

EUnetHTA Joint Action 3 WP4

**Relative effectiveness assessment of pharmaceutical technologies**

[XXX] For the Treatment of [XXX]

**Project ID: PTJA[XX]**

Assessment Report

Version [x], [day] [month] [year]

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# Document history and contributors

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| --- | --- | --- |
| Version | Date | Description |
| **V0.1** | **dd/mm/yyyy** | First draft |
| **V0.2** | **dd/mm/yyyy** | Input from dedicated reviewers has been processed |
| **V0.3** | **dd/mm/yyyy** | Input from medical editor and manufacturer(s) has been processed |
| **V1.0** | **dd/mm/yyyy** | Final assessment report |

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### Conflict of interest

All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the [EUnetHTA Procedure Guidance for handling DOI form](https://eunethta.eu/wp-content/uploads/2019/11/EUnetHTA-Procedure-Guidelines-DOI.pdf) (<https://eunethta.eu/doi>).

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|  |
| --- |
| NOTE TO AUTHORS  Text in grey boxes provide guidance for using the assessment report template. The boxes can be removed when finalizing drafts. Please consult the EUnetHTA SOP’s for methodological information. All template text should be amended if necessary to represent the assessment. Paragraphs not relevant for the assessment can be removed. |

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# List of abbreviations

|  |  |
| --- | --- |
| AE | Adverse Event |
| ARR | Absolute Risk Reduction |
| ATC | Anatomical Therapeutic Chemical [Classification System] |
| ATMP | Advanced therapy medicinal product |
| CI | Confidence Interval |
| CSR | Clinical Study Report |
| DOI | Declaration of interest |
| ECA | EUnetHTA Confidentiality Arrangement |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EUnetHTA | European Network of Health Technology Assessment |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluation |
| HR | Hazard Ratio |
| HRQOL | Health-related Quality of Life |
| HTAi | Health Technology Assessment international |
| ICD | International Classification of Diseases |
| ITT | Intention-to-treat |
| MAH | Market Authorization Holder |
| MD | Mean Difference |
| MeSH | Medical Subject Headings |
| NA | Not applicable |
| NR | Not reported |
| OR | Odds Ratio |
| PP | Per Protocol |
| RCT | Randomized Controlled Trial |
| REA | Relative Effectiveness Assessment |
| RR | Relative Risk |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SMD | Standardized Mean Difference |
| SmPC | Summary of product characteristics |
| SOP | Standard Operating Procedure |
| WP4 | Work Package 4 |

# Executive summary of the assessment of [COMPOUND]

|  |
| --- |
| In general, the summary should present a comprehensive and independently readable overview of the assessment. Tables on the most important outcomes (including adverse events) should be included / copied from the results section. |

## Introduction

|  |
| --- |
| Summarize information on:   * The disease; * Current standard of care; other therapeutic alternatives * Information on compound under assessment (include brand, non-proprietary name (INN), ATC code, route of administration, therapeutic class, relevant registered indication. |

## Objective and scope

|  |
| --- |
| Summarize:   * Objective; * Copy the PICO table including the statement “The PICO presented in this joint assessment report aims to capture a wide range of national requirements for different EUnetHTA partners and is based on the input received via the EUnetHTA PICO survey and consolidated by the authoring team” in a footnote. |

## Methods

|  |
| --- |
| Summarize:   * The methods of the literature search; * Study selection; * Tools used for quality assessment; * Data analysis; * Patient involvement. |

## Results

|  |
| --- |
| Summarize:   * The results of the literature search; * Included studies and their most important/relevant characteristics; * Baseline characteristics of included patients in the studies; * Risk of bias and quality assessment/certainty of the evidence; * Effectiveness outcomes; * Safety outcomes including adverse events.   *Please consider structuring the results summary using the same headers as the main report.* |

## Discussion

|  |
| --- |
| Summarize at least:   * The strengths and limitations of the assessment.   *Please consider structuring the discussion summary using the same headers as the main report.* |

## Conclusion

|  |
| --- |
| The summary of findings table is optional and can be used in case the certainty of the evidence has been assessed with GRADE. Regenerate the table using an applicable online tool (e.g. GRADEpro). |

Table 0.1. Summary of findings of [xxx]

| Outcome | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Certainty of evidence | Comments |
| --- | --- | --- | --- | --- | --- | --- |
| Risk with [comparison] | Risk with [intervention] |
| [Outcome X1] | [X] per 1000 | [x] per 1000 | RR/OR/HR/SMD [XX]  (XX to XX) |  | High/ moderate/ low/ very low |  |
| [Outcome X2] | [X] per 1000 | [x] per 1000 | RR RR/OR/HR/SMD [XX]  (XX to XX) |  | High/ moderate/ low/ very low |  |
| **Source**: [xx].  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | | | | | | |

# BACKGROUND

|  |
| --- |
| The content in “Section1” should be a limited summary format (as a detailed description will be available in the published manufacturer Core Submission Dossier and this usually is not undergoing any “assessment” but just a verification of the most important information).  Consider using subheadings per described comparator (group) to structure the text in the different sections. |

## Overview of the disease or health condition

|  |
| --- |
| Include a description of the disease, its prevalence or incidence (including heterogeneity throughout Europe if existing) and symptoms. |

## Current clinical practice

|  |
| --- |
| The current clinical practice/standard of care should be substantiated based on guidelines. An overview of the relevant guidelines is presented in the appendix. If available, European guidelines should be described. It is not necessary to describe the standard of care for each member state separately, but should be addressed existing heterogeneity. Please indicate the place of the technology in the care pathway, e.g. by showing a diagram showing the care pathway and what the technology might displace if used given its licensed indication and also the size of the target population given the licensed indication.  Below is an example provided on how to report figures. Please use cross-referencing to refer to tables and figures. |



Figure 1.1. Example on how to report figures

**Source:** EUnetHTA logo

## Features of the interventions

|  |
| --- |
| Describe briefly (refer to the tables below as much as possible) the characteristics of the intervention and comparators. Add columns to the tables if necessary. Paste the registered indication relevant for this assessment verbatim. |

Table 1.1. Features of the intervention

|  |  |  |
| --- | --- | --- |
| Non-proprietary name | [COMPOUND] | [COMPARATOR] |
| Proprietary name |  |  |
| Registered EMA indication |  |  |
| Prospective Marketing authorisation holder |  |  |
| Contra-indications |  |  |
| Drug class |  |  |
| Active substance(s) |  |  |
| Pharmaceutical formulation(s) |  |  |
| ATC code |  |  |
| In vitro diagnostics required |  |  |
| Monitoring required |  |  |
| Orphan Designation | [Yes/no] | [Yes/no] |
| ATMP | [Yes/no] | [Yes/no] |
| **Source**: [xx].  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | | |

Table 1.2. Administration and dosing of the technology

|  |  |  |
| --- | --- | --- |
|  | [COMPOUND] | [COMPARATOR] |
| Method of administration |  |  |
| Doses |  |  |
| Dosing frequency |  |  |
| Standard length of a course of treatment |  |  |
| Standard interval between courses of treatments |  |  |
| Standard number of repeat courses of treatments |  |  |
| Dose adjustments |  |  |
| **Source**: [xx].  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | | |

# objective and Scope

|  |
| --- |
| Adapt the text to describe the objective for this assessment. Summarize how the PICO was derived, and refer to the project plan for a more detailed explanation of the rationale for the PICO and justification of chosen elements. If there is more than one research question, additional PICO’s may be added. The PICO(‘s) should be copied from the Project Plan. If there are any additional criteria in the project plan, copy those in as well. Describe any deviations from the Project Plan if relevant.  Table 2.1 should reflect the PICO as reported in the Project Plan, followed by a description of the differences between our PICO and the provided submission dossier, and the implications of the differences (e.g. not able to perform an assessment for comparator x, not able to assess main population, supplementary material included by the assessment team (not the standard)).  EUnetHTA’s position on the concept of PICO can be found in the PICO paper, available in the companion guide. |

The aim of this EUnetHTA Joint Relative Effectiveness Assessment is to compare the clinical effectiveness and safety of [name of technology] in the target patient populations with relevant comparators. The target patient populations and relevant comparators are defined in the project scope below. The PICO presented in this joint assessment report is policy driven and aims to capture a wide range of national requirements for different EUnetHTA partners and is based on the input received via the EUnetHTA PICO survey and consolidated by the authoring team [include reference to project plan].

Table 2.1. Scope of the assessment

|  |  |  |
| --- | --- | --- |
| Description | Assessment scope | |
|  | **PICO 1** | **PICO 2 [Delete if no PICO 2]** |
| **Population** |  | [Leave empty if same as PICO 1] |
| **Intervention** |  |  |
| **Comparison** |  |  |
| **Outcomes** | **Clinical effectiveness**   * Efficacy outcome 1 * Efficacy outcome 2 | **Clinical effectiveness**   * Efficacy outcome 1 * Efficacy outcome 2 |
|  | **Safety**   * Safety outcome 1 * Safety outcome 2 | **Safety**   * Safety outcome 1 * Safety outcome 2 |
| **Study design** |  |  |
| **Source**: [xx].  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | | |

The assessment was based on the Submission Dossier submitted by the MAH [COMPANY], which deviates from the scope described in the project plan as follows:

* Name deviation and provide rationale for deviation, add as many bullets as required (e.g. study population, comparators, study design).

Based on these differences, [note here the implications of the differences (e.g. not able to perform an assessment for comparator x, not able to assess main population, supplementary material included by the assessment team (not the standard))].

# METHODS

|  |
| --- |
| In general, use the Project Plan where possible for this section. |

The assessment is based on the data and analyses included in the Submission Dossier prepared by the MAH. During the assessment, the completeness of data and analyses in the Submission Dossier was verified. Furthermore, the methods for data analysis and synthesis applied by the MAH were checked against the requirements of the Submission Dossier and applicable EUnetHTA Guidelines and assessed with regard to scientific validity.

## Information retrieval

|  |
| --- |
| Briefly describe the main elements of information retrieval by adapting the text and table. For the full details of the search, a reference to the Submission Dossier can be made. If additional inclusion/exclusion criteria beyond those defining the PICO are applied in the conduct of searches please specify them in the list below. Possible additional criteria could e.g. be study type, study duration or language of sources. Only include the last sentence (further supplementary searches…) if applicable.  Consider the use of different subheadings to indicate the MAH literature search and results and if applicable additional searches performed by the assessors. |

The evidence base with regard to the drug under assessment provided by the MAH was reviewed by the authoring team. Search strategies were checked for appropriateness and the results of information retrieval included in the MAH’s Submission Dossier were checked for completeness against a search in study registries and against the studies included in the regulatory assessment report. [Further supplementary searches were conducted to check for possible incompleteness of the study pool.]

Table 3.1. Summary of information retrieval and study selection

| Elements | Details |
| --- | --- |
| List of studies submitted by MAH |  |
| Databases and trial registries searched |  |
| Search date |  |
| Keywords |  |
| Inclusion criteria |  |
| Exclusion criteria |  |
| Date restrictions |  |
| Other search limits or restrictions |  |
| **Source**: [xx].  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | |

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the Submission Dossier:

* Study list of MAH on [intervention] (status:[date]);
* Bibliographical databases (last search on [date]);
* Trials registries (last search on [date]).

Check of the completeness of the study pool:

* Trials registries (last search on[date])

[Additional Option 2: Further supplementary searches were conducted to check for possible incompleteness of the study pool:

* Search in [database(s)] for studies on [intervention] (last search on [date]) (see for complete search strategy section x.x.

The check identified [no or number of] additional relevant studies.]

## Data extraction

Information used for the assessment of clinical effectiveness and safety were extracted from the Submission Dossier and verified against the Clinical Study Reports (CSR) or other original documentation provided in the Submission Dossier.

[in case of supplementary searches or analyses please report those here as well]

## Risk of bias assessment

|  |
| --- |
| Adapt the text to reflect the method of assessment of risk of bias used. In case the Cochrane Risk of Bias tool 2.0 is used in the current assessment, make sure to update references and the template text according. Add a reference to ROBINS in case non-randomized trials were assessed. |

The quality rating tool developed by the Cochrane Collaboration (version 5.1.0; March 2011) (ref) was used to assess the risk of bias in randomized trials. Risk of bias at study level was assessed for six different domains:

* Method used to generate the sequence of randomisation (random sequence generation);
* Method used to mask the sequence of allocation to treatment (allocation concealment);
* Measures used to ensure the ‘blindness’ of the study with respect to treatment assignment (blinding of participants, medical personnel and outcome assessors);
* Completeness of the data for each outcome considered (incomplete outcome data);
* Selective description of the results (selective outcome reporting);
* Other sources of bias (e.g., bias due to the early interruption of the study because of the benefits without an appropriate stopping rule, use of a non-validated measurement instrument, incorrect statistical analysis).

For each domain, two independent assessors judged the risk of bias (‘low risk’, ‘high risk’ or ‘unclear’) on the basis of the information retrieved from the full-text publications, the protocols and the Submission Dossier. The results of the risk of bias assessment at both the study level and the outcome level. For non-randomized trials, ROBINS-I was used [ref].

## Analyses of included studies

|  |
| --- |
| Adapt the generic text to reflect the methods used. Delete the subparagraphs in case they are not relevant for the assessment. |

The information in the Submission Dossier on the study design, study methods, populations, endpoints (patient relevance, validity, and operationalization) and study results were evaluated. The results of this evaluation is presented and was used for identification of relevant analyses and considered for the conclusions of the assessment report.

### Meta-analysis

During the assessment, the methods applied for the meta-analyses presented in the Submission Dossier, and, if applicable, the justification for deviations from the procedures described above were evaluated.

### Sensitivity analysis

To evaluate the robustness of results, sensitivity analyses with regard to methodological factors presented in the Submission Dossier and the corresponding methods applied were evaluated. These methodological factors arise from decisions made within the framework of the retrieval and assessment of information, for example, the specification of cut-offs for the time point of data collection or the choice of effect measure.

### Subgroup analysis and other effect modifiers

During the assessment, the subgroup analyses examining potential effect modifiers presented in the Submission Dossier and the corresponding methods applied were evaluated. The evaluation also includes the justification for the choice of cut-offs if quantitative characteristics were categorized.

### Indirect comparisons

The methods of indirect comparisons applied, and, if applicable, the justification in the event of deviations from the required approaches were evaluated [10].

### Certainty of the evidence [IF APPLICABLE]

For rating the quality of the evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE)-method was applied [ref].

## Patient involvement

|  |
| --- |
| Describe the method used for patient involvement and how this was used in the assessment process. |

# Results

## Information retrieval

|  |
| --- |
| Check all steps of the information retrieval and summarize the results. For full details, including the PRISMA flow chart, a reference to the Submission Dossier is sufficient if the search strategy of the MAH was adequate.  If the search strategy of the MAH was inadequate and therefore supplementary searches have been conducted use also the template text provided in additional Option 2 (in the methods section) using subheadings to clearly indicate the difference between assessor performed and manufacturer performed searches. Supplementary searches are carried out to check that the study pool is complete rather than to augment the study pool with additional studies. |

## Studies included in the assessment

|  |
| --- |
| Give an overview of the included studies for the assessment. Under available documentation, list all references to published literature for the study and whether CSRs are available for assessment. |

The studies listed in the following table 4.1 were included in the assessment.

Table 4.1. Study pool – list of relevant studies used for the assessment

|  |  |  |  |
| --- | --- | --- | --- |
| Study reference/ID | Study category | | |
|  | Study for marketing authorization of the technology under assessment (yes/no)a | Sponsored or third-party studyb | Available documentationc |
| <Study1> [Include acronym]  [Study register ID] | [yes/no] | [sponsored/third party] |  |
|  |  |  |  |
| **Source**: [xx].  a If "yes," also indicate the respective reference of the data reference(s).  b Study sponsored by the MAH or in which the MAH participated financially in some other way.  c Include references of the study registry entries and, if available, the reports on study design and/or results listed in the study registries.  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | | | |

## Excluded studies

Table 4.2 lists the studies that were included in the Submission Dossier provided by the MAH but were excluded for further consideration in this assessment.

Table 4.2. Excluded studies

|  |  |
| --- | --- |
| Study reference/ID | Reason for non-consideration of the study |
|  |  |
|  |  |
| **Source**: [xx].  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | |

## Characteristics of included studies

|  |
| --- |
| Use the table templates provided in the SOP on data extraction and follow the process of data extraction as described in the SOP. Columns in the tables can be added or removed to account for the trial design (e.g. number of comparators).  Provide a description of the included studies (consider e.g. design, inclusion and exclusion criteria, prior therapy, relevant subpopulations (if applicable), stratification, countries conducted, details on interventions (dosing) including subsequent therapies, primary and secondary outcomes, data cut offs). Refer to the tables for details. Describe how the studies were used to answer the research question (e.g. as direct comparison or indirect evidence). The tables are partly pre-filled to give an example. Use the headers within the table of characteristics of the studies included to indicate for which comparison the studies were used. |

Table 4.3 and Table 4.4 describe the studies used for the assessment.

Table 4.3. Characteristics of the studies included

| Study reference/ID | Study design | Patient population | <Intervention> (number of randomized patients) | <Comparator(s)> (number of randomized patients) | Study duration and data cut off(s) | Primary outcome; patient-relevant secondary outcomes |
| --- | --- | --- | --- | --- | --- | --- |
| **Direct comparison: xxx vs. xxx** | | | | | | |
| <Study 1> | RCT,  double blind/single blinded/open, parallel/cross-over, etc. | relevant characteristics, e.g. degree of severity | Group 1  (N = XX)  Relevant subpopulation:  Group 1 (n = XX) | Group 2  (N = XX)  Relevant subpopulation:  Group 2 (n = XX) | Study duration  Follow-up  Type of analysis (interim, final, extended follow-up); planned/unplanned | Primary:  (ITT/PP)  Secondary:  (ITT/PP) |
| **Indirect comparison: xxx vs. xxx** | | | | | | |
| <Study 2> |  |  |  |  |  |  |
| <Study 2> |  |  |  |  |  |  |
| **Source**: [xx].  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | | | | | | |

Table 4.4. Characterisation of the interventions and comparators

|  |  |  |  |
| --- | --- | --- | --- |
| Study reference / ID | <Intervention> | <Comparator> | <Optional additional column with treatment characteristics  e.g. pre-treatment, treatment during the run-in phase, concomitant/prohibited medications as required> |
| <Study 1> | xxx 250 μg, 1  Inhalation bid  +  Placebo 2  Inhalations bid | yyy 200 μg, 2  Inhalations bid  +  Placebo 1  Inhalation bid | Pre-treatment: zzz 1000 μg per day, 4 weeks prior to study start  PRN medication: aaa |
| <Study 2> |  |  |  |
| **Source**: [xx].  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | | | |

|  |
| --- |
| Provide here a description of planned duration of follow-up observation and mean and median treatment duration. See SOP on data extraction for table templates. Add or delete columns if necessary. |

Table 4.5 shows the planned duration of follow-up observation and [mean and/or median] treatment duration of the patients for the individual outcomes.

Table 4.5. Information on the course of the [study/ies] (including planned duration of follow-up) and testing again for the table of contents

| Study reference / ID  Outcome category | Planned follow-up | <Intervention> | <Comparator> |
| --- | --- | --- | --- |
| <Study 1> |  | N = | N = |
| Treatment duration [<month/weeks>] | | | |
| Median [Min; Max] | – |  |  |
| Mean (SD) | – |  |  |
| Observation period [<months/weeks>] | | | |
| <outcome> | <Until disease progression/x days after end of treatment, … > | | |
| Median [Min; Max] | – |  |  |
| Mean (SD) | – |  |  |
| <outcome> | <Until disease progression/x days after end of treatment, … > | | |
|  |  |  |  |
| <Study 2> |  | N = | N = |
| <.....> |  |  |  |
| **Source**: [xx].  **Abbreviations**: max=maximum; min=minimum; N=number of analysed patients; NR=no reported; RCT=randomized controlled trial; SD=standard deviation; vs.=versus. | | | |

|  |
| --- |
| Provide here a brief description of characteristics of the study populations. See SOP on data extraction for table templates. In the text, describe also data on treatment and study discontinuation (e.g. lost to follow up). Add or delete columns if necessary. |

Table 4.6 shows the characteristics of the patients in the studies included.

Table 4.6. Baseline characteristics of the study populations

| Study reference / ID  Characteristics  Category | <Intervention> | <Comparator> |
| --- | --- | --- |
| <Study 1> | N = | N = |
| Age [years], mean/median (SD) |  |  |
| Gender [f / m], n (%) |  |  |
| <more characteristics>, n (%) |  |  |
| <Category 1> |  |  |
| <Category 2> |  |  |
| … |  |  |
| Treatment discontinuation, n (%) |  |  |
| Study discontinuation, n (%) |  |  |
| <Study 2> | N = | N = |
| <.....> |  |  |
| **Source**: [xx].  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | | |

## Outcomes included

|  |
| --- |
| This section can be used to illustrate which outcomes (according to the project plan) from each study have been included in the analysis. When there is no great complexity in studies and outcomes, it can be considered not to include this section.  Use the table „matrix of outcomes“ provided in the SOP Data extraction. |

Table 4.7 shows for which of the outcomes to be included in the assessment data were available in the studies included.

Table 4.7. Matrix of outcomes in the included RCTs

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study reference/ID | Outcomes | | | | | | | | |
|  | <Outcome 1> | <Outocme2> | <Outcome 3> | <Outcome 4> | <Outcome 5> | <Outcome 6> | <Outcome 7> | <Outcome 8> | <Outcome 9> |
| <Study 1> | yes | no | yes | yes | yes | no | no | yes | yes |
| <Study ..> |  |  |  |  |  |  |  |  |  |
| **Source**: [xx].  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | | | | | | | | | |

## Risk of bias

|  |
| --- |
| Describe risk of bias at study level and for the relevant outcomes. Use tables provided in the SOP RoB (for RCT or non-RCT). Differentiate between outcomes if necessary (e.g. if for different outcomes different approaches were used/different judgement is made on blinding, ITT/PP analysis or incomplete outcome data). In that case, additional columns can be added to the RoB table (the template table provides an example on this regarding blinding). Provide a clear explanation for judgements. Make sure to summarize the risk of bias per outcome per study and across studies (in case of pooling of results). When, for non-randomized trials, the ROBINS-I tool was included, add the checklist as an appendix to the assessment.  Please be aware provided tables need updating when the Cochrane Risk of Bias tool version 2.0 is used (always include a reference to the tool used for this assessment). |

Table 4.8 and Table 4.9 describe the risk of bias at study level for the relevant outcomes.

Table 4.8. Risk of bias in randomized studies

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study reference/ID | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias)a | Blinding of outcome assessment (detection bias)b | Incomplete outcome data addressed (attrition bias) | Selective reporting (reporting bias | Other potential sources of bias |
| <Study 1> | H / L / U | H / L / U | H / L / U | H / L / U | H / L / U | H / L / U | H / L / U | H / L / U |
| <Study 2> |  |  |  |  |  |  |  |  |
| **Source**: [xx].  a For self-reported outcomes including pain, function and global assessment  b For outcome assessor reported outcomes  **Abbreviations**: H=high risk; L=low risk; U=unclear risk. | | | | | | | | |

Table 4.9. Risk of bias in non-randomized studiesa

| Trial | Bias due to confounding | Bias in selection of participants into the study | Bias in classification of interventions | Bias due to deviations from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result |
| --- | --- | --- | --- | --- | --- | --- | --- |
| [OUTCOME 1] | | | | | | | |
| Trial 1 | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI |
| Trial 2 | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI |
| [OUTCOME 2] | | | | | | | |
| Trial 1 | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI |
| Trial 2 | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI | L / M / S / C / NI |
| **Source**: [xx].  a Adapted from the risk of bias in non-randomized studies of interventions (ROBINS-I) assessment tool  **Abbreviations**: L=low risk; M=moderate risk; S=serious risk; C=critical risk; NI=no information. | | | | | | | |

## External validity

|  |
| --- |
| Explain the relation to the PICO (external validity). Add a justification for each judgement made. |

## Results on clinical effectiveness

|  |
| --- |
| Use the table templates provided below (if applicable) or refer to the SOP on data extraction for other table templates if necessary. Follow the process of data extraction as described in the SOP.  Describe the effects of the interventions in comparison with the comparators for each outcome per study and pooled estimates of meta-analysis if appropriate. In case of meta-analysis, justify the choice of the model used and assess any heterogeneity and provide the I2 and associated p-value. Include HRQOL (or state when missing), unfavourable effects, discontinuation due to AE and SAE’s/grade 3-4 severe AE’s.  Use the text for a description of the results and findings but refer to the tables where possible. Explain to what extend the evidence the evidence fits with the PICO. Add a justification for each judgement made, e.g. on risk of bias. Refrain from statements such as ‘compound has added / equal / less efficacy / effectiveness / benefit / shows superior / comparable / inferior effects’ etc. If necessary, tables can be added for relevant subgroups (provide clear header explicitly stating that it concerns a subgroup analysis) or sensitivity analyses.  Add figures (e.g. forest plots, Kaplan Meier curves) if applicable.  The example template tables are presented for RCT’s/direct comparisons only. Please adjust those to reflect the study type by adding/removing/adapting columns. For indirect comparisons, adapt or add relevant tables to reflect the chosen method for indirect treatment comparisons and effect presentation. Templates for result presentation such as subgroups, indirect comparisons, sensitivity analyses, adverse events (not reported as outcome) etc. can be found in the SOP on data extraction.  If GRADE is used, insert GRADE evidence profile table and provide judgements in the footnotes. Alternatively, a summary of findings table can be presented here with the GRADE evidence profile table in an appendix.  Consider using subheadings per described comparator (group) to structure the text in the different sections. |

Table 4.10 [and Table 4.11 and Table 4.12] summarize the results of the comparison of [intervention] with [comparator] in [indication]

Table 4.10. Results for <outcome> (dichotomous)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study reference/ID | <Intervention> | | <Comparator> | | <Intervention vs. Comparator> |
| N | n (%) | N | n (%) | RR/OR [95% -CI];  (p-value)  ARR [95% -CI];  (p-value) |
| <Study 1> |  |  |  |  |  |
| …… |  |  |  |  |  |
| **Source**: [xx].  **Abbreviations**: ARR=absolute risk reduction; CI=confidence interval; n=number of patients with (at least one) event; N=number of analysed patients; OR=odds ratio; RCT=randomized controlled trial; RR=risk ratio; vs.=versus. | | | | | | |

Table 4.11. Results for <outcome> (continuous)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study reference/ ID | <Intervention> | | | <Comparator> | | | <Intervention vs. Comparator> |
| N | Values at start of study  Mean/ Median (SD) | Change at end of treatment Mean/ Median (SD) | N | Values at start of study Mean/ Median (SD) | Change at end of treatment Mean/ Median (SD) | MD/SMD [95%-CI];  (p-value) |
| <Study 1> |  |  |  |  |  |  |  |
| …… |  |  |  |  |  |  |  |
| **Source**: [xx].  **Abbreviations**: CI=confidence interval; MD=mean difference; n=number of patients with (at least one) event; N=number of analysed patients; RCT=randomized controlled trial; SD=standard deviation; SMD=standardized mean difference; vs.=versus. | | | | | | | | |

Table 4.12. Results for <outcome> (time to event)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study reference/ID | <Intervention> | | <Comparator> | | <Intervention vs. Comparator> |
| N | Median time to event in months/weeks [95%-CI] Patients with event n (%) | N | Median time to event in months/weeks [95%-CI] Patients with event  n (%) | HR [95%-CI];  (p-value)  Median time to event [95%CI];  (p-value) |
| <Study 1> |  |  |  |  |  |
| …. |  |  |  |  |  |
| **Source**: [xx].  **Abbreviations**: CI=confidence interval; HR=hazard ratio; n=number of patients with (at least one) event; N=number of analysed patients; RCT=randomized controlled trial; SD=standard deviation; vs.=versus. | | | | | |

### Subgroup analyses

|  |
| --- |
| Describe the results for subgroups relevant for the assessment. Add forest plots or Kaplan-Meier curves if applicable/available. Describe if subgroup characteristics and cut-off values mentioned were predefined. For result presentation use the table provided in the SOP Data extraction. |

## Results on safety

|  |
| --- |
| The same instruction applies as for the effectiveness outcomes applies to the safety outcomes.  In the table on AEs, the relevant most common and/or serious AEs on SOC/PT level presented by the company in core Submission Dossier should be shown here. Only add effect estimates when available and appropriate. Summarize the adverse effects profile in the text. AEs (on the SOC/PT level) selected as specific AEs for inclusion in the assessment are extracted into the results tables.  Consider using subheadings per described comparator (group) to structure the text in the different sections. |

Table 4.13. Adverse events

| Study [xxx] | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| System organ/ class/adverse events | Frequency (very common, common, uncommon, rare, very rare, not known | All grades | | | | Grades ≥ 3 | | | |
| Intervention (n = x)  n (%) | Comparator (n = x)  n (%) | Relative risk (95% CI) | Risk difference (95% CI) | Intervention (n = x)  n (%) | Comparator (n = x)  n (%) | RR (95% CI) | RD (95% CI) |
| Class 1 (for example, nervous system disorders) | | | | | | | | | |
| Adverse event 1 |  |  |  |  |  |  |  |  |  |
| Adverse event 2 |  |  |  |  |  |  |  |  |  |
| Class 2 (for example, vascular disorders) | | | | | | | | | |
| Adverse event 3 |  |  |  |  |  |  |  |  |  |
| Adverse event 4 |  |  |  |  |  |  |  |  |  |
| Total serious adverse events n (%) |  | - | - | - |  |  |  |  |  |
| Total deaths n (%) |  | - | - | - |  | NA | NA | NA | NA |
| Discontinuation due to AE (%) |  |  |  |  |  | NA | NA | NA | NA |
| **Source**: [xx].  **Abbreviations**: RR=relative risk; RD=risk difference; NA=not applicable | | | | | | | | | |

### Subgroup analyses

|  |
| --- |
| Describe the results for subgroups relevant for the assessment. Add forest plots or Kaplan-Meier curves if applicable/available. Describe if subgroup characteristics and cut-off values mentioned were predefined. For result presentation use the table provided in the SOP Data extraction. |

# Patient involvement

|  |
| --- |
| Summarize the main results and conclusion of the patient involvement. Use the appendix for details. |

# DISCUSSION

|  |
| --- |
| Place the findings in context with regard to the scope of the assessment. For example, integrate quality of evidence (including internal and external validity), relevance of evidence, interpretation of the outcomes and validity of the outcomes, interpretation of the statistics, evidence gaps (if found, also use and refer to the appendix on evidence gaps) and strengths and limitations of the evidence. Also discuss this in relation to the Submission Dossier by the MAH and critique any methodological issues. Discuss patient involvement. Refrain from statements such as ‘compound has added/equal/less efficacy/effectiveness/benefit / shows superior/comparable/inferior effects’ etc.  Consider the following elements when critiquing the dossier by the MAH:   * Research question and scope (including inclusion/exclusion criteria) - include impact of differences between EUnetHTA PICO and the material provided in the submission dossier; * Information retrieval and study pool; * Data analysis and synthesis of study results; * Results of individual studies; * Strengths and limitations of the evidence.   Please make sure to include headers to structure the different elements in the discussion. As a basis, at least a header for strengths and limitations should be included in the discussion section. |

# Conclusion

|  |
| --- |
| State the factual conclusions on the relative effectiveness (i.e. the effect sizes and confidence intervals) of positive and negative effects. Conclude on the quality/certainty of the evidence and the most important strengths and limitations of the evidence (e.g. internal and external validity). Refrain from statements such as ‘compound has added/equal/less efficacy/effectiveness/benefit / shows superior/comparable/inferior effects’ etc. |

# REFERENCES

|  |
| --- |
| The references must be displayed according to Vancouver style [http://monash.edu/library/skills/resources/tutorials/citing/index.html]. Citations within the text of the report are identified with a number in square brackets (e.g., [1]).  Use of a reference managing software is mandatory (EndNote is preferred). |

# Appendix 1: guidelines for diagnosis and management

|  |
| --- |
| Include the guidelines used for this assessment. Add any sources used which were not covered by the Submission Dossier. Add or adapt tables where needed. |

Table A1. Overview of guidelines used for this assessment

| Name of society/organisation issuing guidance | Date of issue | Country/ies  to which applicable | Summary of recommendation | Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III) |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
| **Source**: [xx].  **Abbreviations**: [xxx]=[xxx]; [yyy]=[yyy]. | | | | |

# APPENDIX 2: PATIENT INVOLVEMENT

|  |
| --- |
| Describe the results of patient involvement. If applicable, please include the following:   * Aim of patient involvement; * Further information on the patients involved (age, gender, demographics, experience with technology under evaluation, disease status etc.) regarding this assessment; * A summary of the main results; report key-messages as reported in the Open Call for Patient Input if approved by the specific patient organisation * Explain how the results of the patient involvement were used/implemented in the assessment report i.e. how they affected the report. |

# Appendix 3: Evidence gaps

|  |
| --- |
| Use the table to provide recommendations for research based on the identified evidence gaps. Structure the research question and provide a rationale for the potential relationship between the intervention and important outcome(s).  The table can be added upon when there is more than one recommendation.  Please note that the first two parts of the table (‘evidence profile of the technology’ and ‘assessment results’) is for internal use only facilitating the linkage between evidence gaps identified in REAs and EUnetHTA Post-Launch Evidence Generation (PLEG) activities, thereby supporting the generation of new and missing evidence. The third part of the table (‘additional evidence generation needs’) will be published in the final assessment report. Please note that the entire table should be completed in the first draft of the assessment report to allow Dedicated Review input. |

Table A2. Recommendations for research

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Evidence profile of the technology (to be shared with WP5B) | | | | |
| **Topic and rationale** | | | | |
| **Title of the assessment** | [Title of the assessment] | | | |
| **Research question** | [Structured research question] | | | |
| **Rationale** | [Clear statement on rationale supporting the use of technology explaining how its intrinsic characteristics can lead to improvement on patient-important outcomes compared to current management, potential of the technology to cover unmet health care need (if applicable), and information on burden of disease] | | | |
| **PICO** | | | | |
| **Population** | [Health status, disease, inclusion/ exclusion criteria] | | | |
| **Intervention** | [Technology and setting of use] | | | |
| **Comparator(s)** | [Relevant comparator(s) and setting of use] | | | |
| **The most important / critical outcomes**  (based on discussions with clinical experts) | [Name of the outcome, measurement tool and desired effect size] | | | |
| [Name of the outcome, measurement tool and desired effect size] | | | |
| [Name of the outcome, measurement tool and desired effect size] | | | |
| [Name of the outcome, measurement tool and desired effect size] | | | |
| [Name of the outcome, measurement tool and desired effect size] | | | |
| (Make copies of the lines above, if needed) | | | |
| **Study design(s)** | [Study design(s) which can produce robust and transferable results; may differ between outcomes] | | | |
| Assessment Results (to be shared with WP5B) | | | | |
| **Most important/critical outcomes where evidence currently lacking or considered insufficient**  [Please see Summary of findings table (if applicable)] | **No. of studies** | **Type of studies** | **Estimate of effect size\*1** | **Certainty of the evidence\*2** |
| [Outcome 1] | [No. of studies] | [Study design(s)] | [Estimate of effect size] | [Level of certainty] |
| [Outcome 2] | [No. of studies] | [Study design(s)] | [Estimate of effect size] | [Level of certainty] |
| [Outcome 3] | [No. of studies] | [Study design(s)] | [Estimate of effect size] | [Level of certainty] |
| [Outcome 4] | [No. of studies] | [Study design(s)] | [Estimate of effect size] | [Level of certainty] |
| [Outcome 5] | [No. of studies] | [Study design(s)] | [Estimate of effect size] | [Level of certainty] |
| (Make copies of the lines above, if needed) | | | | |
| \*1 If differences in results for different sub-populations, please adapt the table in order to allow reporting of these differences  \*2 If no evidence grading system is used, please provide a short narrative statement about the certainty of the evidence | | | | |
| Additional evidence generation needs (to be published) | | | | |
| **Research question 1: [Structured research question]** | | | | |
| **Evidence** | [Current state of the evidence available / reasons for uncertainty] | | | |
| **Population** | [Population and any sub-population(s)of interest] | | | |
| **Intervention** | [The technology/ intervention and setting of use] | | | |
| **Comparator** | [Relevant comparator and setting of use] | | | |
| **Outcome(s)** | [Outcome(s) of interest] | | | |
| **Time stamp** | [Date of recommendation] | | | |
| **Study design** | [Appropriate study design] | | | |
| **Ongoing studies** | [Study registry numbers of relevant ongoing studies, with the date when the search for ongoing studies was performed]  *Please delete the row if no ongoing studies have been identified* | | | |
| **Research question 2: [Structured research question]** | | | | |
| **Evidence** | See above | | | |
| **Population** |  | | | |
| **Intervention** |  | | | |
| **Comparator** |  | | | |
| **Outcome(s)** |  | | | |
| **Time stamp** |  | | | |
| **Study design** |  | | | |
| **Ongoing studies** |  | | | |
| **Research question 3: [Structured research question]**  *(Make copies of the lines above, if needed)* | | | | |