

**Improved methods and actionable tools for enhancing HTA**

**Template for Adaptation by HTA Bodies**

**Outcomes-Based Managed Entry Agreement**

**of a Rare Disease Treatment**

**March 2021**

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

*It uses terminology that comes from the* [*IMPACT HTA Template for OBMEA*](https://www.impact-hta.eu/work-package-10) *and should be adapted to suit the healthcare system.*

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

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

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

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

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

*For any queries contact Karen Facey:* [*karen.facey@ed.ac.uk*](mailto:karen.facey@ed.ac.uk) *.*

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**HTA BODY/HEALTHCARE PAYER NAME**

**OUTCOMES-BASED MANAGED ENTRY AGREEMENT**

**COLLECTING DATA FOR <RARE DISEASE TREATMENT>**

**IN < REIMBURSED INDICATION>**

|  |  |
| --- | --- |
| Rare Disease Treatment | Brand name/  Non-proprietary name |
| Indication | Reimbursed indication[[1]](#footnote-1) |
| Posology | Dosing including method of administration |
| Signatories |  |
| Healthcare Payer/Providers | Signature, name and role  for each signatory |
| HTA body |
| Marketing Authorisation Holder |
| Registry Holder |
| Medical Association/Expert Centre |
| Patient Group |
| Date of Agreement | Date |
| Expected Duration of Data Collection | X years  Start date – End Date[[2]](#footnote-2)  Expected minimum patient follow-up period |
| Planned Re-Appraisal/  Pricing and Reimbursement Decision   * Initiation of Process * Publication of Decision | Date  Date |

Further details from: staff lead email

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# Purpose of this Agreement

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

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

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

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

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

# Basis for this Outcomes-Based Managed Entry Agreement

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

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

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

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

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

## Uncertainties to be Resolved in the OBMEA

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

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

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

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

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

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

The remaining uncertainties are expected to be…….

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

* 1…
* 2…

The number of patients expected to receive treatment under the OBMEA is XX with XXX[[4]](#footnote-4) included in the analysis, with minimum follow-up of YY. These data will be combined with pertinent data from other international sources for re-appraisal.

If an external comparator arm is required to answer the research questions, this should be addressed in the statistical analysis plan outlining methods for case matching, or in a separate protocol.

# Patient Entry Process

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

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

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

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

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

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

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

# Patient Eligibility

## 4.1 Inclusion Criteria

List clinical criteria for inclusion….

## 4.2 Exclusion Criteria

List clinical criteria for exclusion….

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

Patient eligibility will be judged by a central panel.

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

## 4.3 Continuation Criteria

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

List clinical criteria for continuation of treatment

Note how dose adjustments, adverse events, allowance of short drug holidays etc will be managed.

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

# Data Management

Ensure this section addresses details about the

* research design
* outcomes to be collected
* source(s) of data/data platform
* data analysis plan
* ownership of data
* publication rights.

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

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

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

**Table X. Data Collection Plan**

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

Table Y presents more details about the data sources.

**Table Y. Data Sources**

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

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

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

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

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

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

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

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

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

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

# Reviews

A multi-stakeholder Monitoring Committee[[8]](#footnote-8) will be established to review progress and recommend actions to support successful conduct and completion of the OBMEA.

The MAH will provide information about any major alterations imposed by the regulator that may impact treatment[[9]](#footnote-9).

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

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

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

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

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

A review may trigger revision of the end date – to lengthen due to limited data or to expedite.

The Monitoring Committee will report progress to the appraisal committee about half-way through the data collection period and produce a final report for input to the re-appraisal.

# Re-appraisal/Pricing and Reimbursement Decisions

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

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

It is expected that the OBMEA will terminate after re-appraisal resulting in the RDT being fully reimbursed/recommended for routine use, or not being listed/withdrawn from use.

(If the monitoring process has been able to extend the period of data collection to be sufficient and modified the Agreement to address emerging issues, it is unlikely that there will be a need to extend the OBMEA after re-appraisal, but this is also this possibility.)

# Responsibilities

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

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

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

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

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

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

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

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

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

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

1. Throughout this document “indication” refers to reimbursed indication which will be the licensed indication or subset as stated in the appraisal or pricing and reimbursement agreement, with specification of any restrictions. [↑](#footnote-ref-1)
2. The end-date/cut-off for data collection should allow sufficient time for analysis in advance of the initiation of the re-appraisal. [↑](#footnote-ref-2)
3. *Most health systems have exemptions for secondary use of patient data to improve individual patient care, but if a formal clinical trial is established, ethical approval will be required.* [↑](#footnote-ref-3)
4. Include a sample size determination if possible [↑](#footnote-ref-4)
5. See NICE Example, page 16 onwards <https://www.nice.org.uk/guidance/hst12/resources/managed-access-agreement-pdf-6968825245> [↑](#footnote-ref-5)
6. [see example from the MPS Society](https://d422994b-53f1-40f8-a3df-62dbcbf28377.filesusr.com/ugd/8acb9b_c238f04593f547e585a1fcaca3f56658.pdf) – this should be developed with the patient groups, but funded by the MAH/Payer [↑](#footnote-ref-6)
7. E.g. European Reference Network, Specialist Society [↑](#footnote-ref-7)
8. See [IMPACT HTA Monitoring Committee ToR](https://www.impact-hta.eu/work-package-10) [↑](#footnote-ref-8)
9. E.g. eligibility criteria, safety issues to be considered at discontinuation, dosing [↑](#footnote-ref-9)