



# The Agency for Health Technology Assessment and Tariff System

## Health Technology Assessment Guidelines

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# 1. Background

The purpose of these Guidelines for conducting Health Technology Assessment is to indicate the principles and acceptable methods of performing Health Technology Assessment to ensure high quality of analyses and reliable results.

The target group of these Guidelines, in addition to AOTMiT employees, is the broadly understood HTA community, including employees of the Ministry of Health and the authority obliged to finance benefits from public funds, research centres, members of the Transparency Council, pharmaceutical companies, persons preparing HTA reports and members of HTA organisations. The Guidelines may also serve to physicians, patients and any other persons who are aware of the role of HTA.

The Guidelines for conducting Health Technology Assessment were first formulated at the request and with the contribution of the Agency in March 2007, and then updated in April 2009. The current version of the Guidelines is an update of the previous documents.

The need to update is a result of both the progress in methodology, as well as the accumulated experience in the use of HTA in the Polish health care system. Furthermore, European cooperation in the field of HTA led to the measures limiting the duplication of HTA works undertaken in the European Union Member States (Directive 2011/24/EU<sup>1</sup>). The European HTA Network, constituted pursuant to Article 15 of Directive 2011/24/EU, issued a document<sup>2</sup> recommending the use of tools, reports and databases created in the framework of the EUnetHTA in the national health technology assessments. The provisions of HTA Core Model<sup>®3</sup> and EUnetHTA methodological guidelines were taken into account in the development of these Guidelines.

The works on the Guidelines were initially conducted internally within the Agency, and then within the Guidelines Update Team, whose members are listed in Annex 1. The Guidelines have been submitted for public commenting and for the review of the Minister of Health.

## 1.1. The notion of Health Technology Assessment

Health technologies are drugs, devices, diagnostic and therapeutic procedures used in certain indications, as well as supportive organisational systems within which health care benefits are provided<sup>4</sup>. These Guidelines apply to the drug health technologies.

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<sup>1</sup> Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. Official Journal of the European Union 4.4.2011 L 88/45, Article 15.

<sup>2</sup> HTA Network reflection paper on "REUSE OF JOINT WORK IN NATIONAL HTA ACTIVITIES", adopted by the HTA Network, April 2015, Ref. Ares (2015)1982600 – 11/05/2015.

<sup>3</sup> EUnetHTA Joint Action 2, Work Package 8. HTA Core Model<sup>®</sup>, version 3.0 (PDF), 2016.

<sup>4</sup> Health technology definition as per the Act of 27 August 2004 on health care benefits financed from public funds (Journal of Laws of 2015, item 581 as amended).

Health Technology Assessment (HTA) is a multidisciplinary process that allows evidence-based decisions regarding health policy and the clinical practice. This process summarises information from various fields including medicine, epidemiology, biostatistics, economy, law and ethics. It is a process aimed to compile the available information on the health, economic, social and ethical aspects of the use of health technologies, conducted in a transparent and systematic manner, according to generally accepted principles, in order to obtain the highest possible validity of the results.

Health technology assessment consists in the evaluation of incremental benefits (in terms of clinical effectiveness and safety) related to the introduction of a health technology into clinical practice (a comparative evaluation of clinical effectiveness, relative effectiveness assessment, REA<sup>5</sup>) in relation to the associated incremental costs.

## 1.2. Purpose of Health Technology Assessment

The health technology assessments are aimed at providing information required to take decisions, based on reasonable grounds, in the domain of health policies. These decisions should be patient-focused and aim to ensure health safety, health effects of the best value, and the optimum use the available resources for health care.

## 1.3. Health Technology Assessment scope

A complete assessment report on a health technology (a HTA report) comprises the following analyses:

1. decision problem analysis (scoping),
2. clinical analysis,
3. economic analysis,
4. impact on the health care system analysis.

Starting a health technology assessment should be preceded by decision problem analysis, which becomes a specific protocol for the clinical, economic and financial analyses.

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<sup>5</sup> The concept of REA was identified during the 3-year works of the European Pharmaceutical Forum and refers to: 1. relative efficacy – estimation of the ratio of health benefits to health risks when using the assessed intervention compared with one or more optional interventions under ideal test conditions; 2. relative effectiveness – estimation of the ratio of health benefits to health risks when using the assessed intervention compared with one or more optional interventions in the clinical practice settings (European Commission, Enterprise and Industry – Working Group on Relative Effectiveness. Core Principles on relative effectiveness. 2008; <http://ec.europa.eu/DocsRoom/documents/7581?locale=en>; as at 23/03/2016).

## **1.4. Authors of analysis and conflict of interest**

Health Technology Assessment requires information about who ordered the analysis, as well as the authors and the individual contribution of each of them in analysis preparation. It is also necessary to include information about any conflict of interest.

## 2. Decision problem analysis

Decision problem analysis (scoping) is an overview of the basic information necessary for the proper preparation of a HTA report. It is recommended to prepare decision problem analysis as a separate document, which must be a common starting point for the analysis of each health technology associated with a particular health problem. The directions and scope of the analyses and methods, including the rules for the selection of data and information contained in the HTA report, must be presented in the decision problem document.

Scoping allows to correctly build the criteria for including studies in the analysis according to the PICOS scheme (Population, Intervention, Comparators, Outcome, Study):

- the population in which a given intervention will be used (P);
- the proposed intervention (I);
- the proposed comparators (C);
- the health outcomes or endpoints against which the clinical effectiveness will be assessed (O);
- types of included studies (S).

The type of studies included in the analysis depends on the nature of the analysis, as indicated in the following sections of the Guidelines.

In the analyses prepared in accordance with these Guidelines, it is recommended to link the relevant indications and interventions to ICD-9-CM<sup>6</sup> and ICD-10<sup>7</sup> codes; it is also advisable to use these codes for adverse effects, especially when discussing the possibilities and methods to monitor the safety of therapy.

### 2.1. Health problem

When starting the preparation of a HTA report, the relevant health problem should be presented.<sup>8</sup>

A description of the health problem, made on the basis of reliable sources of information, should be concise and should contain basic information relevant to decisions taken later in the HTA report and allowing for a clear identification of the placement of the assessed technology in the diagnostic and therapeutic process for the analysed disease.

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<sup>6</sup> The National Health Fund <http://slowniki.nfz.gov.pl/ICD9/SlownikPrimary/2251> (as at 23/03/2016)

<sup>7</sup> Please refer to the ICD-10 version currently used by the public payer. Additionally, if appropriate, code according to the current WHO version can be used, <http://www.who.int/classifications/icd/icdonlineversions/en/> (as at 23/03/2016).

<sup>8</sup> The development of this section of the Guidelines was based, among others, on the HTA Core Model<sup>®</sup> EUnetHTA Domain 1. Health problem and current use of technology (EUnetHTA Joint Action 2, HTA Core Model, version 3.0, 2016).



### **2.1.1. Health problem definition**

Provide the disease definition with the ICD-10 code and the general classification. If the analysis refers to a specific target population (e.g. with a specific disease stage), provide a concise description of the disease, followed by a detailed characterisation of the target health problem (e.g. specific stage).

#### **2.1.1.1 Aetiology and pathogenesis**

Briefly describe the causes and mechanism of development of the disease, as well as its risk factors.

#### **2.1.1.2 Diagnosis**

Describe the principles and criteria for diagnosis of the disease, including the examinations necessary to make/confirm the diagnosis, taking into account the Polish conditions. Reliable sources should be indicated, preferably clinical guidelines based on a systematic review of scientific evidence. If the diagnosis uses specific scales or tests, they should be characterised with information on cut-off points and validation.

#### **2.1.1.3 Clinical presentation, natural history, complications and prognosis**

Describe the natural course of the disease/syndromes with particular emphasis on those relevant to the patient. The description should include an indication of prognostic factors and the factors affecting the course of the disease, as well as a discussion of the disease-related loss of quality of life. The method to monitor disease progression should be presented.

The information contained in this section should, among others, clearly indicate, which outcomes of the clinical trials can be considered clinically significant outcomes (clinical endpoints).

#### **2.1.1.4 Epidemiology and disease burden**

Provide epidemiological data, including incidence and morbidity, with particular emphasis on data for the Polish population. Furthermore, present the health problem in a general way from the public health perspective (socio-economic burden).

#### **2.1.1.5 Current medical management**

Describe the recommended treatment, preferably on the basis of evidence-based clinical guidelines. Then describe the treatments recommended in the Polish clinical guidelines. This description should concisely present the method of treatment in the various stages of the disease, with emphasis on stage, in which the assessed therapy is to be used.

Keep in mind that the existing current medical practice in Poland may not coincide with that recommended by the international clinical guidelines (see also section 2.4 Comparators).

Complete the description with a summary of treatment options, which are currently reimbursed in Poland in the assessed indication.

## 2.2. Target population selection

Describe the target population, or the population in which the assessed intervention will be used. Compare the approved indications with those reviewed in the analysis; provide a rationale for any narrowing/extension of the indications.

If the assessed technology will be used in a particular subpopulation of patients diagnosed with a given disease (e.g. those with a specific gene mutation), specify separately additional criteria for identifying the evaluated subpopulation. It must be demonstrated that the narrower population can be clearly identified by the indicated criteria; otherwise, the causes and consequences of this should be analysed.

Determine the approximate potential size of the population along with the uncertainty range, and describe the method used in its evaluation. It is especially important to take into account the Polish data, if available.

## 2.3. Intervention

Present the assessed intervention taking into account the following aspects<sup>9</sup>:

- authorisation: Marketing Authorisation Holder and/or applicant. For interventions that are approved in Poland<sup>10</sup>, provide the approval date and all approved indications. For technologies which are not approved in Poland, dates and places of their approval in other countries should be specified along with the conditions determined by the regulatory agencies, in particular the FDA<sup>11</sup>, if such data are available. Please specify whether the marketing authorisation for the medicinal product indicates the special conditions of authorisation, and whether the authorisation has a validity date;
- mechanism of action, therapeutic group, ATC code;
- conditions under which the assessed technology is to be available or reimbursed (e.g. available in pharmacies on prescription of a primary care physician, in secondary care, in inpatient treatment);
- competences necessary to use the technology (e.g. drug prescribed by a medical specialist in a particular field). The necessary information to be provided to the patient/carer;
- the necessary monitoring of the use of the technology (in terms of both effectiveness and safety), and the necessary additional information;

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<sup>9</sup> The development of this section of the Guidelines was based, among others, on the HTA Core Model<sup>®</sup> EUnetHTA Domain 2. Description and technical characteristics of technology (EUnetHTA Joint Action 2, HTA Core Model, version 3.0 (PDF), 2016).

<sup>10</sup> Marketing authorisation in Poland is a result of the regulatory procedures: national procedure, decentralised procedure, European procedures involving the EMA (European Medicines Agency) (<http://www.urpl.gov.pl/pl/produkty-lecznicze/zagadnienia-rejestracyjne/nowa-rejestracja> as at 04/10/2016).

<sup>11</sup> Food and Drug Administration.

- the reimbursement status in Poland, with a list of indications covered by reimbursement, including the scope of off-label indications (ideally by ICD-10 codes).

In addition, based on current clinical guidelines, refer to the place of the assessed technology in the treatment or diagnosis: line of treatment, whether it is a technology used alone or as add-on to the current standard of care. Indicate whether, in accordance with clinical guidelines, treatment should be applied indefinitely, or for a limited period (in this case, provide an indicative duration of therapy with the assessed health technology).

Provide also the current recommendations on the financing of the assessed intervention from public funds in Poland and in other countries.

## 2.4. Comparators

The assessments of incremental benefits (in terms of the clinical effectiveness and safety) related to the introduction of the new health technology into clinical practice within the health technology assessment is made by comparing health outcomes and costs for the new intervention to the consequences of the continuation of the optional practices, i.e. those currently used in the target population. The optional interventions whose effectiveness, safety and cost are a reference point in the assessment of the new technology, are called comparators. Such a comparison is to examine whether the assessed intervention carries an additional therapeutic or economic value.

The optional technology can be any medical procedure/health technology, including a drug, medical device, medical procedure or psychological intervention, radiotherapy, physiotherapy, surgery, and advice (e.g. on smoking cessation), and a combination of health interventions carried out simultaneously or sequentially, as well as the natural course of the disease (no active treatment). Often in the case of the first health technology with proven efficacy in a given indication, or in a given subpopulation, it is the best supportive care (BSC) or technologies with effectiveness of the placebo.

At the initial stage of selection of the comparator, consider all potential optional interventions that could be used in the assessed indication, especially those financed with public funds in Poland. The considerations should include technologies from the given therapeutic group, as well as other technologies, which are used in the assessed indication in order to achieve a similar therapeutic target as for the assessed intervention.

Indicate the unmet needs of patients in the context of the assessed intervention and the currently used therapeutic options.

In the first place, a comparator for the assessed intervention must be an existing (current) medical practice, or a procedure, which in the medical practice would probably be replaced by the assessed technology (see section 2.1.1.5 Current

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medical management). The sources of information on the existing medical practice may include:<sup>12</sup>

- list of guaranteed benefits<sup>13</sup>;
- drug market analysis;
- guidelines for clinical practice, and consultations with clinical experts;
- registers.

If there are substantive reasons, it is recommended to carry out a comparison also with other comparators, e.g. the cheapest intervention or one that is considered to be the most effective (e.g. in accordance with the current guidelines for clinical practice, systematic reviews or clinical expert opinions).

The choice of comparators must be justified based on current guidelines and standard procedures, as well as clinical practice, taking into account the purpose of treatment, e.g. a cure, improved survival, delayed disease progression, symptom prevention and control, preventing/counteracting undesirable effects. Indicate the clinically meaningful adverse effects<sup>14</sup> of the comparators, including adverse effects relevant to the patients' quality of life.

Keep the comparators consistent between the clinical and economic analyses.

## 2.5. Health outcomes

The assessment of health benefits brought by the assessed health technology should be made through analysis of clinically significant outcomes<sup>15</sup> that are of key importance in a given disease. Three main categories grouping the clinically significant outcomes can be indicated:

- mortality-related endpoints;
- morbidity-related endpoints;
- health-related quality of life (HRQoL) endpoints.

The clinically significant outcomes also include the events and adverse drug reactions (classified as serious and non-serious)<sup>16</sup>.

The outcomes reported in the analyses should:

- be defined and justified in the description of decision problem;

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<sup>12</sup> EUnetHTA Guidelines. Comparators & Comparisons. Criteria for the Choice of the Most Appropriate Comparator(s). Summary of Current Policies and Best Practice Recommendations. Amended Nov 2015.

<sup>13</sup> Available on the website of the Ministry of Health at <http://www.mz.gov.pl/koszyk-swiadczen-gwarantowanych> (as at 25/01/2016).

<sup>14</sup> To describe the side effects, it is recommended to use the MedDRA Dictionary – the Medical Dictionary for Regulatory Activities <http://www.meddra.org> (as at 15/08/2016).

<sup>15</sup> EUnetHTA Guidelines. Endpoints Used for Relative Effectiveness Assessment of Pharmaceuticals: Clinical Endpoints. Amended Nov 2015.

<sup>16</sup> The concepts relating to adverse effects, including adverse drug reaction, serious adverse drug reaction, are precisely defined by the Pharmaceutical Law Act of 6 September 2001 (consolidated text, Journal of Laws of 2004, No. 53, item 533).

- refer to the assessed disease and its course,
- reflect the most important aspects of the health problem and at the same time allow to detect the possible differences between the compared technologies,
- be essential for reasonable clinical decision-taking (critical points for a given health problem).

When reporting results for the outcomes, provide a detailed description of the methods used in the case of missing data<sup>17</sup>.

The treatment outcomes should be analysed in the longest available follow-up period. The assessment of treatment outcomes in a short-time follow-up period is sufficient in acute health problems that have no long-term consequences. In chronic diseases, the outcomes obtained in a longer follow-up period have a higher value; however, in some situations, the assessment of treatment effectiveness, due to longer survival, must be made on the basis of results obtained in a shorter follow-up period.<sup>18</sup>

In the survival analysis, it is recommended to report the overall survival; provide unadjusted data, and in justified cases also data adjusted for the cross-over effect.

If the clinical effectiveness assessment is based on the results of surrogate endpoints, the clinical analysis must reliably demonstrate their relationship with the clinically significant outcomes.<sup>19</sup> Validation of the surrogate endpoints should be carried out in relation to the health problem in question.

It is not recommended to include in the analysis the endpoints defined in the post-hoc analysis. In justified cases (e.g. analysis of specific subpopulations) it is allowed to use data from post-hoc analyses; however, the results of such analyses must be interpreted with caution. Post-hoc analyses must be distinguished from the analysis involving the subgroups of patients with different baseline prognoses, assuming the effect of the drug observed in the entire study population.

The use of composite endpoints is recommended only if they have been pre-defined in the study protocol. It is not recommended to analyse complex endpoints defined in the post-hoc analysis; if the analyses in subgroups of patients were pre-defined at the study planning stage, their results are more relevant than in the case of typical post-hoc analyses. When reporting composite endpoints, it is necessary to provide not only the results for the composite endpoint, but also separately for each component, even if they did not reach statistical significance.<sup>20</sup>

When the results of clinical assessment are obtained using scales or questionnaires, information on their validation and the clinical significance of the outcomes should be presented. In the case of conversion of continuous or ordinal variables into dichotomous variables (e.g. healthy – sick), the cut-off point must be justified<sup>21</sup>.

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<sup>17</sup> EUnetHTA Guidelines. Endpoints Used for Relative Effectiveness Assessment of Pharmaceuticals: Clinical Endpoints. Amended Nov 2015.

<sup>18</sup> Ibidem.

<sup>19</sup> Ibidem.

<sup>20</sup> Ibidem.

<sup>21</sup> Ibidem.

## **2.6. Type and quality of evidence**

The clinical effectiveness analysis should include first of all the scientific evidence of the highest quality, whose methodology allows to obtain the most reliable data on the efficacy of the assessed intervention (see Table 1).

In justified cases, the safety analysis should also include evidence of the lower levels of classification (Table 1), especially clinical trials with a long follow-up, and those involving large samples (see also section 3.3.2 Scope of safety analysis). In the absence of data on the safety profile of the intervention in the assessed indication, it is recommended to refer to the results regarding the safety profile of the drug used in other populations. It is of key importance to provide reliable data on the safety of intervention specifically when referring to intermediate or surrogate endpoints in the clinical effectiveness assessment.

If a study included in the clinical effectiveness assessment does not meet the requirements of these Guidelines at least in terms of the selection of the primary endpoints (see section 2.5 Health outcomes), it must be stated that the analysis can only provide limited conclusions on the actual clinical value of the assessed technology.

## 3. Clinical analysis

The clinical analysis refers to health outcomes of the assessed medical technology. It informs about the effectiveness and safety in a specific population compared to the appropriate comparators<sup>22</sup> (relative effectiveness assessment,<sup>23</sup> REA).

### 3.1. Data

The data collected in the course of clinical analysis should refer to efficacy and effectiveness. The data should be searched and selected in a systematic review based on a detailed protocol developed before starting these activities and including the specific criteria for study inclusion in the analysis and their exclusion criteria.

#### 3.1.1. Data sources

Within the clinical analysis, a systematic search for any evidence regarding the assessed question should be performed.

First of all, the existing independent health technology assessment reports (HTA reports) and systematic reviews should be searched for and presented, including those available in:

- The Cochrane Library;
- the MEDLINE database;
- the EMBASE database.

In the next phase of the clinical analysis, conclusions from the identified secondary studies should be presented and the limitations of the identified papers should be discussed, in particular in the context of the purpose and scope of the performed clinical analysis. The identified studies can also be used as a source of information on the analytical practice in a given decision problem. In justified cases, it is allowed to conduct the clinical analysis based solely on the results of the identified systematic reviews (the need to perform the clinical analysis in a short time, the identified review(s) is/are systematic, up to date, they answer the research question, and their methodology meets the quality requirements). In order to verify whether a review is up to date, medical databases should be searched in order to identify the studies published at a later date than that searched for in the published review. The quality of the identified systematic reviews should be assessed using the current version of the AMSTAR scale<sup>24</sup>.

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<sup>22</sup> The development of this section of the Guidelines was based, among others, on the HTA Core Model<sup>®</sup> EUnetHTA Domain 3. Safety and Domain 4. Clinical Effectiveness (EUnetHTA Joint Action 2, HTA Core Model, version 3.0 (PDF), 2016), and HTA Core Model<sup>®</sup> for Rapid Relative Effectiveness Assessment of Pharmaceuticals version 3.0. March 2013.

<sup>23</sup> Relative effectiveness assessment – assessment of health benefits (benefits) and adverse events (harms) of the reviewed health technology compared with the existing drug or non-drug technologies. See also footnote 5.

<sup>24</sup> Biondi-Zoccai G. Evidence synthesis with overviews of reviews and meta-epidemiologic studies. Springer 2016.

The purpose of performing a systematic review of primary studies is to find all scientific reports that meet the analysis inclusion criteria. Firstly, studies in which the assessed technology was directly compared with the selected comparator (head to head trials) should be searched for.

The main databases for searching primary studies are:

- MEDLINE;
- EMBASE;
- Cochrane Library.

In justified cases, it is recommended to search also the other medical information databases, in accordance with the EUnetHTA guidelines<sup>25</sup>.

It is necessary to supplement the search of medical information databases by using other sources, including:

- literature references contained in the publications on clinical efficacy/effectiveness;
- clinical trial registers (at least 2 registers; it is required to search the registries [clinicaltrials.gov](http://clinicaltrials.gov) and [clinicaltrialsregister.eu](http://clinicaltrialsregister.eu)) to find the studies that are completed but unpublished.

Consider also the need for additional identification of the evidence using the following methods:

- consultations with clinical experts;
- non-systematic search for data published in specialist journals in the field of the assessed technology but not indexed in the medical information databases used;
- contacting authors of clinical trials, for example to obtain specific unpublished data and include them in the analysis;
- using the internet search engines;
- consultations with manufacturers, especially as regards information on adverse events/effects (based on periodic safety update reports, PSUR);
- using data from the registration dossier of the drug available on the websites of the regulatory agencies, i.e. the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL), EMA, FDA (including analysis of reports on the safety of given technology).

In any case, data on the efficacy and effectiveness of the reviewed health technology should be sought. Data on the efficacy are mainly obtained by systematic review of randomised clinical trials.

In the case of rare diseases and/or ethical concerns relating to the conduct of clinical trials, it is justified to assess the efficacy based on single-arm studies, especially when this kind of study is recommended by the regulatory agencies.

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<sup>25</sup> HTA Core Model® EUnetHTA Domain 4. Clinical effectiveness (EUnetHTA Joint Action 2, Work Package 8. HTA Core Model, version 3.0 (PDF), 2016) – Methodology/Where to find information? p. 141.



Data relating to effectiveness should come from credible and reliable research conducted in the settings of actual clinical practice (real world data, RWD; real world evidence, RWE). These may be prospective and retrospective studies (pragmatic randomised clinical trials<sup>26,27,28</sup>, observational studies and databases, including patient registries, databases of the payer and other institutions).

In justified situations it is allowed to take into account unpublished clinical data relating to efficacy or effectiveness in the clinical analysis. In each case, the effectiveness assessment should be based on evidence of the highest level of credibility. A comment should be provided on the degree of consistence between efficacy and effectiveness.

### 3.1.2. Search strategy

The search strategy should be developed based on the defined decision problem, and it should be consistent with the Cochrane Handbook recommendations and the Centre for Reviews and Dissemination (CRD) indicated by the EUnetHTA<sup>29</sup>, concerning the proper conduct of a systematic review. It is recommended to use a possibly highly sensitive search strategy. Only in the case of a large number of hits the search specificity can be increased at expense of sensitivity. If strategies that materially differ in sensitivity were used for the different databases, a justification for this procedure should be provided. The search criteria should include the elements of the PICOS scheme presented in section 2 Decision problem analysis. Is not recommended to use keywords relating to the endpoints in the search strategy.

The final effect of a search should be the collection of all available studies and data necessary for a reliable assessment of the efficacy/effectiveness and safety profile of the health technology being assessed.

The data and information search process must be described in detail so that it is possible to evaluate whether it was correct and to make it possible to reproduce it in the case of verification of the analysis<sup>30</sup>. The presentation of the search results should contain the following information:

- key words and descriptors used for the search;
- used Boolean operators;
- used filters;
- time span of the search/date of the last search;
- number of identified records separately for each query used in the search strategy.

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<sup>26</sup> Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chronic Dis* 1967; 20: 637–648.

<sup>27</sup> Chalkidou K, Tunis S, Whicher D, et al. The role for pragmatic randomized controlled trials (pRCTs) in comparative effectiveness research. *Clinical Trials* 2012; 9(4): 436–446.

<sup>28</sup> Treweek S, Zwarenstein M. Making trials matter: pragmatic and explanatory trials and the problem of applicability. *Trials* 2009; 10: 37–46.

<sup>29</sup> EUnetHTA Guidelines: Process of Information Retrieval for Systematic Reviews and Health Technology Assessments on Clinical Effectiveness. July 2015.

<sup>30</sup> Ibidem.

### 3.1.3. Information selection

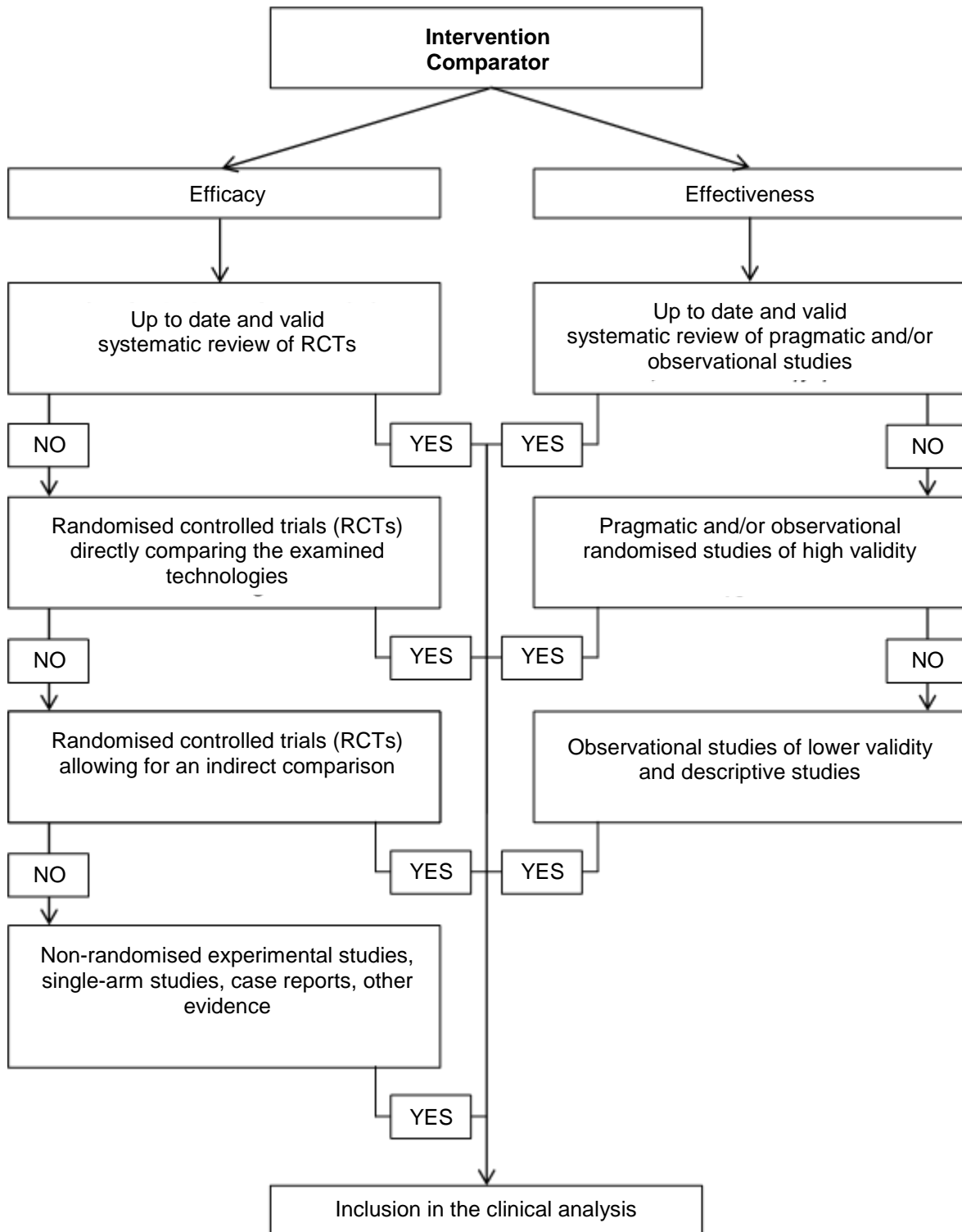
The process of verification whether the identified scientific reports meet the analysis inclusion criteria should be performed in stages. The first stage involves a selection based on titles and abstracts, and subsequently based on full texts of publications. The study selection should be performed based on the inclusion and exclusion criteria selected before starting the search, in accordance with the defined PICOS scheme (systematic review protocol).

In a situation where the target population defined at the stage of scoping does not correspond to the sample assessed in the identified evidence, it is allowed to carry out the clinical analysis in a population similar to the target one. In this situation, the potential effect of differences between the populations on the results obtained in the clinical analysis should be discussed.

The selection process should distinguish evidence forming the basis for the assessment of efficacy and effectiveness.

The selection of primary studies should relate to publications in English, Polish, and others where appropriate.

The algorithm for the selection and inclusion of studies in the analysis of efficacy and effectiveness is presented in Fig. 1.



**Fig. 1. Algorithm for the selection and inclusion of studies in the clinical analysis.**

At all stages, the process of trial selection for the systematic review should be performed by at least two analysts working independently. The degree of consistency<sup>31</sup> between the analysts performing the selection at the stage of full-text analysis should be specified. The preferred method for inconsistency settling is to

<sup>31</sup> For example as the kappa coefficient.

reach a consensus. Initials of the analysts performing each task should be placed in the appropriate places of the report.

The analysis should clearly inform about the number of available scientific reports at each stage of study search and selection. The process leading to a final selection should be presented in the form of a diagram in line with the PRISMA guidelines<sup>32,33</sup>. The reasons for the exclusion of studies at each selection stage, and the detailed reasons for exclusion should be stated for publications assessed on the basis of full texts.

All scales and questionnaires should be presented in the attachments to the systematic review.

### 3.1.4. Information quality assessment

The quality evaluation of the data allows to determine their internal<sup>34</sup> and external<sup>35</sup> validity.

The assessment of the quality of data from the studies included in the analysis requires that several factors are taken into account:

- methodology of each trial;
- risk of bias;
- consistency between the results of the individual studies included in the review;
- degree to which the results of studies may be transposed (generalised) onto the analysed population.

Similarity of clinical study sample and the potential population should be assessed, as well as similarity of interventions (for example class effect in the case of drugs) and correlation of results observed in studies with the expected results (e.g. the surrogate issue)<sup>36</sup>.

The assessment of validity of randomised studies should be carried out in accordance with the bias risk assessment procedure described in the Cochrane Handbook.

Prospective randomised controlled studies should be assessed using the Cochrane Collaboration tool for randomised trials; in other cases (non-randomised studies or

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<sup>32</sup> Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; 151: W-65–W-94.

<sup>33</sup> Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264–269.

<sup>34</sup> Internal validity refers to the extent to which the conclusions from a study correspond to the actual relationship between the studied procedure and the observed study endpoint.

<sup>35</sup> External validity, also referred to as applicability or generalisability, means the possibility of generalising conclusions from a study to the target population for a given health technology, i.e. to what extent the conclusions drawn based on the evaluated sample can be referred to the population in the conditions of routine clinical practice.

<sup>36</sup> EUnetHTA Guidelines: Levels of Evidence: Applicability of Evidence in the Context of a Relative Effectiveness Assessment of Pharmaceuticals. Amended Nov 2015.

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retrospective studies) assessment should use the NOS questionnaire<sup>37</sup>, and for single-arm studies – the NICE scale<sup>38</sup>. To evaluate systematic reviews it is recommended to use the current AMSTAR scale (the evaluation criteria adopted in the literature: <5 low-quality review, ≥5 moderate-quality review, ≥9 high-quality review)<sup>39</sup>. A separate assessment using modified scales may also be considered; however, their selection should be justified<sup>40</sup>.

### 3.1.5. Presentation of included trials and data extraction

To present the studies, all data related to a given clinical problem should be presented in tables. This summary should specify the number and type of the included studies and the characteristics of each study: follow-up period, number of study sites, list of sponsors, study sample size, patient characteristics, details of the intervention and the reported outcomes, as well as other information relevant for external validity assessment.

For each study included in the analysis, a short description should be provided in the annex.

The assumed approach to hypothesis testing (superiority, non-inferiority, equivalence) should be defined for a randomised clinical trial.

The aggregation should be done based on scientific evidence classification provided in Table 1, and should specify the type of each included trial. Definitions of the types of studies indicated in the table below can be found in the dictionary HTAGlossary.net (in English)<sup>41</sup>.

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<sup>37</sup> EUnetHTA Guidelines: Internal Validity of Non-Randomised Studies (NRS) on Interventions, July 2015.

<sup>38</sup> Quality Assessment for Case Series. NICE guidelines (CG3); June 2003 <http://www.nice.org.uk/guidance/cg3/resources/appendix-4-quality-of-case-series-form2> (as at 15/08/2016).

<sup>39</sup> Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol* 2009; 62: 1013–1020.

<sup>40</sup> Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; 7: 1–173.

<sup>41</sup> HTAGlossary.net <http://htaglossary.net/HomePage> (as at 15/08/2016).

Table 1. Classification of scientific reports<sup>42</sup>

| Study type                     | Study category | Subtype description   |
|--------------------------------|----------------|---|
| Systematic review of RCTs      | IA             | Meta-analysis based on the results of a systematic review of RCTs   |
|                                | IB             | Systematic review of RCTs without a meta-analysis   |
| Experimental study             | IIA            | Properly designed randomised controlled trial (RCT), including a pragmatic randomised controlled trial (pRCT) |
|                                | IIB            | Properly designed pseudo-randomised controlled clinical trial (CCT)   |
|                                | IIC            | Properly designed non-randomized controlled clinical trial  |
|                                | IID            | Single-arm study  |
| Controlled observational study | IIIA           | Systematic review of observational studies  |
|                                | IIIB           | Properly designed prospective cohort study with a parallel control group                                      |
|                                | IIIC           | Properly designed prospective cohort study with a historical control group                                    |
|                                | IIID           | Properly designed retrospective cohort study with a parallel control group                                    |
|                                | IIIE           | Properly designed case-control study (retrospective)  |
| Descriptive study              | IVA            | Case series – pretest/posttest study <sup>43</sup> .  |
|                                | IVB            | Case series – posttest study <sup>44</sup> .  |
|                                | IVC            | Other study in a group of patients  |
|                                | IVD            | Case report   |
| Expert opinion                 | V              | Experts' opinion based on clinical experience and reports of panels of experts.                               |

In the final assessment, mainly the trials from the highest available level of evidence are used. Systematic reviews of RCTs (with meta-analysis of individual patient data<sup>45</sup>, meta-analysis of the results of included primary studies, or without a meta-analysis) which reflect the clinical problem in terms of the target population, the comparator, the examined outcome are at the top of the hierarchy of credibility,

<sup>42</sup> The author's modification based on: Undertaking systemic reviews of research on effectiveness: CRD guidelines for those carrying out or commissioning reviews. CRD report #4, University of York, York 1996.

<sup>43</sup> A pretest/posttest study – a descriptive study with data collection before and after the intervention being assessed.

<sup>44</sup> A posttest study – a descriptive study with data collection only after the intervention being assessed.

<sup>45</sup> E.g. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010; 340: c221–c228.

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provided they are up-to-date and conducted in line with the guidelines for such studies. The value of evidence at each stage of hierarchy depends mostly on the methodological quality of the included studies and the fulfilment of health technology assessment requirements<sup>46</sup>.

The procedure of data extracting from the selected trials should define:

- types of information retrieved from publications,
- number of persons extracting data and their initials,
- form for data extraction.

### **3.2. Data synthesis for effectiveness**

The synthesis of the results aims to aggregate the identified data and to determine the related level of estimation uncertainty. The results regarding the effectiveness and safety of the assessed technology versus the comparator must be expressed using a parameter adequate to the nature of the evaluated outcome.

It is recommended to present or estimate the results for outcomes defined within decision problem analysis (section 2.5 Health outcomes).

It is recommended to compile the results using meta-analysis, provided there is no significant clinical, methodological, or statistical heterogeneity of the studies; a detailed discussion of the conditions to carry out a meta-analysis is provided in section 3.2.2 Meta-analysis (quantitative synthesis). If quantitative analysis of the results is not possible, then qualitative analysis should be performed, limited to a qualitative review with a tabular presentation of the results of studies included in the review and their critical evaluation.

#### **3.2.1. Qualitative synthesis**

The effectiveness and safety data for the assessed technology and the comparator should be compiled in a uniform tabular format. The compilation should take into consideration the previous assessment of the source credibility and data quality<sup>47</sup>. The results of all scientific reports that meet the inclusion criteria for the systematic review should be included.

The results for the endpoints of each study should be presented. In case of heterogeneity of the obtained results, it is necessary to identify and discuss the differences.

The listing should be presented in a form allowing comparison of the results of particular trials with respect to specific endpoints. This form of presentation allows to identify potential similarities or differences between the results of the included trials and between the compared health technologies.

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<sup>46</sup> HTA Core Model® EUnetHTA Domain 4. Clinical effectiveness (EUnetHTA Joint Action 2, Work Package 8. HTA Core Model, version 3.0 (PDF), 2016), p. 150.

<sup>47</sup> Ibidem, quality syntheses and evidence tables.

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Numerical data should be presented in a table containing:

- the sample size for each intervention;
- the result for each endpoint, in the form of central measures and the measures of dispersion for continuous variables, and the numbers and percentages of patients with an endpoint for dichotomous variables;
- the parameters allowing for a comparative evaluation of the clinical effectiveness of the health technology being assessed in relation to the comparator (differences between mean results for the compared interventions for continuous data, or relative and absolute parameters for dichotomous data<sup>48</sup>) with confidence intervals and evaluation of the statistical significance of the observed differences.

### 3.2.2. Meta-analysis (quantitative synthesis)

The level and sources of heterogeneity of trial results should be defined before applying statistical methods of synthesis. It should be evaluated and further actions should be taken in accordance with the Cochrane Collaboration guidelines<sup>49</sup>.

In case of doubts concerning the quality of trials or relevance of particular trials to the analysed matter, as part of sensitivity analysis, the results of meta-analyses, conducted with the exclusion of the doubtful trials, should be presented separately. The results of trials of the highest credibility should then be presented separately. A detailed description of the study inclusion or exclusion criteria for the meta-analysis should be provided.

### 3.2.3. Simple and network indirect comparison

In the absence of head-to-head trials directly comparing the assessed technology and a comparator, it is recommended to conduct an indirect comparison. Methodological and clinical heterogeneity of studies included in the analysis should be evaluated, and consideration needs to be given to whether an indirect comparison is valid. If an indirect comparison cannot be performed, a qualitative analysis of the results should be done.

Identification of trials to be used in the indirect comparison should be based on a systematic review. A thorough analysis of methodology used in the studies is advised, as well as an analysis of differences in the population, the intervention used in the reference arm, and the examined endpoints. The identified differences should be presented in tabular form.

Indirect comparison should be carried out with the use of methods adjusted for the result obtained in the control arm, e.g. the Bucher's method<sup>50</sup>, Bayesian mixed

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<sup>48</sup> Fu R, Gartlehner G, Grant M, et al. Conducting Quantitative Synthesis when Comparing Medical Interventions: AHRQ and the Effective Health Care Program. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews. Rockville, MD, 2010.

<sup>49</sup> Higgins JPT, Green S (editors). Cochrane Handbook for systematic reviews of interventions. 9.5 Heterogeneity. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.

<sup>50</sup> When the purpose of the analysis is to compare two drugs via a common control intervention.



treatment comparison<sup>51</sup>, Lumley network meta-analysis, or metaregression. When using the Bayesian approach, special attention should be paid to verify the validity of the results<sup>52,53</sup>.

When it is not possible to perform an indirect comparison via a common reference arm (non-controlled studies), other methods can be considered, including:

- naïve comparison;
- benchmarking with historical controls;
- matching-adjusted indirect comparison.

Before starting calculations, the criteria for selecting a specific analytical method must be justified. The final selection of the analytical method should be based on the type of available data<sup>54</sup>. The results of any indirect comparison should be interpreted with utmost care. In all cases of indirect comparisons a comprehensive interpretation of results should be done together with a description of limitations and a sensitivity analysis, presenting the effects of including and excluding studies that most deviate in terms of methodology from the other studies used for the indirect comparison<sup>55</sup>.

### 3.3. Safety assessment

#### 3.3.1. Purpose

The safety analysis is performed to assess the risk of using a given health technology<sup>56,57</sup>. Adverse events and adverse drug reactions should be considered – while maintaining the distinction between them. An adverse event means any medical event in a patient or clinical investigation subject administered a medicinal product or investigational medicinal product, which causes negative outcomes, regardless of whether there is a causal relationship between the used medicinal product and this event.

In turn, an adverse drug reaction means any medical event in a patient administered a medicinal product or investigational medicinal product, which causes negative outcomes; in the case of adverse drug reactions, there are grounds for believing that there is a causal relationship between the used product and the outcome.

Adverse events and adverse drug reactions are classified as non-serious or serious, depending on the outcomes they cause in the patient.

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<sup>51</sup> When the purpose of the analysis is to compare more than two interventions.

<sup>52</sup> Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: An ISPOR-AMCP-NPC good practice task force report. *Value in Health* 2014; 17: 157–173.

<sup>53</sup> EUnetHTA Guidelines: Comparators & Comparisons. Direct and Indirect Comparisons. Amended Nov 2015.

<sup>54</sup> Ibidem.

<sup>55</sup> NICE: Process and Methods Guides. Guide to the Methods of Technology Appraisal 2013. NICE article [PMG9]. 04 April 2013.

<sup>56</sup> HTA Core Model® EUnetHTA Domain 3. Safety (EUnetHTA Joint Action 2, Work Package 8. HTA Core Model, version 3.0 (PDF), 2016).

<sup>57</sup> Higgins JPT, Green S (editors). *Cochrane Handbook for systematic reviews of interventions*, version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.

Definitions of the above terms – adverse event and adverse drug reaction, and serious adverse event and serious adverse drug reaction, as well as the other concepts used in the safety assessment of medicinal substances, are contained in the current Pharmaceutical Law Act of 6 September 2001 (Journal of Laws of 2001, No. 126, item 1381 as amended). With regard to other issues related to safety monitoring of medicinal substances, e.g. their severity, see international guidelines.<sup>58</sup>

The objectives of safety assessment should include<sup>59</sup>:

- to identify adverse events and adverse drug reactions for a medicinal product;
- to assess these events, also in terms of frequency and clinical significance;
- to compare the safety profile of the assessed health technology with the safety profile of the comparator.

### **3.3.2. Scope of safety analysis**

The scope of safety analysis should be adapted to the decision problem defined and the specificity of the health technology assessed. In some cases, the scope can be similar to that used in effectiveness assessment; however, it often needs to be extended. Safety assessment should be extended in particular in the case of innovative technologies, technologies that often have adverse effects, and technologies causing serious or severe adverse reactions<sup>60</sup>.

If data from the studies included in the effectiveness analysis are not sufficient to assess the safety profile, consider the extension of the inclusion criteria for the systematic review, both in terms of patient population in whom the drug can be used, the intervention (a different dosing regimen, route of administration, etc.), and the methodology of the included studies.

If the search strategy of scientific reports relating to the safety assessment and their inclusion and exclusion criteria differ from those used in the clinical effectiveness assessment, a separate search protocol should be presented.

The safety assessment should also take into account data on adverse events published by the regulatory agencies supervising and monitoring the safety of medicinal products (e.g. EMA, FDA, URPL, WHO Uppsala Monitoring Centre). In addition, it is recommended to present data from reports on adverse events and adverse drug reactions prepared by pharmaceutical companies in the form of PSURs.

If many various adverse events/adverse drug reactions are identified, it is allowed to narrow the safety assessment to the analysis of the most important adverse events/adverse drug reactions (most common, serious and severe adverse events),

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<sup>58</sup> E.g. Common Terminology Criteria for Adverse Events (CTCAE) published by the NCI, or Good Pharmacovigilance Practices published by the EMA.

<sup>59</sup> EUnetHTA Guidelines: Endpoints Used in Relative Effectiveness Assessment of Pharmaceuticals – Safety. Amended Nov 2015.

<sup>60</sup> Higgins JPT, Green S (editors). Cochrane Handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.

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and discuss the remaining events in a more general manner<sup>61,62</sup>. The adopted scope of analysis should be justified.

### 3.4. Presentation of results

The results of clinical trials should be presented by means of parameters showing the differences in the effectiveness and safety profile of the assessed health technology in relation to comparators (results for the dichotomous points should be presented in the form of relative and absolute parameters).<sup>63</sup> If a comparative assessment of clinical effectiveness of the reviewed health technology is not possible (e.g. single-arm studies, safety data analysis), the results of studies included in the analysis should be presented in tables.

The results of meta-analyses should be presented using the appropriate numerical values and a forest plot. The access to partial data, i.e. the results obtained in each study included in the meta-analysis, should be ensured. If possible, an integral part of presentation of each numeric result should be the information on its statistical significance (*p*-value, confidence interval). For each meta-analysis, the results of the heterogeneity test should be presented, in accordance with the Cochrane Handbook methods<sup>64</sup>. The description of the meta-analysis should follow the PRISMA guidelines<sup>65,66</sup>. The results for efficacy and effectiveness should be presented separately.

The principles of using clinically significant outcomes, surrogate endpoints and composite endpoints are discussed in section 2.5 Health outcomes.

The results for individual endpoints, which are of key importance for the conclusions on the effectiveness and safety, should be presented as a tabular summary of numerical data showing the effect size for the assessed intervention as well as data validity (summary of findings table).

When reporting results for the endpoints, provide a detailed description of the methods used in the case of missing data<sup>67</sup>.

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<sup>61</sup> ibidem

<sup>62</sup> EUnetHTA Guidelines: Endpoints Used in Relative Effectiveness Assessment of Pharmaceuticals – Safety. Amended Nov 2015.

<sup>63</sup> Fu R, Gartlehner G, Grant M, et al. Conducting Quantitative Synthesis when Comparing Medical Interventions: AHRQ and the Effective Health Care Program. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews. Rockville, MD, 2010.

<sup>64</sup> Higgins JPT, Green S (editors). Cochrane Handbook for systematic reviews of interventions. 9.5 Heterogeneity. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.

<sup>65</sup> Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; 151: W-65–W-94.

<sup>66</sup> Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264–269.

<sup>67</sup> EUnetHTA Guidelines. Endpoints Used for Relative Effectiveness Assessment of Pharmaceuticals: Clinical Endpoints. Amended Nov 2015.

### **3.5. Limitations**

In the part concerning limitations, the limitations of the analysis and the limitations of the available data should be presented separately. Indicate which of these limitations are relevant to the overall assessment of the technology, and how they can influence this assessment.

The part concerning limitations of the analysis should specify the limitations of the analytical methods used, and the risk of presenting incomplete conclusions.

The part concerning limitations of the available data should specify the limitations resulting from incomplete or ambiguous data in the context of a particular health problem, including limitations of the methodology/types of clinical trials included (superiority, non-inferiority, or equivalence), the risk of bias, discrepancies in the results of the included studies, the lack of evaluation of clinically significant endpoints in the included studies, significant loss to follow-up, the lack of information about the validation of scales used to evaluate the endpoints.

### **3.6. Discussion**

The discussion is a critical description of the obtained results and conclusions in the context of a decision problem specified before the analysis and presented in the decision problem analysis. The discussion involves a polemic with the arguments of the possible critique of the obtained results and conclusions drawn. It is advisable to discuss the available data, applied methods and obtained results, as well as discuss the results in the context of the sensitivity analyses performed. Results of other analyses of the same decision problem should be presented and used as a background for discussing the obtained results, justifying the possible differences.

The weight of evidence should also be discussed, especially for the clinically significant outcomes. If the systematic review includes only experimental trials, the discussion should be completed with a critical assessment of safety in the light of other available evidence.

### **3.7. Final conclusions**

The basic conclusions drawn from the clinical effectiveness analysis should be synthesised. The main element should be the presentation of conclusions based on analysis summary. A comparison of efficacy and effectiveness may constitute a part of final conclusions.

The results with the possible interpretations and the conclusions should be clearly separated. The conclusions should only refer to the purpose of analysis and they should be directly related to the obtained results. The conclusions in the clinical analysis should refer, among other things, to clinical significance, differences in the intervention strength, and should not be limited to statistical significance of the obtained results.

## 4. Economic analysis

Economic analysis<sup>68</sup> consists in comparing the assessed health technology with adequate comparators identified within the decision problem analysis in terms of costs and health outcomes.

In the economic analysis, it is required to conduct a systematic review of literature to identify the previous analyses of the assessed technology used in the indication being the subject of analysis. As part of the systematic review, it is recommended to search at least the MEDLINE database via PubMed, and the Cochrane Library.<sup>69</sup> If a publication is not found in the above medical information databases, they can be sought on the websites of ISPOR (International Society for Pharmacoeconomics and Outcomes Research), SMDM (Society for Medical Decision Making), PTFE (Polish Pharmacoeconomics Society), etc. The results, assumptions, and methodology used in the identified analyses should be referred to the results obtained in the performed economic analysis.

In the case of the first health technology with proven efficacy in a given ultrarare<sup>70</sup> or rare<sup>71</sup> indication, it is recommended to supplement the economic analysis with price justification.<sup>72</sup>

Price justification should include elements specific for a given decision problem, including:

- an uncertainty assessment of clinical effectiveness estimations, and of the strength of the intervention in relation to the optional treatments, and an uncertainty assessment of drug safety estimations,
- an assessment of the target population size,
- an uncertainty assessment of estimations of the most important input data and the presented results of the costs analysis and financial analysis,
- an assessment of the degree of innovation (therapeutic, pharmacological, and technological),
- a drug price proposal and information on prices or price agreements in other countries,
- an assessment of unit therapy costs,
- presentation of business activities and research and development (R&D) activities of the manufacturer in Poland, the EU and EFTA countries,

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<sup>68</sup> [terminology explanations for Polish reader].

<sup>69</sup> The CoreModel<sup>®</sup> EUnetHTA recommends to search the economic analyses in the following databases: Summarized Research in Information Retrieval for HTA (SuRe Info) <http://www.htai.org/vortal/?q=sure-info> and Centre for Reviews and Dissemination (CRD) <https://www.york.ac.uk/crd/> EUnetHTA Joint Action 2, Work Package 8. HTA Core Model, version 3.0 (PDF), 2016.

<sup>70</sup> Ultrarare indication (ultrarare disease) – when the prevalence is less than 1 per 50,000 people, or no more than 700 people in Poland.

<sup>71</sup> Rare indication (rare disease) – when the prevalence is less than 5 per 10,000 people.

<sup>72</sup> It is recommended to present price justification when the criterion of an ultrarare or rare disease is met by the combined population eligible for using a given medical technology, taking into account all approved indications.

- presentation of the R&D costs and production costs (where possible),
- planned marketing costs in the case of reimbursement,
- Risk Sharing Scheme proposals.

#### 4.1. Analytical strategy

Health outcomes included in the economic analysis for the intervention and the comparators should be determined on the basis of the clinical analysis. Also in terms of the selection of comparators, the economic analysis should be consistent with the decision problem analysis and the clinical analysis. The economic model should be editable in terms of input data.

Two strategies of performing the economic analysis are possible:

- conducting an economic analysis de novo based on the conclusions from the previously prepared scoping and the results of the clinical analysis;
- adaptation of an existing analysis – if a previously conducted economic analysis examining the health problem in question is available, it is possible to use such an analysis in a form adapted to the current local conditions of the prepared HTA report.

When adapting the analysis to the current conditions, take into account the local Polish data on resource use and costs. The structure and parameters of the model on the progress of diagnostic and therapeutic procedures should also be adapted to the Polish conditions (e.g. the likelihood of carrying out organ transplantation, depending not only on the patient's condition but also on the possibilities and conditions of the health care system).

#### 4.2. Perspective

The analysis should be performed from the perspective of the authority obliged to finance medical services from public funds<sup>73</sup> (public payer's perspective), and from the joint perspective of the authority obliged to finance medical services from public funds and of the beneficiaries, taking into account co-payment for health technologies (joint perspective of the public payer and the beneficiaries). If there is no co-payment by the beneficiaries, or it is negligible in comparison with the costs incurred by the public payer, it is possible to use only the public payer's perspective.

The above perspectives do not exclude the conduct, in justified cases, of additional analyses from other perspectives, such as the social one (taking into account the indirect costs), the provider's one, or the public finance perspective (taking into account the transfer of benefits such as pensions or allowances ).

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<sup>73</sup> Hereinafter referred to as public payer.

### 4.3. Time horizon

Time horizon of the economic analysis should be sufficiently long to allow the assessment of differences between the results and costs of the assessed health technology and the comparators. It should be the same for cost measurement and for health outcomes. The selected length of the time horizon must be justified.

In case of health technologies for which the outcomes and differing costs occur during the whole life of a patient, the lifetime horizon should be used. The effect of assumptions regarding the length of the time horizon should be tested as part of a sensitivity analysis (the developed model should allow to modify the length of the time horizon).

If the economic analysis aims to minimise the costs and the costs of using the compared health technologies are constant over time, a unit length of the time horizon can be adopted, e.g. 1 year.

### 4.4. Analytical technique

Economic analysis of health technologies is usually a comparative assessment of the use of resources necessary for obtaining a clinical effect. Various techniques (types of analysis) may be used in such assessment:

- cost-utility analysis<sup>74</sup>;
- cost-effectiveness analysis<sup>75</sup>;
- cost-minimisation analysis<sup>76</sup>;
- cost-consequences analysis<sup>77</sup>.

Analytical method is always selected according to the identified and measured health outcomes, and the choice should always be justified.

Cost-benefit analysis is not recommended<sup>78</sup>.

A regular economic analysis should involve cost-utility analysis or cost-effectiveness analysis. It is recommended to perform the cost-utility analysis and cost-effectiveness analysis at the same time. In the cost-effectiveness analysis, health outcomes should be presented in the form of, inter alia, life-years gained (LYG). In the absence of appropriate data to perform cost-utility analysis, cost-effectiveness analysis should be performed, in which health outcomes should be presented, among others, as LYG.

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<sup>74</sup> [terminology explanations for Polish reader] Please remember that health-related and not economic utility of the intervention is analysed.

<sup>75</sup> [terminology explanations for Polish reader] Please remember that clinical and not economic effectiveness of the intervention is analysed.

<sup>76</sup> [terminology explanations for Polish reader]

<sup>77</sup> [terminology explanations for Polish reader]

<sup>78</sup> [terminology explanations for Polish reader]

If the clinical analysis shows clinical equivalence of the compared health technologies, or if the differences between them are not clinically significant, cost-minimisation analysis must be performed.

If cost-utility, cost-effectiveness and cost-minimisation analyses are not possible, it is allowed to perform only the cost-consequences analysis.

Economic analysis can be limited to cost-consequences analysis in the following cases:

- the lack of reliable data to compare the effectiveness and safety of the assessed intervention to the comparators, or ambiguous results of the clinical analysis (e.g., heterogeneous populations in clinical trials, method of endpoint reporting in clinical trials that prevents the comparison, or other reasons, which should be described and justified in the analysis). In this situation, the health outcomes measured in common units should be presented; the preferred units are QALYs (quality adjusted life years), LY (life years), or other natural units. In this case it is not appropriate to determine incremental values or incremental ratios.
- when the reviewed intervention is associated with better (worse) health outcomes and lower (higher) costs (it is necessary to show/justify such a case);
- in the presence of other circumstances that should be described and appropriately justified.

The choice of one technique (type of analysis) does not preclude the use of another method as complementary.

#### **4.4.1. Cost-utility analysis**

The preferred measure of health outcomes in cost-utility analysis is QALY. QALY is calculated as the product of life years and the utilities of a health state, which describes the value of the quality of life in a particular health state.

The choice of the health state utility values in the economic model has a key influence on the results of cost-utility analysis. Various methods of measuring utility can deliver different results for the same health states. What determines the result of the economic analysis is not the absolute utility value but the differences between the utilities of health states used in the model. For this reason, it is advisable to use a consistent method for utility measuring to evaluate all health states included in the analysis.

The preferred instrument for measuring the quality of life in adults is EQ-5D questionnaire (EQ-5D-3L or EQ-5D-5L version); since it is commonly used, it allows for the greatest comparability of the results of economic analyses. A change in the quality of life should be reported directly by the patients (completing the EQ-5D questionnaire), whereas the utility attributed to this change should come from a set of utility values (value set, tariff) obtained by measuring the preferences of the different health states in the general population using one of the choice-based methods. The utility norms based on measurement using a visual analogue scale (VAS) do not meet this requirement.



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A detailed description of the method of searching the utility values for the cost-utility analysis is presented in Annex 2.

The result of the cost-utility analysis is the incremental cost-utility ratio (ICUR), which is the ratio of the cost difference and health outcomes difference (in QALY) for the compared health technologies. In specific cases, an additional result of the cost-utility analysis is the cost-utility ratio (CUR), which is the ratio of the costs and QALY for a given intervention.

#### 4.4.2. Cost-effectiveness analysis

The objective of cost-effectiveness analysis is to determine the difference in costs of the compared technologies corresponding to the difference in health outcome. Cost-effectiveness analysis consists in comparing costs and health outcomes for alternative health technologies; the results has to be expressed in the same natural units for the compared options (such as the number of adverse occurrences avoided, disease symptom-free period, life years). The preferred natural unit in cost-effectiveness analysis are life years (LY).

In the cost-effectiveness analysis, the incremental cost-effectiveness ratio (ICER) is calculated; it is the ratio of the cost difference and health outcomes difference for the compared health technologies. In specific cases, an additional result of the cost-effectiveness analysis is the cost-effectiveness ratio (CER), which is the ratio of the costs and health outcomes for a given intervention. A special case of cost-effectiveness analysis is the cost-utility analysis, in which the health outcomes are presented as quality-adjusted life years (QALY).

#### 4.4.3. Cost-minimisation analysis

Cost minimization analysis may be applied if existing scientific evidence confirms that health outcomes (the effectiveness of the compared health technologies) are therapeutically equivalent.<sup>79</sup> In this case, the analysis consists in comparing the costs only.

#### 4.4.4. Cost-consequences analysis

The cost-consequences analysis consists in the presentation of mean values with the measures of dispersion in the form of tables for:

- health consequences/outcomes;
- component costs defined in the analysis (broken down by cost categories: the cost of the drug, the cost of drug administration, the cost of care etc.).

The cost-consequences analysis should not be limited to the health consequences presented only as a health outcome expressed in natural units used in clinical trials; it should use QALY, LY, and the other health outcomes significant in a given context (e.g. transplant-free life years, progression-free life years). When assessing health outcomes by QALY or LY, the values of CUR/CER ratios should also be presented.

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<sup>79</sup> A discussion of cases in which the cost-minimisation analysis is/is not appropriate is presented e.g. in Briggs AH, O'Brien BJ. The death of cost-minimization analysis? *Health Economics* 2001; 10(2): 179–184.

## 4.5. Modelling

Modelling is performed when the available data are insufficient to determine cost-effectiveness. If modelling is necessary, the model structure should be presented. The complexity of the model and the modelling method should correspond to the decision problem defined<sup>80,81,82,83</sup>.

It is recommended that the model is kept as simple and transparent as possible<sup>84,85</sup>, while maintaining, however, the detail level necessary to properly determine the cost-effectiveness of the compared health technologies. The model assumptions should be clear, well justified and tested in a sensitivity analysis.

Except for justified situations, the models should be developed using commonly available tools<sup>86</sup>. It should be technically possible to verify the developed model.

Modelling may not be necessary if no statistical significance of differences relating to the clinical effectiveness were shown for the results of the clinical analysis regarding the key input data for the model<sup>87</sup>.

If the model includes the key input data, for which no statistically significant differences were obtained, the sensitivity analysis should include calculations using only parameters with shown statistical significance; the remaining parameters should be excluded from modelling or should be neutral for the result of the model.

Principles of good practice of modelling and guidelines for critical assessment of models are presented in Table 2.<sup>88</sup>

**Table 2. Principles of good practice of modelling and critical assessment of models.**

| Subject of assessment  | Principles of good practice   | Questions for critical assessment   |
|------------------------|---|---|
| <b>Model structure</b> |   |   |
| <b>Health states</b>   | Structure of the model should be as simple as possible and, at the same | Are the decision-related problem, the context and the perspective clearly |

<sup>80</sup> Roberts M, Russell LB, Paltiel AD, et al. Conceptualizing a model: a report of the ISPOR-SMDM modeling good research practices task force-2. *Value Health* 2012; 15: 804–811.

<sup>81</sup> Karnon J, Stahl J, Brennan A, et al. Modeling using discrete event simulation: a report of the ISPOR-SMDM modeling good research practices task force-4. *Value Health* 2012; 15: 821–827.

<sup>82</sup> Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: a report of the ISPOR-SMDM modeling good research practices task force-3. *Value Health* 2012; 15: 812–820.

<sup>83</sup> Marshall DA, Burgos-Liz L, IJzerman MJ, et al. Applying dynamic simulation modeling methods in health care delivery research – The SIMULATE checklist: report of the ISPOR simulation modeling emerging good practices task force. *Value Health* 2015; 18: 5-16.

<sup>84</sup> Caro JJ, Briggs AH, Siebert U, et al. Modeling good research practices-overview: a report of the ISPOR-SMDM modeling good research practices task force-1. *Value Health* 2012; 15: 796–803.

<sup>85</sup> Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM modeling good research practices task force-7. *Value Health* 2012; 15: 733–743.

<sup>86</sup> Software like MS Excel, TreeAge is often used.

<sup>87</sup> Key input data for the model – data that may determine the result of the economic analysis. They relate to clinical endpoints relevant to assess the effectiveness and safety of the technology being assessed. The equivalence of the compared interventions is inferred in the clinical analysis based on the results of these endpoints. See also: Identification of input data in Table 2.

<sup>88</sup> See also e.g. Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technology Assessment* 2004; 8: 1–158.

| <b>Subject of assessment</b>  | <b>Principles of good practice</b>   | <b>Questions for critical assessment</b>   |
|---|--|--|
|   | <p>time, it has to correspond to the decision problem defined and be compliant to generally accepted knowledge on the course of the modelled disease, as well as cause-effect relationship between the variables.</p> <p>Lack of data does not justify elimination of states or simplification of the model.</p> | <p>defined?</p> <p>Are important details of the course of the modelled disease described?</p> <p>Are the model assumptions described and justified?</p> <p>Is the selection of the model states justified? If so, is it compliant to the knowledge on the disease?</p> <p>Are any important health states missing?</p> |
| <b>Comparators</b>  | <p>The model should take into account the comparators selected in accordance with the criteria defined in the decision problem analysis.</p>   | <p>Were comparators identified?</p> <p>Does the model take into account the comparators in accordance with the criteria defined in the decision problem analysis?</p>  |
| <b>Time horizon</b>   | <p>Time horizon of the model should be sufficient to show durable differences in costs and outcomes of the compared strategies.</p>  | <p>Was the time horizon of the analysis defined? If so, is it appropriate to the analysed situation?</p>   |
| <b>The length of cycles (when using models, whose structure requires that a cycle is defined)</b> | <p>A cycle should be the shortest period in which changes of examined parameters, corresponding to the typical disease process, are expected.</p>  | <p>Was the length of cycles defined in the model?</p> <p>Was the cycle length justified? If so, does it correspond to the disease process?</p>   |

| Subject of assessment                   | Principles of good practice  | Questions for critical assessment  |
|---|--|--|
| <b>Input data for the model</b>         |  |  |
| <b>Identification of input data</b>     | <p>The model should use the best data available (epidemiological, clinical, cost-related), corresponding to the Polish conditions. A systematic review of literature should be carried out to obtain the key input data for the model. The key data include:</p> <ul style="list-style-type: none"> <li>• data on the effectiveness and safety of the compared interventions,</li> <li>• health state utilities,</li> <li>• variables for which even a small change in the value results in a significant change of the analysis result.</li> </ul> <p>This systematic review should include the search of at least one medical information database (MEDLINE or EMBASE). Proof of such review or a justification of its absence should be presented. If experts' opinions are the source of data, the methods of obtaining the data and the source data should be provided.</p> | <p>Are the data sources presented in the model?</p> <p>Have the proper methods of data source searching been implemented?</p> <p>Has the range of parameter variability been determined?</p> <p>Does anything suggest that the data have been used selectively?</p> <p>If values of certain parameters have been estimated on the basis of experts' opinions, are the data collection methods described (e.g. expert selection criteria, number of experts, information collection methods, conflict of interest)?</p> |
| <b>Data modelling</b>                   | Data modelling should be carried out on the basis of generally accepted statistical methods.   | Have the methods used for data modelling been described? Have the generally accepted criteria of biostatistical and epidemiological methods been complied with?  |
| <b>Inclusion of data into the model</b> | <p>Measurement units, time intervals and population characteristics must be mutually compatible in the entire model.</p> <p>In order to standardise and eliminate the effect of time-dependent estimations, half-cycle correction should be used for longer cycles.</p>  | <p>Are the measurement units, time intervals and population characteristics mutually compatible in the model?</p> <p>Has the half-cycle correction been implemented?</p>   |
| <b>Sensitivity analysis</b>             |  |  |
| <b>Sensitivity analysis</b>             | Each model must include the sensitivity analysis of the key parameters and a justification of the analysed variability range for these parameters. The sensitivity analysis should involve both simple analysis (at least one-way sensitivity analysis of the key parameters) and a probabilistic analysis. Failure to provide a probabilistic analysis should be justified (e.g. economic analysis in the form of cost comparison). The decision not to provide a probabilistic analysis  | <p>Have sensitivity analyses been carried out for all key parameters? Has the scope of variability of the parameters tested in sensitivity analysis been justified?</p> <p>Was a probabilistic sensitivity analysis performed?</p> <p>If no probabilistic sensitivity analysis was done, has adequate reasoning for its lack been presented?</p> <p>Is the lack of the probabilistic</p>   |

| Subject of assessment         | Principles of good practice  | Questions for critical assessment   |
|-------------------------------|--|---|
|                               | should be supported by adequate reasoning included in the economic analysis document.  | sensitivity analysis justified?   |
| <b>Model validation</b>       |  |   |
| <b>Internal validation</b>    | In order to identify errors related to data introduction and the model structure, the model should be systematically tested; for instance, it should be checked, whether expected results are obtained when zero or extreme input values are used; the code of the software should be analysed to identify syntactic errors or reproducibility of results should be tested by means of equivalent input values. If there are external sources of input and output data (independent of those used in the model), the model should be calibrated.   | Has internal validation been performed?   |
| <b>Convergence validation</b> | The model should be compared to other models focused on the same decision problem; in the case of varying results, the reasons for such differences should be identified.  | Have any other models of the same decision problem been identified? If so, have the results of different models been compared, and in the case of varying results, have the reasons for such differences been identified? |
| <b>External validation</b>    | <p>External validation focuses on compatibility of modelling results with direct empirical evidence. It can consist, for instance, in comparing indirect output data of a model with published results of long-term research (if there are any).</p> <p>The model should be verifiable so as to make it possible to compare the results generated by the model (resource use, cost-generating events, or other natural units) with data from the IT resources of the public payer, or other data sources (actual clinical practice, medical registers, cost registers etc.) in the future.</p> | <p>Has any research been identified, the results of which could be compared to the model results?</p> <p>Have the results been compared?</p> <p>Have any differences been identified and their reasons explained?</p>     |

#### 4.6. Health outcomes assessment

The data included in the economic analysis on health outcomes should be obtained from the best available sources. The data on the relative effectiveness of the compared interventions should come from the performed clinical analysis.

In the case of the availability of data on effectiveness (including data from the payer) and efficacy, the validity of these data should be presented separately, and the effect of data source on the result of the analysis should be analysed.

To evaluate the health outcomes associated with the natural course of the disease, data on effectiveness should be sought. When using data from clinical trials to describe the natural course of the disease, provide arguments for their validity (see Table 2 Identification of the input data).

## 4.7. Cost assessment

The economic analysis should comprise the costs corresponding to resources used when applying a given technology in everyday clinical practice. The identification of the cost categories and the definition of the method of their measurement and assessment are closely linked to the perspective and the time horizon chosen for the analysis.

### 4.7.1. Cost categories

Depending on the selected perspective, the analysis should identify:

- direct medical costs resulting from the use of resources needed to provide medical care and supporting the process of its provision, directly related to medical care, such as expenses incurred for the purchase of medicines, diagnostics, hospitalisations, medical staff's labour;
- direct non-medical costs resulting from the use of resources needed to provide medical care and supporting the process of its provision, not related to medical care, such as expenses incurred for hospital administration, non-medical staff, transport to the hospital; from the perspective of public finances, the direct non-medical costs also include social benefits such as pensions, sickness benefits and rehabilitation services, as well as reduced revenues from social security contributions and taxes;
- indirect costs, defined as costs of resources lost due to the disease and its consequences; in health technology assessment reports these are the costs of lost productivity of patients and their informal caregivers; the category of indirect costs should include the costs associated with paid work only.

The categories of costs that should be included in the analyses conducted from various perspectives are presented in Table 3.

**Table 3. Examples of direct and indirect costs depending on perspective.**

| Perspective                       | Direct costs  |   | Indirect costs |
|-----------------------------------|---|---|----------------|
|                                   | Medical   | Non-medical   |                |
| <b>Public payer + beneficiary</b> | Costs associated with the process of treating the disease and its complications: drugs, medical devices, diagnostic tests, vaccines, medical visits, nursing services, hospitalisations, rehabilitation – partially | –   | –              |
| <b>Public payer</b>               |   | –   | –              |
| <b>Patient</b>                    |   | Non-medical transport, diet, domestic help, house adaptation<br>Lost earnings minus pension and benefits (net lost wages) | –              |

| Perspective        | Direct costs  |   | Indirect costs |
|--------------------|---|---|----------------|
| Service provider   | financed by the given entity  | Expenses on hospital administration, non-medical staff  | –              |
| Public finances    |   | Pensions and benefits for patients and caregivers<br>Lost social security contributions and taxes | –              |
| Social perspective | Costs associated with the process of treating the disease and its complications – understood as an alternative cost<br>Non-medical transport, diet, paid domestic help, house adaptation – understood as an alternative cost<br>Lost productivity of the patient and caregivers |   |                |

#### 4.7.2. Identification and measurement of used resources

Identification of used resources involves the need to determine, which resources are appropriate for an examined problem (disease, intervention). The consideration of cost-generating resources should be consistent with the description of the health problem and the assessed intervention presented in the decision problem analysis (section 2 Decision problem analysis).

Used resources can be measured in two ways: either by collecting primary data within a properly designed research, or by collecting secondary data from existing databases or available publications.

The choice of data sources depends on the required degree of detail to be analysed. The choice should be based on the following criteria:

- analysis perspective;
- share of a given component in the total or incremental cost;
- data availability and validity.

High accuracy is the advantage of the primary data, while their disadvantage consists in the fact, that their collection is time-consuming and labour-intensive. Another disadvantage is the fact that the data collected within the framework of a clinical trial also contain information on resources, the use of which is induced by the study protocol. Secondary data, e.g. from national registers, are usually characterised by high external validity. However, they may turn out to be incomplete, as such databases do not cover all types of resources.

Both the micro-costing method<sup>89</sup> and the gross-costing method<sup>90</sup>, differing in the precision of used resources assessment, can be applied to measure used resources. Both methods can be used in a single analysis. The higher the impact of a given cost

<sup>89</sup> The micro-costing method is based on the analysis of detailed data on all resources used in a given intervention; it is often associated with the collection of original data.

<sup>90</sup> The gross-costing method is based on the more aggregated data about the used resources compared to the micro-costing method. The characteristic features of the gross-costing method include its simplicity, practicality and (intended) resistance to details specific for site or patient characteristics.

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component on the total or incremental cost, the higher should be the precision of its assessment.

#### 4.7.3. Determination of unit costs

Unit costs of the used resources must be determined in accordance with the analysis perspective. The following methods of assessing the monetary value of used resources can be implemented:

- list of standard costs;
- formerly published research;
- local scales of charges or service tariffs for specific procedures;
- direct calculation;
- data from tenders (inpatient procurements).

The choice of the monetary method of assessing units of used resources should be based on the choice of the method of measuring the used resources<sup>91</sup>.

The use of local tariffs is particularly recommended when the assessed intervention is available only at health care institutions of a certain type, the scale of charges includes a large number of procedures and benefits, and the data are available for the investigator without additional work and expenses. Oftentimes, it is the best method and the only one available, but the charges not always correspond to actual costs. The use of charges is a method of choice in the case of analyses carried out from the perspective of a public payer, and from the joint perspective of the public payer and the beneficiaries. In other cases, it may be justified to determine the relationship between charges and the actual costs. When using a list of standard costs, for units of used resources with considerable share in the total or incremental cost, it may be indispensable to use more precise methods, e.g. the direct calculation of a unit cost.

It is recommended to use the friction costs method for the loss of productivity caused by disease or premature death<sup>92</sup>. The results obtained with this method, due to their limitation to the friction period, better reflect the actual economic losses caused by diseases among the employees. The length of the friction period should be determined based on the data for the Polish economy; in the absence of such data, it is recommended to use one universal value (3 months).

On the contrary, the estimates obtained using the human capital method illustrate the hypothetical maximum values associated with loss of productivity. The estimates obtained using the human capital method can be presented as part of the sensitivity analysis.<sup>93</sup>

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<sup>91</sup> For example, there is no sense to perform monetary evaluation of the used resources by direct calculation if national registers were used for the measurement of the used resources.

<sup>92</sup> Employers' Association of Innovative Pharmaceutical Companies INFARMA. [Indirect costs in health technology assessment. Methods, pilot study and recommendations.] December 2014. Document in Polish.

<sup>93</sup> Ibidem.



The unit cost of lost productivity associated with paid work should be determined on the basis of the gross domestic product (GDP) per one employed person, adjusted to marginal productivity.<sup>94</sup>

#### 4.8. Discounting

The assumed discount rate is equal to:

- in the basic analysis – 5% for costs and 3.5% for health outcomes,
- in the sensitivity analyses – 0% for costs and 0% for health outcomes.

Differentiation of the discount rate for costs and health outcomes is justified mainly due to rising social expectations with regard to maintaining good health, as well as time-varying willingness to pay for health outcomes<sup>95</sup>.

#### 4.9. Data presentation

All data should be presented with dispersion measures, in a clear manner, in table form, with the data source. The input variable distribution should be defined and justified in probabilistic analyses. The method of data collection and analysis should be described and justified. The forms used to collect data should be attached as annexes to the report.

#### 4.10. Presentation of results

The results of the economic analysis should be presented in the following form:

- total health outcomes considered in the economic analysis and, separately, total costs of the compared technologies, various categories of costs, the difference in total costs and health outcomes, the difference in the individual cost categories. The results should be presented as the mean value with dispersion measures (from the probabilistic analysis);
- incremental (ICER/ICUR) and absolute (CER/CUR) ratios of costs to health outcomes, if their presentation is justified.

The presentation method should be clear enough to ensure proper interpretation of the analysis and the possibility of data recovery and use in the future.

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<sup>94</sup> Ibidem.

<sup>95</sup> Claxton K, Paulden M, Gravelle H, et al. Discounting and decision making in the economic evaluation of health-care technologies. *Health Econ* 2011; 20: 2–15.

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## 4.11. Sensitivity analysis and result uncertainty assessment

### 4.11.1. Sensitivity analysis

Result uncertainty may be due to missing data, estimation precision, and methodology-related assumptions. The sensitivity analysis allows to tackle the problem of generalising the results of the economic analysis by examining whether and to what extent the results based on measurements in a given sample of the patient population and/or in a specific context are true for the entire population and/or in a different context.

The sensitivity analysis should focus on the input data, for which the estimation uncertainty is the highest, and also those having a significant impact on the result of the economic analysis.

In the economic analysis it is necessary to conduct at least a one-way sensitivity analysis<sup>96</sup> and a probabilistic sensitivity analysis<sup>97</sup>. The probabilistic analysis should test at least the parameters that have the greatest effect on the results. A decision not to conduct the probabilistic analysis should be supported by adequate reasoning (e.g. economic analysis in the form of cost comparison), included in the economic analysis document.

The sensitivity analysis should:

- identify uncertain parameters (subject to estimation error);
- define and justify the scope of variability of uncertain parameters<sup>98</sup>;
- calculate the main results of the analysis (health outcomes and their difference, total costs and their difference, ICER/ICUR, CER/CUR), assuming a specific variability of uncertain parameters.

The results of the sensitivity analysis should be presented in tabular form and, where applicable, also in graphical form, e.g. as a scatter plot on the cost-effectiveness plane, cost-effectiveness acceptability curve (CEAC), tornado plot, cost disutility plane<sup>99</sup>.

### 4.11.2. Result uncertainty assessment

The uncertainty in the results of the economic analysis should be estimated using the appropriate statistical methods in the context of probabilistic sensitivity analysis.

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<sup>96</sup> A simple sensitivity analysis evaluates the consequences of using in the model different values for one (one-way sensitivity analysis) or more variables (multi-way sensitivity analysis).

<sup>97</sup> A probabilistic sensitivity analysis takes into account the likelihood of occurrence of individual values from the variability range of a given parameter.

<sup>98</sup> The scope of parameter variability should be determined on the basis of a literature review, or, in case no data are available, on expert opinion. It is also possible to assume a probable range of parameter variability or, in the absence of data on the size of dispersion, it is allowed to adopt an arbitrary dispersion range in order to investigate the effect of changing the value of a given parameter on the results of analysis. The variable distribution used for the uncertainty assessment of the input parameters should be defined and justified in probabilistic analyses.

<sup>99</sup> Eckermann S, Briggs A, Willan AR. Health technology assessment in the cost-disutility plane. *Med Decis Making* 2008; 28: 172–181.

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A probabilistic analysis can be performed using analytical methods or the Monte Carlo method<sup>100</sup>.

The distribution of the possible results of the model, resulting from the probabilistic analysis, should be presented graphically in the cost-utility (cost-effectiveness in the case of cost-effectiveness analysis) coordinate system. On the basis of this distribution, determine the mean value and confidence intervals for the results (e.g. 95%) or present them in a different way, e.g. using the acceptability curve or net monetary benefit (NMB)<sup>101</sup>.

The selection of methods to assess the uncertainty of the results should be described and justified<sup>102,103</sup>.

## 4.12. Limitations and discussion

The limitations and discussion should be clearly separated.

### 4.12.1. Limitations

The part concerning limitations should discuss the characteristics of the analysis and the available initial data, the sources of uncertainty for these data, and the properties of the scope of analysis in the context of the specific decision problem. Describe the phenomena that significantly affect the uncertainty of the obtained results and the conclusions made on their basis, and the validity of the presented analysis. When discussing the limitations, it should be specified whether the economic analysis was based on clinical effectiveness data that reached statistical significance.

### 4.12.2. Discussion

The discussion is a critical description of the obtained results and conclusions in the context of a specific decision problem. In particular, the discussion should refer to the available data, used methods, and obtained results. Provide the results of other analyses of the same decision problem (conducted in Poland or in other countries, identified in a systematic review of medical information databases), and discuss the possible differences in the results and assumptions of the analyses.

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<sup>100</sup> O'Brien BJ, Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: An introduction to statistical issues and methods. *Stat Methods Med Res* 2002; 11: 455–468.

<sup>101</sup> The net monetary benefit (NMB) is an additional effect of using the new therapy, expressed in monetary units, minus the additional cost associated with the new therapy. Source: Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998; 18: S68–S80.

<sup>102</sup> Glick HA. Economic Evaluation in Clinical Trials (revised 07/21/15), chapter 9: Confidence intervals for CER, CI for NMB, and acceptability curves; [www.uphs.upenn.edu/dgimhsr/eeinct\\_cicer.htm](http://www.uphs.upenn.edu/dgimhsr/eeinct_cicer.htm) (as at 15/08/2016).

<sup>103</sup> Glick H, Doshi J. Evaluating sampling uncertainty in cost-effectiveness analysis: statistical considerations in economic evaluations. ISPOR 16th Annual International Meeting, May 2011, [www.uphs.upenn.edu/dgimhsr/](http://www.uphs.upenn.edu/dgimhsr/) (as at 23/03/2016).

### **4.13. Final conclusions**

The basic conclusions drawn from the clinical effectiveness analysis should be synthesised.

The results should be clearly separated from their possible interpretation, and from the conclusions. The conclusions should refer to the purpose of analysis and they should be directly related to the obtained results. In the economic analysis, the conclusions should refer to cost-effectiveness (or the lack thereof) of the reviewed technology in relation to alternative technologies (comparators).

## 5. Analysis of impact on health care system

The analysis of impact on health care system in Poland should possibly comprehensively assess the consequences of the decision on the financing of the health technology from public funds.

The analysis of impact on health care system includes a budget impact analysis, which can be supplemented by analysis of ethical, social, legal and organisational consequences of a decision to finance the assessed health technology from public funds.

### 5.1. Budget impact analysis

The budget impact analysis (BIA) determines the financial consequences of the introduction, withdrawal from reimbursement, or other change in financing of the assessed health technology in the Polish health care system. It is a quantitative analysis, whose results are presented in monetary units.

#### 5.1.1. Perspective

The budget impact analysis should be conducted from the perspective of the authority obliged to finance services from public funds, and, in the case of co-payment, from the joint perspective of the payers: the public payer and the patients. Additionally, in the case of co-payment it is recommended to present the costs incurred by the patient, their average values, and in appropriate cases also the range.

If there is no co-payment by the beneficiaries, or it is negligible from the patient perspective, it is possible to use only the public payer's perspective.

In justified cases, budget impact analysis can additionally be performed from the social or another perspective, e.g. the health care provider, public finance.

#### 5.1.2. Time horizon

The budget impact analysis involves an assessment of impact of a given health technology on the annual health care budget in the period of a few years after the introduction of a new technology or withdrawal from financing a previously reimbursed technology. It is recommended to use the time period sufficient for the market to reach the state of equilibrium (i.e. reaching the target stable sales or number of treated patients), or at least the first 2 years (24 months) from the start date of financing a given health technology from public resources.

#### 5.1.3. Elements of analysis

The budget impact analysis should include the following elements:

- the size and characteristics of the examined population;
- the scenario corresponding to the current practice (“current scenario”);

- the scenario expected after the introduction of the new technology/withdrawal of the currently reimbursed technology (“new scenario”);
- the costs of the above scenarios;
- incremental results;
- sensitivity analysis.

#### 5.1.4.Data sources

The following data sources can be used: published and unpublished epidemiological studies, national statistical data, market research, registers, various databases, expert opinions, and opinions of patient-oriented non-governmental organisations. The search strategy, criteria for data source selection, strengths and weaknesses of the used sources, and the criteria for data selection and methods of analysis should be presented. The analysis should use the data that will result in the lowest estimation error.

The first step is to use the Polish epidemiological data; the use of epidemiological data from other countries should be justified. In the case of uncertainty of the epidemiological data, sales/reimbursement data can be used to estimate the target population size.

When using data from unpublished sources (e.g. expert panels, marketing research, opinions of patient-oriented non-governmental organisations), it is important to present the conflicts of interest and the possible sources of bias.

The cost data should reflect the actual cost associated with the use of the assessed intervention and the comparators, taking into account the existing Risk Sharing Schemes, if possible.

#### 5.1.5.Population

In the budget impact analysis, the examined population includes all patients in whom a given health technology can be used in accordance with the assessed medical indications. In order to determine the population, in which the assessed technology will be used if it is reimbursed, consider the degree of implementation of the new technology in the reviewed time horizon, and changes in the degree of using previous technologies. It is important to take into account the possible increase in population induced by the availability of the new technology on the market<sup>104</sup>.

In contrast to the clinical effectiveness analysis and the economic analysis, where the examined population is closed (a cohort of patients is defined at the beginning and all included patients remain in the examined population throughout the reviewed time horizon), the population examined in the budget impact analysis is open. It means that particular patients enter or leave the population, when they meet or fail to meet the defined inclusion criteria at a given moment. In some cases, when the technology applies to a well-defined group of patients, the budget impact analysis may require to define a closed population.

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<sup>104</sup> E.g. a certain percentage of patients who remained “untreated” will use the technology because it is more effective and has a better safety profile.

The size of the patient population should be assessed by the following sequence of operations (if applicable to a given technology):

- identify the prevalence of a given disease;
- assess the number of persons, who would have indications for using the technology;
- estimate the market position of the technology in each indication based on the population percentage expected to use the technology in question, compared to the part of the population, which shall use alternative technologies for a given indication.

The size of the population in which the technology would be used in the case of a positive reimbursement decision should be assessed by constructing alternative variants based on factors most affecting the use of the technology, and various prevalence estimations of the disease. Take into account the dissemination of the new technology, and how it would replace the previously reimbursed technologies. Consider the effect of current legal regulations regarding the reimbursement of medicinal products.

#### **5.1.6. Compared scenarios**

The budget impact analysis is based on the concepts of the “current scenario” and the “new scenario”. The “current scenario” takes into account the interventions currently used in a given population (including no intervention or interventions used in different conditions, e.g. in the framework of Diagnosis Related Groups (DRG)); the “current scenario” should coincide with the “current practice” as indicated in the decision problem analysis (2.1.1.5 Current medical management). The “new scenario” reflects the market after the introduction of the new technology (which may be added to the existing ones, or may replace all or some of them), or withdrawal of the technology. The assumptions concerning the “current scenario” and the “new scenario” should be described and justified in the analysis.

#### **5.1.7. Cost analysis**

Cost analysis in the budget impact analysis should be in line with the perspective of this analysis. The methods used to estimate the costs should be clearly described and justified, with all their assumptions, also those adopted in the sensitivity analysis.

Budget outlays should be assessed in a manner, which ensures their correspondence to actual payments and actual savings achieved by a public payer/patient.

The budget impact analysis should especially focus on determining, whether the calculated savings are going to be noticeable in the actual practice. It is desirable to present in quantitative terms the impact of the technology on medical services, because the introduction of the new technology can have practical implications for the organisation and functioning of the health care system.

Depending on the type of the assessed intervention, it may be important to describe the costs of its introduction, including the need to train the staff or the patient, or to change the diagnostic principles.

Separate assessments should be prepared for particular types of outlays<sup>105</sup>.

The estimation of the total incremental change in the outlays should comprise:

- the outlays related to the assessed technology;
- the cost of additional outlays in the health care system, related to the implementation of the assessed technology;
- the reduction in outlays related to the reduced use of the current technologies, in case the assessed technology takes over;
- the reduction in costs related to the savings in the domain of other services (e.g. less hospitalisations).

By principle, the budget impact analysis does not discount costs, as the analysis presents the flow of financial resources in time.

#### **5.1.8.Sensitivity analysis**

The sensitivity analysis should address first of all those input data for which the dispersion measures and estimation uncertainty are the highest, and the input data that has the greatest effect on the result. The values from the variability ranges of the input data and the assumptions should be selected so as to estimate the minimum and maximum incremental change in outlays, respectively. The sensitivity analysis should therefore test any uncertainties concerning the estimation of the population size (e.g. the degree of possible abuse of the assessed technology), the prevalence of use of each technology, and the costs of use and reimbursement conditions of the considered technologies. The sensitivity analysis should also test different price proposals for the drug being evaluated.

In the absence of precise data for Poland, or divergent preliminary estimates, the most important input data should be evaluated in multi-way sensitivity analysis based on different data sources.

#### **5.1.9.Presentation of results**

For each year within the examined time horizon, both total and incremental impact on the budget should be presented. The consumption of resources and the outlays should be presented in separate tables to show the changes in each year within the time horizon.

#### **5.1.10.Limitations and discussion**

The presented results should be supported by a discussion, including a discussion of the limitations of the analysis.

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<sup>105</sup> E.g. drug reimbursement, hospital treatment expenditures, specialist outpatient care expenditures.



## 5.2. Ethical, social, legal aspects, impact on the organisation of service providing

If the decision on financing the reviewed technology could result in significant expenses for the patients, or the budget impact analysis is performed from an additional perspective, e.g. when financing of the technology could have significant consequences for public spending in sectors other than health care, discuss the conclusions resulting from these analyses, including the important ethical and social aspects.

The following issues should be taken into consideration:

- Which groups of patients, if any, could be favoured or discriminated as a result of the assumptions adopted in the economic analysis?
- Is the access to the medical technology guaranteed to be equal, when the needs are equal?
- Is a narrow group of persons expected to receive a big benefit, or the benefit is small but of general character?
- Does the technology constitute a response for the persons with significant health needs, who are not offered any available treatment method at the moment or whose access to treatment is limited?

Verify whether the decision on financing the assessed technology would affect the current organisation of health care services. Depending on the type of the new intervention, it may be important to describe the conditions of its introduction, such as the need to train the personnel, patients or their caregivers, to change the diagnostic principles and the related costs.

It should be considered, whether a decision to finance the assessed technology could lead to any social problems, including:

- an impact on the level of patient satisfaction with the received medical care;
- a threat of rejection of the procedure by particular patients;
- can it result in or change patient stigmatisation;
- can it cause excessive anxiety;
- can it lead to moral dilemmas;
- can it cause any sex- or family-related problems.

It should be determined, whether the use of the technology imposes special requirements related to the patients' rights<sup>106</sup>, such as:

- the need to provide specific information to the patient/caregiver,
- the need to ensure the patient's right to dignity and privacy, and confidentiality of his/her information,

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<sup>106</sup> The patients' rights are set out in the Act of 6 November 2008 on Patients' Rights and the Commissioner for Patients' Rights (Journal of Laws of 2012, item 159, as amended).

- the need to take into account individual preferences, after providing the patient/caregiver with information as required by law.

It should also be analysed, whether the decision concerning the technology in question:

- is not in contradiction with the legal regulations currently in force;
- requires any amendments to the current laws/regulations;
- has an impact on the rights of a patient or on human rights.

In justified cases, this part of the analysis of the impact on the health care system can discuss additional aspects identified in the HTA Core Model®<sup>107</sup> and not listed above.

A summary of the social, ethical, and organisational impact of the new technology can be presented as a SWOT analysis<sup>108</sup>.

### 5.3. Final conclusions

The conclusions should refer to the purpose of analysis and they should be directly related to the obtained results.

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<sup>107</sup> HTA Core Model® EUnetHTA Domains 6.–9. Ethical analysis, Organisational aspects, Patients and social aspects, Legal aspects (EUnetHTA Joint Action 2, HTA Core Model, version 3.0 (PDF), 2016).

<sup>108</sup> Strengths Weaknesses Opportunities Threats; a type of strategic analysis based on identification of strengths and weaknesses of a given procedure as well as the related opportunities and threats.

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### **Annex 2. Utilities**

When preparing the cost-utility analysis, the categories of utility sets should be borne in mind (obtained using the same method, if possible – from a single study, well-matched to the health states used in the model and the characteristics of the analysed population). Health state utilities obtained by different methods should not be combined and compared in an individual economic model.

When searching for the utility values for the economic model, the authors of a HTA report may adopt one of two strategies:

- reliance on secondary sources (1);
- conduct of an independent primary study of health state utilities (2).

Each of these two strategies can be referred to one of three categories of the utility measuring methods: (a) indirect methods, (b) direct methods, or (c) questionnaire mapping. The preferred approach is to rely on secondary sources and health state utility values obtained by indirect methods, preferably by means of the EQ-5D questionnaire.

#### **Secondary sources of information about health state utilities**

The choice of a strategy based on secondary sources results in the need to conduct a systematic review of literature. This systematic review should base on the definition of the publication inclusion and exclusion criteria, and the search of at least one medical information database (MEDLINE or EMBASE). It is also possible to find data in other sources and web search engines. The identified utility values meeting the review criteria should be presented along with their characteristics – the method of obtaining, study population, details on the subjects' health state, and a summary of utilities finally selected for the economic model.

The strategy based on secondary sources and health state utility values obtained by indirect methods (1a) is the preferred approach to searching the utility values for the economic model. The advantage of this approach is the standardisation of the used tools and the simplicity and reproducibility of the measurement. The following data sources can be used to obtain utility values: (1) publications on the results of original utility studies, (2) unpublished data, usually from a clinical study evaluating the assessed technology, (3) systematic reviews of health state utilities.

If the identified systematic review of utility has no methodological issues (regarding the systematic nature of the search), is up to date (less than 5 years from the date of publication), and includes utilities for health states used in the model, then no more search for original publications on utility studies is necessary. The identified publications of economic analyses quoting the original utility studies or other economic analyses cannot be used as a source of the utility values, unless the determined values are taken from a clinical study of the assessed intervention and the methods used to obtain them are described in detail, and there is no separate

publication on utility (it is always advised to try to identify the original utility study in order to extract and assess the details of the utility measurement method). When no utility values obtained using the EQ-5D questionnaire are found (or, less commonly, the EQ-5D questionnaire is inadequate for the analysed health problem), in the second step, utility values obtained using the SF-6D or HUI methods should be sought; in the possible further step, other indirect methods for utility measuring can be used.

In some health situations, the EQ-5D questionnaire may not be appropriate for measuring the utility, and it is advisable to use another method. Such situation should be justified on the basis of published data on the validity or responsiveness of the selected tool in the target population of the economic analysis.

Strategy based on secondary sources and health state utility values obtained by direct methods (1b). Direct methods are not generally standardised (except for those used by certain research groups, e.g. EuroQol), and may be implemented by various investigators in different variants, which can directly result in additional variability in their results. An approach based on the search for published utility values obtained by direct methods can be considered when strategy 1a fails or when indirect methods are not appropriate for the health problem in question.

Strategy based on secondary sources and health state utility values obtained by questionnaire mapping (1c). Mapping disease-specific questionnaires to generic ones, or generic quality of life questionnaires to generic utility measures always involves uncertainty, but sometimes it can be the only available method to obtain the utility values for the economic model. In practice, one of two situations can occur: (1) published (or unpublished) results of the mapping are available, (2) clinical study results are available on the quality of life measured with a generic or disease-specific questionnaire, and the mapping algorithm has been published, and the authors of the economic analysis translate the quality of life results to the utility values. The mapping method used and its fit statistics should be properly documented. It is advisable to conduct a systematic review of literature in order to identify the optional mapping methods.

### **Independent primary health state utilities study**

An independent primary utility study is not recommended as the primary source of utility values for economic models in Poland.

Strategy based on original health state utility study with the use of indirect methods (2a). It is the easiest and most standardised approach to the primary measurement of utility. The instrument of choice is EQ-5D. While measuring preferences with the EQ-5D-3L questionnaire, it is advised to use the Polish time trade-off based health state utility values set. For the EQ-5D-5L questionnaire it is recommended to use the norms obtained by the crosswalk method<sup>109</sup> until norms obtained with direct methods are available. If alternative values sets are available for the Polish population, the different utility values should be tested in the sensitivity analysis.

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<sup>109</sup> Golicki D, Niewada M, van Hout B, et al. Interim EQ-5D-5L value set for Poland: first crosswalk value set in Central and Eastern Europe. *Value in Health Regional Issues* 2014; 4: 19–23.

Strategy based on original health state utility study with the use of direct methods (2b). Direct measurement of utility is a complex and costly task. The methods are not fully standardised. Considering the above, the presented approach is not recommended except in the case of failure of strategies based on secondary sources (1) and strategy 2a.

Strategy based on original health state utilities eliciting study with the use of mapping methods (2c). Development of a new mapping algorithm is a complex and non-standardised task. Considering the above, the presented approach is not recommended except in the case of failure of strategies based on secondary sources (1) and strategies 2a and 2b.

### **Concluding remarks on the health state utility values**

The measurement of utility in children is currently not standardised, although the methods of such measurement are extensively developed. Besides the general recommendation of relying on secondary sources, no preferred group of methods can be indicated. Any analysis concerning the use of a health technology among paediatric patients requires an individual approach, which should be subject to conditions specific to a given paediatric problem and the availability of published data.

In the rare situation of access to the individual patients data on the results of quality of life measurements by indirect methods, derived from a clinical study, it is worth to adapt the obtained utility values for the preferences of the Polish society (the Polish health state utility values set).

If justified by the subject of analysis and if the economic model has such functionality, the utility set used in the economic analysis can be adjusted to the Polish age- and sex-specific population norms.

If an alternative utility set has been identified and it meets the search conditions, corresponds to the health state characteristics of the model, and is methodologically acceptable, its impact on the results of the economic analysis should be tested in the context of sensitivity analysis.

Because of the crucial effect of the selection of utility values on the results of economic analysis, this process must be described in a particularly careful and transparent way. A description of the methods and results of the search alone, without a description of the process of value selection for the model, is insufficient.



## Annex 3. Abbreviations used in the document

AMSTAR – a measurement tool to assess systematic reviews and meta-analyses

AOTMiT (Agencja Oceny Technologii Medycznych i Taryfikacji) – The Agency for Health Technology Assessment and Tariff System

ATC – Anatomical Therapeutic Chemical Classification System of drugs and other agents and products used in medicine

BIA – budget impact analysis

BSC – best supportive care

CCT – controlled clinical trial, non-randomised

CEAC – cost effectiveness acceptability curve

CER – cost-effectiveness ratio

Cochrane (Cochrane Handbook) – an independent international non-profit organisation whose aim is to help make informed therapeutic decisions by, among others, conducting analyses in accordance with the principles of evidence-based medicine (EBM); Cochrane Handbook – a handbook describing the methodology for the conduct of these analyses

CRD – Centre for Reviews and Dissemination; a unit dedicated to the analyses of scientific evidence (systematic reviews, data meta-analyses) and their dissemination

CUR – cost-utility ratio

EBM – evidence-based medicine

EFTA – European Free Trade Association

EMA – European Medicines Agency

EMBASE – Excerpta Medica dataBASE; a biomedical-pharmacological bibliographic database of Elsevier

EQ-5D (EQ-5D-3L, EQ-5D-5L) – EuroQol five dimensions quality of life questionnaire

EUnetHTA – a project forming the framework for the European cooperation in the field of health technology assessment; it has been operating since 2005 on the basis of repeated contracts for subventions from the European Commission, <http://www.eunetha.eu> (as at 31/08/2016)

European Network for HTA – organisation founded pursuant to Article 15 of Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare to promote cooperation between the European Union member states in the field of HTA, [http://ec.europa.eu/health/technology\\_assessment/policy/network](http://ec.europa.eu/health/technology_assessment/policy/network) (as at 31/08/2016)

FDA – Food and Drug Administration

HRQoL – health-related quality of life

HTA – health technology assessment

HTA Core Model® – a tool developed by the of EUnetHTA, implementing a method to create common European health technology assessment reports, <http://www.eunethta.eu/hta-core-model> (as at 31/08/2016)

ICD-9-CM – International Classification System for Surgical, Diagnostic and Therapeutic Procedures

ICD-10 – International Statistical Classification of Diseases and Related Health Problems

ICER – incremental cost-effectiveness ratio

ICUR – incremental cost-utility ratio

ISPOR – International Society for Pharmacoeconomics and Outcomes Research

DRG – Diagnosis Related Groups

LY – life years

LYG – life years gained

MedDRA – Medical Dictionary for Regulatory Activities; an organ and system classification used to describe adverse effects of medicinal products

MEDLINE – Medical Literature Analysis and Retrieval System Online; a bibliographic database maintained by the National Library of Medicine

NICE (scale) – a scale used in the validity evaluation of non-controlled studies

NMB – net monetary benefit; an additional effect obtained by using a new therapy, expressed in monetary units, reduced by the additional cost related to the use of the new therapy

NOS – Newcastle-Ottawa Scale; a scale for assessing the quality of observational studies

PICOS – patient/population, intervention, comparison, outcome, study; a mnemotechnic acronym for the search strategy elements in a systematic review: P – population, in which a given intervention will be used; I – intervention; C – comparators; O – health outcomes or endpoints, against which clinical effectiveness will be assessed; S – type of studies included

GDP – gross domestic product

PRISMA – Reporting Items for Systematic Reviews and Meta-Analyses; a scheme of study selection for systematic reviews of literature and meta-analyses

PSUR – Periodic Safety Update Report

PTFE – Polish Pharmacoeconomics Society (ISPOR Poland Chapter)

QALY – quality-adjusted life year

R&D – research and development

RCT – randomized controlled trial

REA – relative effectiveness assessment (European Commission, Enterprise and Industry – Working Group on Relative Effectiveness. Core Principles on relative effectiveness, 2008; <http://ec.europa.eu/DocsRoom/documents/7581?locale=en>; as at 23/03/2016)

RWD – real world data

RWE – real world evidence

SMDM – Society for Medical Decision Making

SuRe Info – Summarized Research in Information Retrieval for HTA; a medical information database

SWOT – strengths, weaknesses, opportunities, threats; a type of strategic analysis based on the identification of strengths and weaknesses of a given procedure, as well as the related opportunities and threats

EU – European Union

URPL – Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal Products

VAS – visual analogue scale

WHO (WHO Uppsala Monitoring Centre) – World Health Organisation Uppsala centre for pharmacovigilance