population-level decision-makers such as HTA/regulators.
- As capture of in-hospital data improves, access to these data needs to be explored across national borders.
- Need to collaborate across EU and engage with ERNs and the European Joint Project for Rare Diseases to ensure HTA/Payer needs are understood when disease registries are developed and to ensure Payers can have access to relevant data.

In 2021, RWE4Decisions is focusing on the use of OBMEA for highly innovative technologies and members of the IMPACT HTA team will continue to be involved beyond the end of the project.

8.2 Critical assessment of RWD – Beyond the HTA norm

An important aspect for consideration in the use of RWD is to ensure appropriate critical assessment. In clinical trials, there are many checks that ensure the integrity of a trial such as ethical committee review, publication of protocols and results, regulatory review etc. However, these aspects may not be part of an RWE study. So, the role of an HTA body in reviewing a RWE study goes beyond critical assessment and must carefully determine study purpose, how data were curated and whether analyses were pre-specified and appropriate.

These issues are starkly exemplified in the study of hydroxychloroquine for treatment of Covid-19 in the Lancet (Mehra et al. 2020), which shows the pitfalls of being involved in RWE studies and not thoroughly checking data sources and methods. This study of 96,032 Covid-19 patients admitted to 671 hospitals around the world, concluded that hydroxychloroquine increased mortality and cardiac arrhythmias. This led to a halt in recruitment in several important trials internationally and caused major concerns to the patients were involved in those trials. Within a few days of publication an open letter was published signed by 120 experts from around the world to the authors and the Lancet. They expressed severe, wide-ranging concerns about methodological and data integrity. As a result, the lead author and two of the other three authors (highly experienced physicians from a highly respected US research hospital) had to issue a retraction within a few weeks of publication (Mehra, Ruschitzka, and Patel 2020). They indicated that after the criticisms they had tried to evaluate the origination of the database elements, to confirm the completeness of the database and to replicate the analyses presented in the paper. However, the third-party organisation holding the dataset would not transfer it or any related hospital contracts or audits due to confidentiality requirements. As a result, they could no longer provide assurance about the veracity of the data sources and so retracted the study. The Lancet has since updated its publication policy to require more than one author of the paper to directly access and verify data reported in a manuscript.

Conversely the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial organised by the National Institutes of Health Research in the UK, is undertaking high-quality real-world RCTs of hospitalised Covid-19 patients testing a range of treatments. At the end of March 2021, 39,329 patients had been enrolled from 177 centres. Results have influenced care internationally: with dexamethasone found to be effective and convalescent plasma found to have no effect. The protocols, statistical analysis plans and a document clearly outlining data curation (derivation of baseline characteristics and outcomes) are publicly available and show evolution over the study. Alongside this there is a page for site staff with information about site setup, specific actions for pharmacists and physicians to handle different clinical situations,

training materials, patient materials and online randomization and follow-up and safety reporting requirements. All this information is publicly available and much can be learnt from the conduct of this study and how it should be appraised.

HTA bodies are realizing the need to develop capacity in review of RWD as shown by the INAMI initiatives. NICE announced in March 2021 Data Analytics Methods and Standards Programme to develop capacity for all staff to be able to evaluate RWE. This is targeted not just at HTA staff or those who do critical assessment, but also appraisal committee members.

9. DEVELOPMENT OF THE CHECKLIST FOR WHEN TO DO AN OBMEA OF AN RDT

It was clear from all discussions that despite developments in RWD, OBMEA were still seen as a major burden to all stakeholders and should only be used when they were likely to be successful in providing good quality RWE that would inform re-appraisal decisions. As a result, one of the first tools WP10 developed was a checklist for when to do an OBMEA of an RDT.

This drew on literature identified as relevant for the development of a checklist from a COMED[3] systematic review (internal report, 30 June 2019), with key additional grey literature in the form of a systematic review from KCE (Gerkens et al. 2017) and the PBAC Framework for introduction of a Managed Entry Scheme (2011) that was identified in our case study workshop. Elements thought to be of particular relevance for a checklist for an OBMEA of an RDT were highlighted and are presented in green.

Klemp et al (2011) suggested that MEA should be the exception and not the norm and only be used when HTAs identify issues about outcomes, costs or organisational issues that are material to the reimbursement/coverage decision and when traditional reimbursement routes are deemed inappropriate. Our research shows that appraisal of RDTs using standard processes often result in one or more of these issues. So, to avoid over reliance on OBMEA, supplemental appraisal processes that take account of the specificities of RDTs might be needed as suggested in our overarching framework.

From the KCE report (Gerkens et al. 2017) checklists to evaluate the need for an OBMEA, particularly CED, were identified from (Bail 2013), Comité Economique des Produits de Santé (CEPS) - Rapport d'activité (2015), (McKenna et al. 2015) and also from the 2014 PPRS Pharmaceutical Price Regulation Scheme report in the UK about Patient Access Schemes at NICE.

Bail et al (2013) outlined the following conditions to be considered before establishing an OBMEA

1. Doubts over the transferability of the clinical trial results to real life practice, (e.g., need for better defining the most appropriate target population to optimise the efficiency of the product).
2. Incomplete clinical data in a context of unmet/important therapeutic needs.
3. Absence of a comparative study, due to either a lack of an appropriate comparator for a specific indication, or in the context of clinical trials designed at a time when treatment alternatives were not available.
4. Need to reduce uncertainties over the medical and economic value of a product, (particularly important in case of an expected large budget impact).

Appendix 4 of the 2014/2015 CEPS annual report defines four pre-requisites for an OBMEA:

[3] COMED - WP7 Coverage with evidence development for medical devices (comedh2020.eu)

1. The anticipated, yet unproven, benefit could not reasonably have been demonstrated during the clinical trials carried out prior to marketing authorisation, or for example can only be demonstrated in real-life practice.
2. If a benefit exists, it must represent a clear advantage, preferably in terms of public health.
3. A study must be developed that by the end of the fixed-term trial period (generally nor more than 3 years) will allow to unequivocally demonstrate that a benefit exists and the extent of this benefit.
4. The medicine manufacturer must agree to conclude a MEA at the end of which he will have to bear, at least partly, financial costs in case of product failure.

McKenna et al. (2015) published a checklist for determining if a CED scheme would be of value:

1. Is the technology cost effective?
2. Are there significant irrecoverable costs?
3. Does more research seem worthwhile?
4. Is research possible with approval?
5. Will other sources of uncertainty resolve over time?
6. Are the benefits of research greater than the costs?
7. Are the benefits of approval greater than the costs?

Depending on the answers to the questions, different guidance was provided.

The NICE Decision Support Unit (DSU) developed a report that created a framework for analysing risk in HTAs to apply to MEAs (Financial and Outcomes-Based). They suggested that the following questions should be considered:

MEA design guidance questionnaire (NICE DSU)
1. What are the (number and characteristics of) treatment options?
2. What is the base-case cost-effectiveness?
3. What is the nature and scale of risk in this appraisal?
3a What is the nature and scale of risk captured by the probabilistic sensitivity analysis (PSA)?
3b What is the nature of uncertainty not captured by the PSA?
3c What is the temporal nature of uncertainty, e.g., is there more uncertainty beyond the trial period or is it resolvable with open-label follow up?
4. What is the uncertainty caused by individual / groups of parameters?
5. What alternative treatment strategies might be available?
6. What measures of patient-based outcomes are available and measurable?
7. Is price a substantial part of overall costs associated with treatment?
8. Are there any precedent Patient Access Schemes *[financial MEAs]* in place?
9. Could price agreements be national or local?

The NICE DSU then established five key questions about the potential need for an MEA. These questions are complex to answer and they present economic analyses to illustrate how they may be answered.

Key Questions to Establish the Potential Need for an MEA (NICE DSU)
Q1) Which intervention do we expect to be most cost-effective given proposed prices and current evidence?
Q2) How uncertain are we?
Q3) How useful would it be to eliminate uncertainty?
Q4) Given current evidence and proposed prices, what is the strategy-specific risk to the NHS?
Q5) How much would the NHS expect to gain by eliminating the risks associated with both uncertainty and the strategy?

Complex algorithms were then created (Claxton et al. 2016) to support appraisal decisions and the need for additional research based on principles of whether

- the technology is expected to be cost effective
- the technology has significant irrecoverable costs

- additional research is needed and possible
- there are opportunity costs that once committed by approval cannot be recovered
- there are effective price reductions.

Other groups in the UK have proposed the use of Value of Information analysis to help determine the value of additional data collection, but such analyses have been rarely used in HTA decision-making. However, we are aware that work is underway by the Institute of Health Economics in Canada to propose an OBMEA approach based on a Value of Information approach (IMPACT HTA WP10 webinar 2).

(Pouwels et al. 2019) note that a successful CED scheme is one that addresses important uncertainties in an appraisal and so a CED scheme must be informed by

1. Systematic identification of uncertainty
2. Description of the direction and magnitude of uncertainty
3. Exploration of the impact of uncertainty on cost-effectiveness results and decision-making
4. Exploration of how uncertainty and its impact on cost-effectiveness can be reduced by collecting additional evidence.

EUnetHTA use the following criteria to select topics for their PLEG pilots:

1. Can you identify any critical evidence gaps during HTA?
2. Is the research question explicitly defined? (Objectives, PICO etc.)
3. Is Additional Data Collection feasible (especially in terms of timeframe, type of study, population and costs)? (yes, no)
4. Is this study necessary taking into account similar planned/ongoing studies?
    a) Yes, because there is no similar planned/ongoing study elsewhere.
    b) Yes, because even though there is a similar planned/ongoing study elsewhere, there is an additional value of performing this one too.
    c) No, because the similar planned/ongoing study will bring sufficient information.
5. Will the additional data to be collected bring a significant added value for the subsequent HTA and decision making? (yes, no).

With additional selection criteria of:

1. Burden of target disease
2. Expected benefit of the technology (on the burden of disease/on the management of disease/economic benefit/organisational/social benefit)
3. Potential of the technology to cover unmet health care needs or to substantially improve the health care compared to existing alternatives
4. Importance of Additional Data Collection for confirming expected benefit and/or monitoring/optimizing the conditions of use.

In rare diseases, the first three of the “additional selection criteria” are a requirement for all treatments designated as OMPs (and may be seen as more relevant to the coverage decision itself), so the fourth additional criterion is most important. This can be combined with the “primary eligibility criteria” and the OECD criteria. Furthermore, in the framework of cost-effectiveness it may be helpful to refer to uncertainties, rather than evidence gaps.

Bringing all this evidence together, with knowledge gained from multi-stakeholder workshops undertaken at NICE and HTAi, a checklist for when to do an OBMEA for RDTs was developed by the team. It was consulted upon with HTA/Payer experts in our OBMEA case study workshops. It was then revised and issued for consultation by sending it to all stakeholders with whom we had discussed OBMEA during the project and issued publicly via LinkedIn. The areas where there were differences of opinions submitted via consultation comments were discussed with experts at WP10 webinar 2. The final checklist now available on our website incorporates these comments.

10. DEVELOPING THE TOOLS FOR OBMEA

Over the past decade, OBMEA have been used to enable access to treatments that have large predicted added benefit, but where there are major uncertainties in the clinical effectiveness or economic modelling.

As there is often a paucity of data available for appraisal of RDTs, there has been interest in the use of individual or population-based OBMEA to provide access to RDTs in areas of high unmet need, particularly by MAH's seeking to provide access to their (high cost) treatment.

However, OBMEA are not the "holy grail" that will solve the challenges associated with appraising RDTs. Even in the most streamlined of data collection processes, there are many administrative burdens relating to data collection and human resource costs, alongside challenges in collecting sufficient data to actually resolve the uncertainties. Furthermore, taking a decision on the basis of an OBMEA may be challenging, particularly if it is a disinvestment decision and many stakeholders have spent years contributing to the data collection. Therefore, the consistent message we had in all our activities with HTA bodies was that OBMEA, even for RDTs, should be the exception and not the norm. However, few HTA bodies had systematic processes for deciding when to use an OBMEA and although processes have been developed by individual HTA bodies to overcome some of the challenges, these have not been widely shared.

As reported in the Month 18 Interim Project Report, insights from the WP10 WS4 work to that point suggested that guidance on use and implementation of OBMEA in RDTs should:

1. explain burden and challenges of OBMEA in rare diseases particularly in relation to gathering data of sufficient quality to act upon or reassess.
2. define criteria to determine when OBMEA might be appropriate taking account of uncertainties that need to be addressed and feasibility of OBMEA implementation and data collection (country-specific).
3. encourage early identification of products that might potentially use an OBMEA and engage all stakeholders to discuss how it could be optimally implemented and consider legal (country-specific) setting for the agreement.
4. provide guidance on the form of protocol and statistical analysis plan that should be prepared and published.
5. encourage cross-country sharing of information about OBMEA and use of core outcome sets to ensure interoperability and potential for amalgamated data analysis.
6. Develop a guide for patient groups to understand the legal, ethical and procedural issues related to engagement in an OBMEA and how they can best support the patients that participate.
7. develop a guide on real world data collection (referencing recent guides about registries, use of electronic health data etc) and appraisal (linking to EUnetHTA JA3 WP5 PLEG, regulatory guidelines on RWD and RWE (FDA), EMA patient registries pilot and other European initiatives).
8. ensure that there is regular multi-stakeholder oversight of the OBMEA and actions taken to address procedural challenges in data collection.
9. ensure ethicists are involved in oversight to address challenging issues that arise (e.g., potential treatment discontinuation at the end of an MEA after patients and clinicians have given a major contribution in terms of data collection).
10. recommend public reporting of the design, conduct and analysis of OBMEA to develop learnings.

As required by the EC H2020 Project call, we were keen to develop practical tools to overcome some of these practical issues and first began discussion about the tools at the NICE workshops in 2019, where stakeholders requested:

- criteria/indicators/scenario to identify when an OBMEA for OMP or ultra-OMP might be appropriate[4]
    - taking account of different types of rare diseases (rare vs ultra-rare, lifelong vs in severely life limiting, cancer vs non cancer, good natural history or not, etc.)
    - explaining that the use of OBMEA is exceptional, not routine
    - identifying what uncertainties OBMEA realistically can and cannot answer – considering what reassurance can be obtained from 3.5 years RWD collection and recognising that long-term data is always an uncertainty, but cannot be collected by an OBMEA, also identifying that clinical, policy and methods changes may happen
    - explaining the challenges inherent in RWD in terms of quality and completeness
    - outlining the major resource requirements for all stakeholders
    - considering a structure for early engagement among HTA, health service and industry to discuss
        - evidence generation plans to ensure trials are designed to collect data relevant for HTA, appropriate RWD sources are found and agree how RWE will be appraised by HTA bodies
        - early economic modelling results to flag the need for commercial agreements.
- guidance on development of the formal OBMEA document to get wider agreement of those who will be responsible for data collection (clinicians and patients)
- educational materials/FAQ/process guides for stakeholders to understand the process and share best practice to support patients and their families in the OBMEA
- methods for oversight on the conduct of the OBMEA when it is underway, to resolve issues including all stakeholders and other relevant professionals (such as ethicists)
- considerations for re-appraisal with OBMEA data including
    - guidance on collection and use of RWD
    - stakeholder submission forms that focus on gathering real-world experiences of patients eligible to receive the treatment in the OBMEA (those who were in the scheme and those who weren't)
- considerations for decision-making after the reappraisal.

Later that year, the OECD report (Wenzl and Chapman 2019) identified four good practices for OBMEA:

- Define a strategy to guide use of OBMEA ensuring they are used only where the benefit of additional evidence outweighs the cost of negotiating and executing the MEA.
- Clearly identify uncertainties in each coverage/reimbursement decision and design OBMEA to ensure that data sources and research designs are appropriate to address the uncertainties.
- Implement a governance framework that ensures transparency of process and allows Payers to act upon the additional evidence, including exiting from the MEA and potential withdrawal of temporary coverage.
- Ensure a minimum level of transparency of content, limiting confidentiality to those parts of the MEA that may be commercially sensitive (in particular prices).

[4] This will be amalgamated with other checklists identified in the COMED literature search, from the HTAi workshop small group 1 discussion, The NICE Cancer Drugs Fund[4], The HST Interim Methods Guide (2017) - sections 56 and 57 and EUnetHTA PLEG selection – see Box 1 for modified version.

These issues and proposals for guidance were to be debated with policy makers at a workshop in March 2020 and then July, but these workshops had to be cancelled due to the pandemic. Instead, they were replaced by the virtual workshops with the OBMEA case study respondents in winter 2020.

After all our engagements with experts we converted the challenges of Table 2 into considerations for implementing successful OBMEA for RDTs as shown in Table 5.

TABLE 5: CONSIDERATIONS FOR SUCCESSFUL IMPLEMENTATION OF OBMEA FOR RDTS

OBMEA phase	Consideration
Establishment to provide assurance of viable data	Clear process to decide whether an OBMEA is required (and feasible) that could be used by HTA bodies or MAH not just at appraisal, but also in earlier dialogues.
	Explicit purpose (documentation of decision-relevant uncertainties to be resolved) and how data will be used in re-appraisal (full re-appraisal or review of the specific uncertainties).
	Timely commercial/pricing agreements in parallel with the development of the data collection plans.
	Sharing intelligence with other jurisdictions to discuss uncertainties and plans for data collection, to align where possible.
	Justification for study design (research study or health service evaluation), planned/anticipated sample size, duration of data collection, ethical approval if needed, informed consent mechanism.
	What credentials/accreditation are needed to be a treatment centre?
	If provision is in one/a few treatment centres, how is equity of provision across the jurisdiction ensured?
	Agreement of stakeholder responsibilities, and commitments.
	Agreement on clinical and patient outcomes that can be measured in clinical practice/daily life that will address the uncertainties.
	Identification of data sources/methods to collect data (such as apps for patient reported data) and possibility to link datasets.
	Create a “covenant” where all parties agree to do their best to collect sufficient data for re-appraisal
Implementation/ conduct	Does service infrastructure exist to provide treatment (particular issue for rare diseases with no other treatments)?
	Can patients be identified?
	Criteria to determine patient eligibility and treatment continuation.
	How to reduce the administrative burden of the data collection on all stakeholders.
	Initial training for clinicians who must identify and assess patients and enter data.
	Ongoing support for centres to ensure good quality real-world data (RWD) is collected and to address issues that will arise in clinical practice (missed visits, patients unable to do assessment etc)
	Monitoring of recruitment in each centre; data quality, completeness and sufficiency
	Funding – administrative duties, data management, data analysis.

OBMEA phase	Consideration
Re-appraisal/ Pricing and Reimbursement Renegotiations	Timely compilation and analysis of data for input to re-appraisal
	Processes to capture other insights from treating clinicians, patients and carers i. Were there issues in conduct that affected data collection? ii. Do new analyses help resolve original uncertainties/validate or refute modelling assumptions? iii. Did other benefits or dis-benefits of treatment emerge? iv. How does the additional information contribute to re-appraisal? v. Does each stakeholder consider the CED Agreement has been of value? vi. What has the CED cost to each stakeholder?
	Implementation of decision after re-appraisal – if disinvestment, what happens to patients on treatment (that may have invested a lot of effort into the CED)?

Alongside this, we created several different forms of tools to overcome the challenges that stakeholders had identified in the implementation of OBMEA and the considerations in Table 4. These are presented in Table 6 and can be found on the IMPACT HTA website WP10 web page.

TABLE 6. IMPACT HTA WP10 TOOLS FOR OBMEA OF RDTS

Tool	*Issue* and Resolution	Method of development
Checklist to determine feasibility of an OBMEA	*OBMEA should be the "exception not the norm" given the burden to the system (even in web-based platforms like those of AIFA).* Clear criteria are presented that seek to ensure the OBMEA will be able collect sufficient good quality data to reduce the uncertainties in HTA.	As outlined in section 9 • literature review • consultation with HTA/Payer experts involved in the OBMEA case studies • targeted and public consultation discussion of the most challenging issues arising in consultation at WP10 webinar 2.
Template for an OBMEA	*The data collection elements of an OBMEA need to be separated from confidential pricing agreements into public documents. Data collection needs to be more purposeful to address decision-relevant uncertainties.* A template for adaptation by HTA bodies and use by all stakeholders involved that outlines the key elements of an OBMEA to be presented in a public document. This includes • purpose of the OBMEA - linking to the appraisal and uncertainties to be resolved • the legislative or policy basis for the OBMEA • patient entry and approval process • data sources, data management and information governance • reviews to monitor data quality and sufficiency • re-appraisal • responsibilities of all involved.	A draft was developed early in the project based on a NICE Data Collection Agreement for an RDT in the HST programme. As part of the OBMEA case study, respondents were asked to share the documents relating to their case studies. Some of these were web-based and in languages we could not translate. So, we focused on documents 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. We updated the initial draft to amalgamate elements from these other documents and to incorporate learnings from the case study workshop. A draft template was then issued for the targeted and public consultation and amended.

Tool	***Issue* and Resolution**	**Method of development**
Terms of Reference for an OBMEA Monitoring Committee	*When data are not collected in a national registry system and come from a variety of sources, careful oversight is needed to ensure the data collected in clinical practice are of high quality and that clinical centres undertake clinical assessment of patients appropriately.* To ensure purposeful monitoring of the progress of the OBMEA a "Monitoring Committee" is proposed that includes all signatories and key stakeholders (such as clinicians). A Terms of Reference for this committee is presented for adaptation by HTA bodies that presents issues the committee should keep under careful review and so be able to take remedial action if any issues arise. The governance of the committee is also outlined.	The NICE HST programme has a Managed Access Oversight Committee (MAOC) for each of its OBMEAs. One such committee was observed in WS2 with follow-up interviews and interactions with the lead (EK). The NICE Terms of Reference for the MAOC was adapted for international use and it was checked with the case study experts whether this would be of use. All agreed it would be, so a draft template was issued for the targeted and public consultation and then updated.
Tool	***Issue* and Resolution**	**Method of development**
Patient Group Submission Form for Re-Appraisal after an OBMEA	*OBMEA data collection is often shaped by the construct of the original clinical trial and may miss other benefits or disadvantages of a treatment as perceived by patients and their carers and families.* A patient group submission form is provided for adaptation by HTA bodies. This draws out experiences of patients, carers and families about what life was like before and after treatment in the OBMEA and any practical issues in the OBMEA. This may also be used as a topic guide for HTA bodies to interview patients or run focus groups in advance of re-appraisal.	The HTAi Patient Organisation Submission for Medicines (2014) and NICE Patient Organisation Submission for Elosulfase Alfa re-appraisal (February 2020) were combined. Alterations were made to take account of the insights from the NICE MAA patient group workshop and from WS2 observations and interviews with patient experts – with a major refocus to the additional issues beyond the data collection. Amendments were made to a draft document following feedback from patient group representatives whom it was felt would understand the OBMEA re-appraisal context.

11. DISCUSSION

11.1 Emerging OBMEA initiatives

We were interested to hear of the establishment of Valtermed in Spain in 2019, which is national web-based data collection platform for medicines with a high health and economic impact to determine real-world therapeutic value. National protocols are developed by clinical experts and staff and available online. Data quality checks and regular validation reports are produced similar to the Italian system. However, it intends to go further, to link with other data sources. Furthermore, in a second phase, it is intended that patients will be able to enter quality of life information using validated questionnaires. This will be an important initiative to follow.

In WS2 we observed the first treatment (voretigene neparvovec) to go through the new ultra-orphan pathway of the Scottish Medicines Consortium (SMC) in 2019. This involved an initial assessment by the SMC with delineation of the key uncertainties. The interim report indicates (page 15) that 3 patients per year are expected to be eligible for treatment in Scotland. After this initial assessment, the MAH was required to submit a three-year data collection plan to Scottish Government to generate further evidence on effectiveness. It is presumed that this will be focused on resolving the uncertainties, but this is unclear as there is no public information about the data collection plan. Furthermore, given the sample size of 9 patients, it will clearly be necessary for the subsequent re-appraisal to include data beyond Scotland, which is recognised by Scottish Government.

In 2019, Germany passed the GSAV law that that gives the Federal Joint Committee increased authority to impose data collection requirements and price reductions if data do not support added value. It is anticipated this will be used for OMPs, but no further guidance has been issued.

In consultation on the templates, responses from Austria, CADTH in Canada, INESSS in Quebec and Estonia who valued the development of the tools, particularly the template for the OBMEA in RDT and the checklist, recognising that CED should only be undertaken when they can generate sufficient data to inform re-appraisal. The Austrian contact indicated that new OBMEA processes were being developed in Austria and that processes to support this would be helpful. Furthermore, CADTH indicated that specific work in relation to use of OBMEA and RWD for RDTs was underway. They provided detailed comments indicating that there is potential for this work to be used outside the EU but cognisance of different regulatory settings is needed. A response from an HTA expert in the USA indicated that in their context where patients change health systems frequently and digitisation of health care is more advanced, these tools may be less relevant.

Experience with the one-off cell and gene therapies is increasing. Our case study of tisagenlecleucel showed that beyond questions of real-life and long-term effectiveness, there were important questions about successful administration of treatment (given a 20-day leukapheresis period) that were explored in some OBMEA. Another issue that was raised by patient representatives was that when patients have been “cured” they do not want to keep returning to their clinicians for assessment. More needs to be done to consider how such situations can be handled and the potential for apps to be used. Important work is emerging in Sweden where patients collect real-world data that is important to them and share it with their physician and can allow it to be used with multiple stakeholders for specific purposes (Hager A, Lindblad S, Brommels M, Salomonsson S 2021).

11.2 Funding and linking to digital health initiatives

Funding of an OBMEA can be expensive, as outlined by the Netherlands estimated costs for the nusinersen OBMEA. As shown in our case studies, costs are distributed among different stakeholders in different ways, mainly depending on who is the data owner. However, it has also been noted that individuals' time (particularly clinicians) has often been under-resourced. This came out strongly in the NICE workshops and even in the simpler Italian system the burden on clinicians was still seen as substantial. Furthermore, in individual-based OBMEA, refund systems can be complex and difficult to operationalize.

These issues need to be carefully considered when implementing an OBMEA and stakeholders responsible for additional duties beyond standard clinical care should be appropriately recompensed. This may push up the cost of OBMEA, however as discussed in IMPACT HTA WP10 webinar 2, as the cost of some new RDTs is several €100,000s - €1,000,000 per patient, this could be money well spent to determine their real-life value and optimize their use.

It is clear that the AIFA national web-based prescribing system is much cheaper and efficient and learning from such systems and that of Valtermed in Spain will be important. In countries with good data linkage there is an opportunity to harness the potential of new health system initiatives bringing together health and social care data (such as Findata in Finland or HDR in the UK) to address questions of importance to Payers.

Furthermore, much has been learnt during the pandemic about the value of robust RWE to inform decision-makers about effective treatments, but the care needed to ensure veracity of data and high-quality analytical methods. This has been recognised by NICE, as they develop new methods guides for data analytics evaluation that will inform all their work from provision of scientific advice, through to appraisal, OBMEA establishment and re-appraisal. In Canada, an action plan to optimize use of RWE into reimbursement decision-making for high cost RDTs is in development (Tadrous et al. 2020) and various activities are underway as a result of this with much attention paid to OBMEA.

This sits in the wider context of the development of the EU Health Data Space and as the WHO report indicates (Wenzl and Chapman 2019), digital health strategies need to be underpinned by a robust strategy combining financial, organisational, human and technological resources, recognizing legal constraints and national contexts. This will be complex, but there are major opportunities here not just to inform pricing and reimbursement decisions but to optimize use of treatment and care. This use of OBMEA not just for re-appraisal, but also for optimization (e.g., honing eligibility criteria and treatment continuation rules and for long-term therapies specifying treatment duration) was not clear to us from the literature. We think it is an important purpose that needs to be explained more clearly to all stakeholders.

11.3 Collaboration

(Bouvy, Sapede, and Garner 2018) have suggested that if countries could agree on data to be collected post licensing within their health systems this could substantially improve timeliness, cost and efficiency of data collection. This is more important for the small populations that can be expected in rare diseases. Indeed, we can expect more treatments for very small populations as a recent study identified that 85% of the 5,304 rare diseases with a recorded prevalence in the EU have a prevalence of <1/1,000,000 (Nguengang Wakap et al. 2020) This is much lower than the ultra-rare definition used by most organisations and shows that many future RDTs may have very limited numbers for study.

EUnetHTA undertook a PLEG pilot for the RDT, nusinersen in spinal muscular atrophy. However, from our case study it is unclear how successful it was given the different data collection approaches taken by the countries who responded to us. We wonder if this could

be because too many research questions were specified and it was not possible to focus on those that were decision-relevant for the Payer. This shows the need to involve Payers in these discussions to focus analysis on elements that are essential for pricing and reimbursement. Parsimony seems an important concept in OBMEA to agree a minimum dataset across jurisdictions.

The OECD report (Wenzl and Chapman 2019) found that little information was published about OBMEA; neither the products subject to MEA, the MEA design (including the outcomes collected) nor the results (the data and the decision). As CED schemes are deemed by Morel et al (2013) as “research” and given the move to transparency in clinical research over recent years, the OECD note ethical concerns about this non-disclosure.

Greater sharing of information would also reduce duplication of effort across countries, both by enabling learning about the schemes and through use of data. This is particularly important for RDTs, where populations in individual countries may be very small. Furthermore, such transparency should increase trust of all stakeholders, particularly patients. Clearly some elements of the OBMEA are commercially sensitive (particularly pricing negotiations), but OECD calls for Payers to agree on which information to share, in which form and through which mechanism (e.g., exiting website or initiative, central repository).

We agree wholeheartedly with the need for more clarity and hope that our template for an OBMEA, provides a way for HTA bodies/Payer to construct their Agreements to separate out the data collection elements from the pricing elements, so that the former can be published. This would greatly enhance transparency. We also propose that these plans be stored on a portal, alongside data management and statistical plans, interim reports of progress in data collection and the final re-appraisal. We have suggested in our case study paper that the INAHTA HTA database could be extended to include this information. We have not proposed the EUnetHTA database as this is not public nor international.

Our case study workshop included HTA/Payer experts from Australia, Belgium, England, Ireland, Italy, Netherlands, Poland and our Spanish Partner. Respondents from the Payers in Latvia and Lithuania were unable to contribute but indicated strong interest in our work. The HTA leaders found the confidential workshop valuable to be able to discuss processes, methodological challenges associated with RWD collection, information governance, the uncertainties for specific products and an upcoming OBMEA publication that would be advising on a new discontinuation rule for a specific product. The potential for a Payer network on OBMEA is clear and this will be discussed further in the RWE4Decisions initiative, with INAHTA and OECD.

Macleod and Mitton (2010) stated that standard principles of accountability for reasonableness should be applied to MEA considering stakeholder involvement, transparency and openness of the basis for decision-making, the basis for review and appeal, assertive leadership including acceptance of accountability.

We hope that this report and our tools, as presented on our website, will help all HTA bodies achieve those principles for OBMEA in RDTs and that the tools will be adapted and used by HTA bodies and developed with experience to have real impact in HTA.

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APPENDIX 1: WS1 ORIGINAL QUESTIONNAIRE RESPONSES TO Q3.3 RE FORMS OF MEA

(Extraction 13 March 2020 from information received in 2018-2019)

Country	MEA (within standard appraisal process)	MEA (within special appraisal process for RDTs)
Austria	None, only rebates (inpatient)[5]	Increasingly conducted, but on regional agreements, not public/ not transparent (outpatient)
Belgium	- Confidential rebate based on clinical outcome in clinical studies (population level) - Budget cap - OB scheme to collect additional evidence for later reassessment - OB for individual patients - Other	
Bulgaria	- Confidential discount with finalised contract between (Marketing Authorisation Holder) MAH and National Health Insurance Fund or MoH before placing the medicinal product in the Positive Drug List. - Budget cap - Routine monitoring of drugs not cost effective or that lack effectiveness data, not linked to MEA. *COMED work indicates that they have CED*	
Canada: Federal	OB to collect additional evidence for later reassessment (though not widely used by public drug plans currently).	
Quebec	Not permitted by law	
Croatia	None	N/A
Cyprus	*No response*	
Czech Republic	MEAs can be used. They are used by the MAH to cope with parameters required by the cost effectiveness requirement of HTA, as well as to reach an agreement with reimbursement funds about an acceptable budget impact. SUKL (the Ministry of Health) does not participate in concluding MEAs, but takes them into account. MEAs may also be submitted as confidential documents. MEAs are often connected with (or part of) the MAH´s obligatory commitment for highly innovative drugs. May also be applicable for OMPs.	
Denmark	No	
Estonia	- Confidential discount, payback - Budget cap - Outcome based scheme for individual patients, only paying for performance - Other, not specified	
Finland	MEA: Outpatient: As a part of conditional reimbursement. No restrictions on the type of agreement MAH can propose have been issued. All of the agreements, however, have been financial. Inpatient: there is limited information on the use of MEAs in Finnish hospitals. Simple discounts are common and other types of financial agreements are also in use. So far there is little experience with outcome-based agreements.	
France	None	

[5] This implies individual scheme

Country	MEA (within standard appraisal process)	MEA (within special appraisal process for RDTs)
Germany	None	
Greece	Yes, but it is not clear what types of agreements are considered (financial, outcome-based or a combination of both)	
Hungary	- Reimbursement volume agreements - Confidential list of MEAs published - None in inpatient sector - products go through procurement, but the contract is designed in a way that it has risk-sharing elements	
Iceland	None - No resources to monitor effectiveness	
Ireland	MEAs, where they exist, are most often (but not limited to) the following: - Price discounts - Budget Caps - Outcome based	
Italy	MEAs are part of the overall assessment so PBRSAs are the responsibility of CTS and FBAs part of CPR opinion as: - Cost-sharing - Price/ volume - Cap ceiling Case by case decisions and occasionally a MEA is discussed collegially by the two Committees (e.g., Chronic Hep C or the incoming CART-T) If the product is innovative data collection is mandatory by Law. Exception for OMPs: early access tools[6] are present and for 648/96 Law PBRSA with registry could be possible. In this case the Committee involved is only CTS.	
Latvia	- Confidential discount - Budget cap - Outcome based scheme to collect additional evidence for later reassessment	
Liechtenstein	May be used (Art. 65 abs 5 KVV)	
Lithuania	?	- Confidential discount - Budget cap - Outcome based scheme for individual patients, only paying for certain performance (less common)
Luxembourg	None?	N/A
Malta	No	
Netherlands	Other, not specified Note: In the Netherlands relative effectiveness must be proven for reimbursement. However, when there is not enough evidence yet, but the intervention is very promising (plus other criteria), there is some budget for conditional reimbursement. Evidence of (cost)effectiveness must be gathered during this period of conditional reimbursement. If quality of evidence is low to very low and will be reimbursed, an OMP arrangement is required in which appointments are made about start- and stop criteria, use of an indication committee and data gathering, so in the long run it can be concluded if an effect on the critical endpoint is found.	

[6] http://www.aifa.gov.it/content/normativa-di-riferimento-usi-speciali-e-sperimentazione-clinica

Country	MEA (within standard appraisal process)	MEA (within special appraisal process for RDTs)
New Zealand	- Confidential discount via rebates - Budget cap - Access criteria to target treatment to specific patients	
Norway	Confidential discounts[7]	
Poland	Risk sharing schemes are widely used. Proposals for MEAs are often received and assessed during the HTA process. HTA assessors provide comments on these proposals (e.g., can give advice to enhance the proposal due to uncertainty as a condition for positive reimbursement decision).	
Portugal	- Risk sharing agreements (financial and performance based) - Conditions of use - Reassessment of technologies on the market - Conditional reimbursement [5]	
Romania	- Confidential discount - Budget cap – limited number of patients Only price - volume agreements	*No price-outcomes agreements*
Slovakia	- Confidential discount - Budget cap - Outcome based scheme to collect additional evidence for later reassessment (since Jan 2018 but in reality, not used yet) - Outcome based scheme for individual patients, only paying for certain performance (since Jan 2018 but in reality, not used yet) Outcome-based MEAs are rare due to implementation challenges. Negotiations most often about price, e.g., simple discounts and budget caps.	- Confidential discount - Budget cap Outcome based scheme to collect additional evidence for later reassessment (since Jan 2018 but in reality, not used yet) - Outcome based scheme for individual patients, only paying for certain performance (since Jan 2018 but in reality, not used yet) Outcome-based MEAs are rare due to implementation challenges. Negotiations most often about price, e.g., simple discounts and budget caps
Slovenia	Discount cap, price volume Yes, to OBMEA	
Spain	Confidential discount - Budget cap - Outcome based scheme to collect additional evidence for later reassessment - Outcome based scheme for individual patients, only paying for certain performance - Restriction of ex-ante use - Based on previous treatments received or subpopulations of patients as evidence **Very few MEAs at national level, more often at regional level*	
Sweden	Confidential discounts - Other, RSA e.g., based on treatment length	
Switzerland	May be used (Art. 65 abs 5 KVV)	

[7] Corrected following email clarification from TR in April

Country	MEA (within standard appraisal process)	MEA (within special appraisal process for RDTs)
UK/England	MEAs can be considered within the standard appraisal process - Confidential discount - Budget cap - Outcome based scheme to collect additional evidence for later reassessment Commercial and Managed Access Function in place at NICE	- Confidential discount - Budget cap - Outcome based scheme to collect additional evidence for later reassessment
UK/Scotland	Confidential discount (*Can be for all indications or specific indications if feasible to isolate utilisation data.) all schemes are assessed by the Patient Access Scheme Assessment Group and must be feasible to operate in NHS Scotland) - Budget cap (less common) - Outcome based scheme for individual patients, only paying for certain performance (less common)[8]	

[8] New UOMP pathway is population based, individual scheme is rarely used

APPENDIX 2 CASE STUDY TEMPLATE

WP10. Outcome-Based Managed Entry Agreements Case Studies for Rare Disease Treatments

Organisation:

1. Medicinal product *(INN, pharmaceutical form and posology)*	xxxxx
a. HTA/ Pricing and Reimbursement therapeutic indication *(indicate if any restriction to EMA label indication)*	xxxxx
b. Indicate if rare or ultra-rare condition, adult/child indication, one-off treatment or long-term posology	Xxxxx
c. HTA/ Pricing and Reimbursement authorisation date	Xxxxx
d. Status of reimbursement from NHS *(conditional reimbursement, any positive drug list or any innovativeness' list?)*	Xxxxx
e. Is OBMEA part of HTA appraisal or Pricing & Reimbursement process? *(If known, add here the length time of Pricing & Reimbursement contract)*	Xxxxx

2. Name/Type of OBMEA *(Individual or population level, financial-based, performance-based or the combination of both)*	Xxxxx
a. Purpose of OBMEA *(Uncertainty to be resolved; add the link if known)*	Xxxxx
b. Date of OBMEA *(add the link if known)*	Xxxxx
c. Length time of OB- MEA *(add the link if known)*	Xxxxx
d. Validity at national, regional or local (hospital) level or other - describe here if the process is transparent *(add the link if known)*	Xxxxx
e. Are there any legal agreements/ contracts between the parties, or just an informal agreement? - describe and add link if known	Xxxxx
f. Type of commercial agreement, if known (*add the link if known*)	Xxxxx

3- Which stakeholders are involved in the OBMEA? *(Healthcare body, regulatory agency, payer, patient group, clinician, pharmacist, expertise center, other)* - describe	Xxxxx
a. What responsibilities do they have? *(for each category and specify who are the signatories)* - describe	Xxxxx
b. Who developed, or is developing, the OBMEA criteria?	Xxxxx
c. Who is responsible for the OBMEA data analysis?	

4. How/where is data collected for OBMEA? *[Disease or drug-based, registry, drug utilisation, or other, bespoke or not (if not, add the source of data)]*	Xxxxx
a. Do patients have to sign any consent forms for data collection/ sharing to receive treatments? - describe	Xxxxx
b. Summary of eligibility and clinical data to start treatment *(Any restriction criteria to target treatment to specific patients? Provide link if public)*	Xxxxx
c. Summary of data to be collected during the OBMEA period - describe *(Prescription, dispensing, follow-up, re-assessment, end of treatment et al; provide link if public)*	Xxxxx
d. Treatment stopping criteria	Xxxxx
e. Are there any PROMS being collected? - describe	Xxxxx
f. Who collects which data? - describe referring to the items above (4b-4e)	Xxxxx
g. Is it clear who owns the data?	Xxxxx

5. Data analysis for OBMEA?	Xxxxx
a. How is data collected used? - describe referring to the items above (4b-4e)	Xxxxx
b. How often is data collected? - describe referring to the items above (4b-4e)	Xxxxx
c. Are there any data reviews included during the period of the OBMEA?	Xxxxx
d. Is a dashboard (structured ad hoc based on aggregated reports) being used? Which stakeholders' have access to these reports? Is the data (both raw and analysed) presented in a visual format (charts, graph)? - describe	Xxxxx
e. Is there a data quality process in place? - describe	Xxxxx
f. Who funds the data collection?	Xxxxx
g. Who funds the data processing post-agreement?	Xxxxx
h. How does the OBMEA re-assessment work? - describe the process of refining reimbursement criteria, new stopping rules, re-negotiating price, longer-term follow-up	Xxxxx

Document History

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May 2021	Following review by NICE to check no redactions needed, modifications made to Table 4 and addition of cc license and citation. Deletion of confidential in title.