Agency for Health Technology Assessment

Guidelines for conducting Health Technology Assessment (HTA)

Version 2.1

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All members of the Team participated actively in discussions and contributed to the improvement of the document by submitting their remarks orally and in writing.
Zbigniew J. Król was in charge of the Teams activities and he is responsible for the final redaction of the dokument.
Guidelines (Version 2.0) where revised by Consultative Council of AHTAPol. The revision was an editorial only. Consultative Council of AHTAPol gave positive opinion on revised document (Version 2.1).
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1. Introductory information --

1.1. The notion of Health Technology Assessment --

Health Technology Assessment (HTA) is a multidisciplinary process that allows taking scientific evidence-based decisions regarding health policy and the clinical practice. This process summarizes information from various fields including medicine, epidemiology, biostatistics, economics, law and ethics. HTA provides scientific bases for taking reasonable decisions regarding the use and financing of health services. --

1.2. Health Technology Assessment scope --

A complete assessment of health technology comprises the following analyses: --

1) clinical effectiveness analysis, --
2) economic analysis, --
3) analysis of impact on health care system. --

1.3. Purpose of Health Technology Assessment --

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

1.4. Purpose of the guidelines --

The purpose of the guidelines is to indicate the principles and basic methods of performing Health Technology Assessment to ensure high quality of analyses and reliable results. --

1.5. Author and conflict of interest information --

Health Technology Assessment requires information about who ordered a study, 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 --

2.1. Problem definition --

The first stage of the performed analysis is to clearly precise the assessed technology, diagnostic, preventive or therapeutic intervention used in a specific clinical situation. --

A full description of the clinical context issues is required according to the PICO[1] scheme: --

- the population in which a given intervention is to be used (P); --
- the proposed intervention (I); --
- the comparators (C); --
- the health outcomes, i.e. clinical trial endpoints (O). --

In the case of analyses enclosed to applications for technology financing from public resources, the clinical context of the analyses must correspond to that described in the application. It should also be indicated which technologies and to what extent may be replaced by the assessed technology. --

2.1.1. Population --

The target population or the population that will undergo the assessed intervention should be described. The description should contain the basic information about the decision or health problem taking into account the natural disease history, prognosis and the currently used diagnostic or therapeutic methods. --

The potential population size should be specified and the estimation method should be described and justified. --

2.1.2. Intervention --

The assessed health intervention should be described. In the case of an intervention registered in Poland, the registration date or the date of the first conformity declaration of the medical device and the approved indications should be specified and compared to the indications discussed in the analysis. 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 EMEA[2] and FDA[3]. --

2.1.3. Comparators --

The clinical analysis consists in a comparison of the efficacy and safety of the assessed intervention (procedure) with the outcomes of other interventions (optional procedures) used in the target population. --

[1] Population, Intervention, Comparison, Outcome.

[2] *European MEdicines Agency* – the institution responsible for the registration of medicinal products and medical devices at the central level in the European Union.

[3] *Food and Drug Administration* – the institution responsible, among other things, for the registration of medicinal products and medical devices in the USA.

The primary comparator for the assessed intervention must be the so-called existing practice. It is the procedure that will likely be replaced by the assessed technology in medical practice.

It is also recommended to perform a comparison with other comparators, i.e. the following technologies: --

- the most frequently used, --
- the cheapest, --
- the most efficient, --
- compliant with the standards and guidelines for clinical management. --

It is important for the selected comparators to correspond to the Polish reality. Their selection should be adequately justified and data sources should be provided. --

2.1.4. Health outcomes --

The clinical analysis should evaluate the health effects which represent clinically significant endpoints[4], playing an important role in a given disease, i.e.: --

- deaths, --
- cases or recoveries, --
- quality of life, --
- adverse effects (divided into serious and non-serious) and/or medical events[5]. --

The endpoints in the clinical analysis should: --

- 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 interventions compared, --
- be essential for reasonable decision-taking (critical points of a given health problem). -

If no clinical trials with patient-oriented clinically significant endpoints have been found, surrogates can be assessed as the outcomes. In this case it is recommended to present the relationship between the surrogates used and the clinically significant endpoints in the analysis. --

If 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. --

A patient-oriented clinically important endpoint (*clinically important endpoint, clinically relevant endpoint, patient important outcome, patient-oriented endpoint*) – a parameter/outcome, a change of which as a result of treatment would make the treatment preferred for the patients. It reflects the treatment effects: life prolonging, improving the patient's well-being or allowing to live without disease complications or treatment.

[5] These terms are defined in the Act on Medical Devices of 20.04.2004 (Journal of Laws No. 93 item 896 of 2004 and No. 64 item 565 of 2005), Pharmaceutical Law of 6.09.2001 (consolidated text in Journal of Laws No. 53, item 533 of 2004) and the Ordinance of the Minister of Health of 20.12.2002 on clinical trials of medical devices.

3. Clinical analysis --

The clinical analysis refers to health outcomes of the assessed medical technology. It also informs about its efficacy and safety in a specific population compared to the appropriate comparators. --

3.1. Data --

The data collected in the course of clinical analysis refer not only to experimental efficacy but also to practical effectiveness. The data should be searched and selected based on a detailed protocol developed before starting this activity and containing the specific criteria for study inclusion in the analysis and their exclusion criteria. --

3.1.1. Data sources --

In the initial part of an analysis, a systematic search for any clinical trials regarding the appraised question should be performed. The data and information search process must be described in detail so that it is possible to evaluate whether it was correct and so that it can be repeated in case of HTA analysis verification. --

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

- Cochrane Library, --
- MEDLINE database, --
- EMBASE database, --
- Centre for Reviews and Dissemination database. --

In the next phase of clinical analysis, conclusions from the identified secondary studies should be presented. The studies can also be used as a source of information on the analytical practice in a given decision problem. If they do not provide sufficiently up-to-date and comprehensive information, the appropriate original studies should be searched for. --

An important condition of performing a systematic review of original studies is to find all scientific reports regarding the compared interventions and meeting the analysis inclusion criteria. Firstly, studies in which the assessed technology was directly compared with a selected comparator should be searched for[6]. --

The main databases for searching original studies are: --

- Medline, --
- EMBASE®, --
- Cochrane Library (CENTRAL). --

It is also recommended to search other medical information databases such as: --

- BIOSIS Previews®, --

[6] Head to head trials.

- CINAHL® Database, --
- PsycINFO®, --
- European Public Assessment Report (EPAR)[7], --
- Health Canada[8], --
- Netherlands Pharmacovigilance Centre Lareb[9], --
- The Uppsala Monitoring Centre[10], --
- Thompson Micromedex®[11]. --

It is also necessary to search for reports from other sources than the medical information databases by: --

- using literature references contained in clinical trial publications, --
- review of clinical trial registers, --
- consultations with clinical experts. --

It is also necessary to consider the need to obtain additional information by: --

- searching data published in specialist journals in the field of the assessed technology, which were not included in the search strategy, --
- contacting the authors of clinical trials, --
- use of Internet search engines, --
- consultations with manufacturers, especially as regards information on adverse effects (so called PSUR[12]). --

It should be assessed whether the inclusion of only published studies can lead to incorrect reading of the review results due to publication bias[13,14]. --

Data on the experimental efficacy are mainly obtained by systematic review of controlled clinical trials. Effectiveness data are from pragmatic clinical trials[15]. They can also be obtained from observational studies and databases (including patient registers) collecting information on the use of a given technology. The data should also be collected in the form of a systematic review. A comment should be provided on the degree of consistence between efficacy and effectiveness. --

[7] www.emea.europa.eu/htms/human/epar/eparintro.htm

[8] www.hc-sc.gc.ca

[9] www.lareb.nl

[10] www.WHO-umc.org

[11] www.micromedex.com

[12] Periodic Safety Update Report.

[13] The publication bias is associated with the fact that scientific reports in which positive results were obtained are published in scientific journals more often than those in which the results were negative or no differences were seen.

[14] The results of non-published studies can deliver important data; therefore, in co-operation with the manufacturer of the analysed drug or device, it should be checked if there are no such studies.

[15] Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. Journal of Chronic Diseases. 1967; 20: 637-648. Armitage P. Attitudes in Clinical Trials. Statistics In Medicine. 1998; 17: 2675-2683.

3.1.2.Search strategy --

An analyst should develop a search strategy appropriate for the defined clinical problem. It is recommended to use a possibly highly sensitive search strategy. Only in the case of a large number of hits the search specificity should be increased. When using strategies that significantly differ in sensitivity in various search engines, reasons should be provided. The search criteria can include the following elements (PICOS scheme[16]): --

- (P) Population, --
- (I) Intervention, --
- (C) Comparators, --
- (O) Outcomes, --
- (S) Study type. --

The search of original studies should be performed in the following languages: English, Polish, German and French, and other languages where relevant. --

The final effect of a search should be the collection of all available studies and data concerning the analysed clinical problem. --

The presentation of the search results should describe the strategy used with emphasis to: --

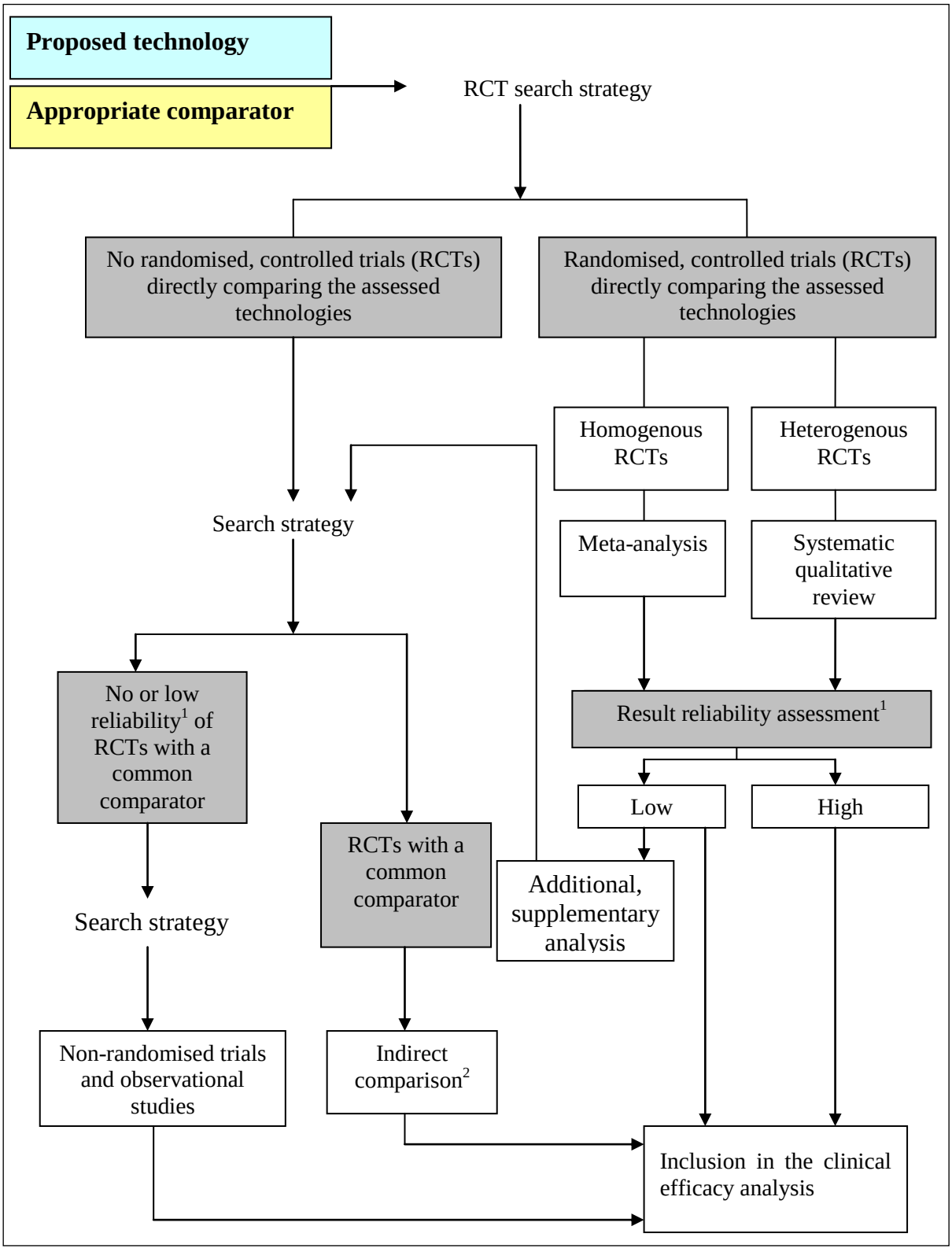
- key words and descriptors used for the search; --
- used elements of Boolean logics; --
- used filters; --
- the time span of the search. --

3.1.3.Information selection --

The process verification whether the found scientific reports are suitable for analysis goes is a stage procedure. The first stage involves a selection based on abstracts, and subsequently based on full texts of publications. The study selection should be performed based on the inclusion and exclusion criteria defined before starting the search. --

If studies of very high reliability (clinical and statistical) are available, then the efficacy analysis of the assessed technology can be limited only to these studies. --

[16] Population, Intervention, Comparison, Outcome, Study.



[1] It may refer to the entire studies and to individual beneficial and adverse effects (events, endpoints evaluated in the studies).

[2] The recommended method for performing indirect comparisons of studies with a common comparator depend on the outcome measures used – in the case of odd ratios, it is recommended to use logical regression or metaregression, and in the case of measures such as relative risks, risk difference, difference of mean values or hazard ratios, the recommended methods include adjusted indirect comparison Bucher or metaregression. In justified cases, network meta-analysis can be used.

At all stages, the process of clinical trial selection for the systematic review should be performed by at least two analysts working independently. The degree of consistency between the analysts performing the selection at the stage of full-text analysis should be specified. The method of presenting the degree of compatibility should take into account the specification of publications for which there is an inconsistency between the analysts, and a list of causes of this inconsistency, as well as the final settling method. The preferred method for inconsistency settling is to reach a consensus. Initials of the analysts performing each task should be specified 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 QUOROM guidelines[17]. The reasons for exclusion of studies at each selection stage should be stated. --

3.1.4.Information quality assessment --

The quality evaluation of the data allows to determine its reliability (internal[18] and external[19]). The assessment of data from the studies found and included in the analysis should identify several issues: --

- methodology of particular trials; --
- risks to the credibility of the trial results (methodological shortcomings) – systematic error estimation is advised (selection bias, detection bias, implementation bias, loss from study bias) which might distort results; --
- stability of health outcomes observed in particular trials; --
- degree to which the results of scientific studies may be transposed (generalized) onto the population for which the recommendation is to be issued – similarity of clinical study sample and the potential population should be assessed, as well as similarity of interventions (for example class effect in case of drugs), correlation of results observed in scientific studies with the expected results (for example the question of surrogate endpoints). --

Experimental trials on therapies should be scored on the Jadad scale[20], and diagnostic studies on the QUADAS scale[21]. Observational studies should be assessed using the NOS questionnaire[22] recommended by the Cochrane Non-Randomized Studies Methods Working

[17] Moher D, Cook DJ, Eastwood S et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999; 354(9193): 1896-1900.

[18] Internal reliability 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.

[19] The external reliability refers to the problem of generalising conclusions from a study to the target population for a given health technology (e.g. to what extent the conclusions drawn based on the evaluated sample can be referred to the population in the conditions of routine clinical practice).

[20] Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996; 17(1):1-1.

[21] Whiting P, Rutjes A, Reitsma J, Bossuyt P, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:25.

[22] Wells GA , et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. URL: http://www.lri.ca/programs/ceu/oxford.htm.

Group. A separate assessment using modified scales may also be considered[23]; however, their selection should be justified. All scales and questionnaires should be presented in the attachments to the systematic review. --

3.1.5.Presentation of included trials and data extraction --

All results related to a given clinical problem should be presented in tables. The list should contain characteristics of each study: observation period, number of study sites, list of sponsors, number and type of studies, study sample size, patient characteristics, details of intervention and the outcomes as well as other information relevant for external validity assessment. --

For each study included in the analysis, a short critical appraisal should be provided in accordance with the Cochrane Collaboration principles[24]. --

The aggregation should be done based on scientific evidence classification according to Table 1 or Table 2, and should contain an indication of the type of each included trial. --

Table 1. Classification of scientific reports related to therapy.[25]

Type of study	Subtype of study	Subtype description
Systematic review of RCTs	**IA**	Meta-analysis based on results of a systematic review of RCTs.
	IB	Systematic review of RCTs without a meta-analysis.
Experimental study	**IIA**	Properly designed randomized controlled trial (RCT).
	IIB	Properly designed pseudo-randomized controlled trial.
	IIC	Properly designed non-randomized controlled trial.
Observational study with a control group	**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).

[23] Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. Health Technol Assess 2003;7(27).

[24] Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

[25] 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.

Descriptive study	**IVA**	Case series – pretest/posttest study[26].
	IVB	Case series – posttest study[27].
	IVC	Other study of a group of patients.
	IVD	Case study.
Experts' opinions	**V**	Experts' opinions based on clinical experience, descriptive studies and reports of panels of experts.

The assumed approach to hypothesis testing (*superiority*, *non-inferiority*) should be defined for experimental research.

Table 2. Classification of scientific reports related to diagnostics.[28]

Type of study	Description
D I	Systematic review of D II level trials.
D II	Clinical trial assessing accuracy of a diagnostic method where blinding is used and the assessed method is compared to a referential test (gold standard) in a group of patients with the same clinical condition included subsequently into the trial.
D III-1	Trials assessing the accuracy of a diagnostic method where blinding is used and the assessed method is compared to a referential test (gold standard) in a group of patients with the same clinical condition included into the trial in a non-subsequent way.
D III-2	Trials comparing the assessed diagnostic method with a referential test where the trials do not meet the requirements of D II and D III-1 levels.
D III-3	Diagnostic case-control trials.
D IV	Trials describing diagnostic results without using a referential test.

In the final assessment mainly the trials from the highest available level of evidence are used. Systematic reviews (with or without a meta-analysis) are at the top of the hierarchy of credibility. They are relevant to a clinical problem in terms of the examined outcome, population and a comparator, provided they are up-to-date and conducted in line with the accepted guidelines. If data from controlled clinical trials are limited to a narrow population or a short time horizon, they should be completed by observational studies of good quality. The value of evidence at each stage depends mostly on the methodological quality of the trials and the fulfilment of health technology assessment requirements. --

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

[26] A pretest/posttest study – a descriptive study with data collection before and after the assessed intervention.

[27] A posttest study – a descriptive study with data collection only after the assessed intervention.

[28] According to Medical Services Advisory Committee. Guidelines for the assessment of diagnostic technologies. August 2005.

- types of information retrieved from publications; --
- number of persons extracting data and their identification; --
- form for the extracted data. --

A quantitative compilation of efficacy-related data (positive results) and safety-related data (noxiousness, i.e. negative results) of the assessed technology should be done by entering them into a uniform table. The compilation should take into consideration the previous assessment of the source credibility and the data quality. The compilation should comprise clinically significant endpoints (positive and negative). The listing of results should be prepared on the basis of all trials found for the purpose of the systematic review, which cover the technology assessed or the selected clinical problem. --

3.2. Data synthesis

The preparation of the synthesis of results is aimed at gaining information, and at defining the level of estimation uncertainty. It covers a systematic review of literature (with or without a meta-analysis) and a summary. --

Meta-analysis is an advisable method of processing the results. If a meta-analysis is not possible, then the analysis may be limited to a qualitative review. In this case, individual examinations are critically assessed and their results presented in tables. Conclusions are drawn from the result synthesis. --

3.2.1. Qualitative synthesis --

It is recommended to present or estimate the effects for each analysed endpoint of each trial, taking into account the confidence intervals and/or statistical significance. --

The results obtained for each endpoint of each trial should be discussed separately. In case of heterogeneity of obtained results it is necessary to track and discuss the differences. --

The listing should be presented in a form allowing comparison of particular trials in respect to each particular endpoint. This form of presentation allows to identify potential similarities or differences between the included trials and between the compared technologies. --

Numerical data should be presented in a table containing: --

- sample size for each intervention, --
- the result for each endpoint, in the form of central measures and the measures of scatter for continuous variables, and the numbers and percentages of patients who reached an endpoint for dual variables, --
- differences between average results of compared interventions for each endpoint of particular trials, with the confidence intervals and/or statistical relevance for continuous parameters, and relative and absolute parameters with confidence intervals and/or statistical significance for dual parameters. --

3.2.2.Meta-analysis (quantitative synthesis) --

The level and source 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[29]. --

In case of doubts concerning the quality of trials or relevance of particular trials to the analysed matter, 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.Indirect comparison

In case of lack of head to head trials comparing directly an assessed and an alternative technology, it is recommended to conduct an indirect comparison. --

Availability of reliable clinical trials where each of the examined technologies was compared to a third one (placebo or an active intervention) constitutes a necessary requirement for an indirect comparison[30]. Identification of trials to be used in the indirect comparison should be based on a systematic review. A thorough analysis of methodology is advised as well as an analysis of differences in the application of the third intervention, of the population receiving it and of the examined endpoints. The differences should be presented as a table-form listing. If the differences are judged as too big, the compilation of results should be stopped, as the reliability of such a comparison would be low. 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. --

Indirect comparisons can be performed and presented independently of direct comparisons. In the case of mixed comparisons involving both direct and indirect comparisons, the results of direct comparisons alone should be presented separately and independently from the results of the mixed comparison. --

3.3. Safety assessment --

3.3.1.Purpose: --

The safety analysis is performed to assess the risk of using a health technology. Adverse effects and medical events should be considered, even those that occur during long-term follow-up and are rare. The results of safety analysis should be taken into account in the health technology assessment. --

HTA reports can use the data available to the regulatory agencies (e.g. EMEA, FDA, URPL, WHO – Uppsala Monitoring Centre). --

[29] Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

[30] I.e. the research, which compares directly both the assessed intervention to a third intervention, and the comparator research to a third intervention.

3.3.2.Scope of safety analysis --

The scope of safety analysis should be adapted to the decision problem and the specificity of the health technology assessed. Other scope should be adopted when assessing drugs, medical devices, medical and surgical procedures, and other in the case of diagnostic test assessment. In some cases, the scope can be similar to that used in efficacy assessment; however, it often needs to be extended. Safety assessment should be extended in particular in the case of innovative technologies, drugs with an innovative mechanism of action or adverse events, generating high costs. --

Safety assessment data from RCTs previously included in the efficacy assessment are often not sufficient due to too short follow-up period or too few patients included in these trials. To assess various adverse effects, both identified in RCTs and other, a possibly widest systematic review should be performed (both in terms of search strategy and types of studies included). This type of review may be very labour-consuming and may require, among other things, case series analysis or data from patient registers. It also includes data from adverse event reports, both collected by the pharmaceutical companies in the form of Periodic Safety Update Reports (PSUR) and regulatory agencies (e.g. EMEA, FDA, URPL, WHO Uppsala Monitoring Centre). It is allowed to narrow the safety assessment by: --

1) Identification of the possible adverse effects based on: --

- EPAR (EMEA), in particular SPC, --
- FDA analyses. --

2) Limitation of the scope of studies in the safety assessment if the basis for review are RCTs included in the clinical efficacy analysis, if they evaluate all adverse effects selected for assessment, the follow-up period was long enough for them to occur and the number of subjects was sufficient, or the RCTs were designed for evaluation of adverse effects (i.e. adverse effects are a clinically significant endpoint). --

It is indicated to extend the criteria of clinical trial inclusion in the review to non-randomised trials, and if not available – observational studies, if the identified experimental trials are not sufficient to assess the previously identified, and in particular rare adverse events, occurring during long-term follow-up (i.e. when the requirements in item 2) are not met). --

In each of the above cases, the extension of the inclusion criteria to studies performed in the entire population of patients in whom a given technology can be used should be considered. Also the group of patients who do not have the primary indication for efficacy assessment (e.g. off-label indications). --

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

The adopted scope of analysis should be justified. --

3.4. Presentation of results --

The results of clinical trials should be presented by means of relative parameters[31] and absolute parameters[32]. --

The results of meta-analysis should be presented in numerical form, mapped in a forest plot graph. The graph should allow accessing particular data used for calculating a cumulated result of the meta-analysis. For each meta-analysis the results of heterogeneity test should be presented as well as the types of statistical modelling used for aggregation of clinical trial results. The description of conducted meta-analysis should follow the QUOROM guidelines[33]. Data for clinical effectiveness analysis and for efficacy analysis should be presented separately. --

The results for each efficacy and safety endpoint should be presented in accordance with the GRADE proposal[34]. --

3.5. Limitations and discussion --

The limitations and discussion should be clearly separated. --

3.5.1. Limitations --

In the part concerning limitations, the characteristics of the analysis and the available initial data, as well as the scope of analysis in the context of the specific decision problem, should be discussed. All phenomena that significantly affect the degree of uncertainty of the obtained results and the conclusions should be described. In this part it should be pointed out which clinical trial type (*superiority* or *non-inferiority*) was the basis for the analysis and what are the related limitations; in particular, how did this affect the method selection for the pharmacoeconomic analysis. --

3.5.2. 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 report. 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. Results of other analyses of the same problem should also be presented and used as a background for discussing the obtained results, justifying possible differences. --

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

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[31] Relative risk (RR), relative risk reduction (RRR), odds ratio (OR).

[32] Absolute risk reduction (ARR); number needed to treat (NNT).

[33] Moher D, Cook DJ, Eastwood S et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999; 354:1896–900.

[34] Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group. Grading quality of evidence and strength of recommendations. British Medical Journal 2004;328:1490-1494.

3.6. Final conclusions and summary --

The basic conclusions drawn from the clinical effectiveness analysis should be synthesized. The main element should be the presentation of conclusions based on analysis summary. Comparison of effectiveness and efficacy 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. --

A summary should be provided at the beginning of the report. --

4. Economic analysis

Economic analysis[35] consists in comparing an assessed health technology with an adequate comparator in terms of costs and health consequences. --

4.1. Analytical strategy --

Three strategies of conducting economic analysis of health technology are foreseen: --

1) There is a relevant economic analysis examining a decision-related problem in question. It is possible to use the model (e.g. prepared in another country but relevant for the Polish practice) on which the analysis was based as well as clinical data. The analytical task consists in taking into account Polish data concerning the use of resources and costs. --
2) There is a recent and valid cost-effectiveness analysis (systematic review) made abroad or in Poland. The analytical task consists in performing an economic analysis based on the data from this analysis or on modelling using those data. --
3) Conducting both, cost-effectiveness analysis and the economic analysis *de novo*. After having defined the cost effectiveness by means of the systematic review, clinical efficacy, the gathered data are used in the economical analysis. --

4.2. Perspective --

First line perspective of the analysis is the one of the entity financing health care services (public payer, patient, other payers). Another analysis adopting a social perspective, specifying the indirect costs, may be justified when: --

- not only do health effects of a particular technology concern the patient, but they also affect other members of the society to a considerable extent (eg. family, guardians); --
- the optimal allocation of resources on a social level is a desired effect of the analysis. -

The social perspective is advised when the HTA report author considers it significant in the process of specifying the recommendations for those taking the decision on technology financing. --

4.3. Time horizon

Time horizon of the economic analysis should be long enough 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 results. --

In the case of heath technologies in which the results occur during the whole life of the patient, a time horizon extending to patient's death is appropriate; it is particularly justified if two compared technologies have a different impact of mortality. To meet this requirement, it

[35] Also referred to as cost-effectiveness analysis. [NO REF.]

may be necessary to extrapolate the results beyond the time horizon of clinical trials which provide primary data. In this case, the analysis should comprise primary data and the modelling; and the short- and long-term results should be presented separately. If this time horizon is not adopted, reasons should be provided. --

4.4. Analytical technique

Economic analysis of a health technology is usually a comparative assessment of the use of resources necessary for obtaining a clinical effect. In this assessment various techniques (types of analysis) may be used: --

- cost-effectiveness analysis[36], --
- cost-utility analysis[37], --
- cost-minimisation analysis, --
- cost-consequences analysis, --
- cost-benefit analysis. --

Analytical method is always selected according to heath effects identified and measured and the choice should always be justified. --

A standard economic analysis as part of a HTA report should be composed of: --

- cost-consequences analysis, --
- cost-effectiveness analysis or cost-utility analysis; if there are no differences in clinical effectiveness between health technologies compared the cost-effectiveness analysis may be replaced with cost minimisation analysis. --

It is not recommended to use cost-benefit analysis as the basic method. --

The choice of one method does not exclude using another one as an additional analysis, if the author finds it justified. --

4.4.1. Cost-consequences analysis --

The listing of costs and consequences means the presentation of mean values with the measures of scatter in the form of tables for: --

- health consequences; --
- resource use; --
- unit costs. --

The source of the presented data must be indicated in the technology comparison process. --

[36] Please remember that clinical and not economic effectiveness is analysed.

[37] Please remember that health-related and not economic utility of an intervention is analysed.

4.4.2.Cost-effectiveness analysis --

Cost-effectiveness analysis consists in comparing costs and health results of alternative health technologies; the results have to be expressed in the same natural units (such as number of adverse occurrences avoided, period free from symptoms of disease, years of life gained). Its goal is to define what difference in costs of compared technologies corresponds to a difference in health effect. The incremental cost-effectiveness ratio[38] constitutes a ratio of cost difference to health effect difference. --

4.4.3.Cost-utility analysis --

The cost-utility analysis should be used when:

- the health-related quality of life is one of the significant outcomes of the analysed technologies (health programs), --
- the compared technologies give very different clinical effects and it is necessary to find a common denominator enabling their comparison. --

The state of health utility values can be sought based on data from published research. It is admissible to perform the quality of life measurement in the patient population or the preference measurement in the general population. It is a requirement to maintain the standards accepted in the literature and to present a detailed description of the methods used.--

If published data are used, the variation of the utility values in each study should be emphasised. A utility set which to the largest extent will correspond to the target characteristics of the economic analysis population should be selected. The choice of the utility set should be justified and the methods used by the study authors should be presented. A review of the *Cost-Effectiveness Analysis Registry* (https://research.tufts-nemc.org/cear/default.aspx) should be made for other utility values of the analysed states of health, and the found extreme values should be used in the sensitivity analysis. --

The preference measurement for the purposes of utility assessment is possible by using direct or indirect preference measuring methods. It is recommended to use indirect methods for preferences measurement – validated questionnaires in Polish. While measuring preferences with the WuroQol (EQ-5D) questionnaire, it is advised to use the Polish utility standard set obtained by means of the "time trade-off" method[39]. --

The use of direct tools of preference measurement is not excluded if needed for the subject. Performing a utility measurement requires a rationale for tool selection, a detailed characterisation of the population and a description of the methods used. --

The aim is to ensure that the utility weights adopted in the analysis, based on literature or the author's studies, are obtained using a single measurement method. --

[38] Incremental cost-effectiveness ratio = ICER.

[39] Golicki D, Jakubczyk M, Niewada M, Wrona W, Busschbach JJ. Valuing EQ-5D with time trade-off for the Polish population. Working Paper presented during 25th EuroQol Plenary Meeting, Baveno on Lake Maggiore, Italy, 11-13th September 2008. Discussant: Craig B.

4.4.4. Cost-minimisation analysis --

Cost minimization analysis may be applied if valid scientific evidence confirms that health effects (the effectiveness of the compared health programs) are equal. In such a case, the analysis consists in comparing the costs only. --

4.5. Modelling --

The situations in which modelling is recommended include: --

- the need to extrapolate the results beyond the time horizon of the clinical trials included in the clinical analysis, --
- the need to transpose the experimental effectiveness measured (i.e. indirect results expressed on a disease-specific scale) to final utility results (e.g. life-years gained, gained QALY), --
- the need to evaluate the results in real practice when only the results of experimental tests are available and the results obtained in one country can be transposed into another one, --
- indirect comparative synthesis if relevant direct trials are missing, --
- providing estimates if direct measurements are missing, --
- preliminary assessment and scheduling of trials, --
- early stage of development of a new technology if comprehensive trials are missing. --

If modelling is necessary, the model structure should be presented. Assumptions of the model should be clear, well justified and tested in a sensitivity analysis. If data in the model are extrapolated over time horizon of the primary trials, the following scenarios should be analyzed: optimistic, pessimistic and neutral. --

Table 3. Principles of good practice of modelling and guidelines for critical appraisal of models.

Subject of assessment	*Principles of good practice*	*Questions for critical appraisal*
Model structure		
States of health	Structure of the model should be as simple as possible and, at the same time, it has to correspond to the decision-related problem and compliant to generally accepted knowledge on the course of the modelled disease, as well as cause-effect relation between the variables. Lack of data does not justify elimination of states or simplification of the model.	Are the decision-related problem, the context and the perspective clearly defined? Are important details of the course of the modelled disease described? Are the model assumptions described and justified? Is the selection of the model states justified? If so, is it compliant to the knowledge on the disease? Are any important health states missing?
Comparators	The model should take into account comparators defined in these guidelines, especially those used in real-life practice.	Were comparators identified? Do they cover all the scope of options justified and possible to be made in the model?
Time horizon	Time horizon of the model should be sufficient to show durable differences in costs and results of the compared strategies.	Was the time horizon of the trial defined? If so, is it appropriate to the analyzed situation?
Cycle length (if Markov model is applied)	A cycle should be the shortest time span in which changes of examined parameters are expected; it should correspond to characteristics of the disease process.	Was the length of cycles defined in the model? Was the cycle length justified? If so, does it correspond to the disease process?
Input data for the model		
Identification of input data	The model should take advantage of the best data available. A systematic review of the relevant literature should be carried out to obtain the crucial input data for the model. Proof of such review or a justification of its absence should be presented. If experts' opinions are the source of input data, the methods of obtaining the data should be described.	Are the data sources presented in the model? Have the proper methods of data source searching been implemented? Has the range of parameter variability been determined? Are there premises, suggesting the data have been used selectively? Is the manner of obtaining data provided (e.g. criteria for selecting experts, their number, the method of obtaining information) if values of certain parameters have been assessed on the basis of experts' opinions?
Data modelling	Data modelling should be carried out on the basis of generally accepted biostatistical and epidemiological methods.	Have the methods used for data modelling been described? Have the generally accepted criteria of biostatistical and epidemiological methods been complied with?

Subject of assessment	*Principles of good practice*	*Questions for critical appraisal*
Inclusion of data into the model	Measurement units, time intervals and population characteristics must be mutually compatible in the entire model. Both deterministic and probabilistic simulations are acceptable. The half-cycle correction should be implemented to adjust time-dependent assessment.	Are the measurement units, time intervals and population characteristics mutually compatible in the model? Has the half-cycle correction been implemented?
Sensitivity analysis		
Sensitivity analysis	Each model must include the sensitivity analysis of the crucial parameters and a justification of the analyzed range of parameter variability.	Have sensitivity analyses been carried out for all crucial parameters? Has the scope of variability of the parameters tested in sensitivity analysis been justified?
Model validation		
Internal validation	In order to identify errors related to data introduction and the model structure, the model should be tested systematically; for instance, it should be checked, whether expected results are obtained in the case zero or extreme input values are used; the code of the software should be analysed to identify syntactic errors or repeatability 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 a report on internal validation been provided?
Convergence validation	The model should be compared to other models focused on the same problem; in case of varying results, the reasons for such differences should be identified.	Have any other models of the same problem been identified? If so, have the results of different been compared, and in case of varying results, have the reasons for such differences been identified?
External validation	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).	Has any research been identified, the results of which could be compared to the model results? Have the results been compared? Have any differences been identified and their reasons explained?

4.6. Health effects assessment --

Economic analysis is aimed at assessing the actual consequences of the implementation of a given technology real daily clinical practice. Measurements should focus on effectiveness (i.e. the results obtained in real conditions) rather than efficacy (the results obtained in controlled clinical trials). Data for effectiveness analysis and for efficacy analysis should be presented and assessed separately. It is infrequent to obtain in daily practice such results which can be obtained in the optimized conditions of a clinical trial (clinical experiment). Thus, the results of effectiveness obtained from observational studies are better than experimental results assessed in a systematic review, which should be treated with utmost care. Arguments confirming their reliability should be provided in the case they are used for economic analysis. --

Sometimes, especially in the case of new technologies, the data on its efficacy are the only data available. Apart from the standard analysis based on efficacy, modelling and sensitivity analysis should be carried out to extrapolate the data onto the conditions of actual practice and to examine the impact of various interrelations between effectiveness and efficacy on the final conclusions of an analysis. It should also be emphasised that effectiveness is in the great majority of cases lower than efficacy – the adoption of different assumptions in the modelling requires a solid scientific basis or must result from a consistent logical reasoning. --

4.7. Cost assessment --

The economic analysis of medical technologies should comprise only the costs corresponding to consumable resources used during the application of a given technology in daily clinical practice. The perspective and time horizon of cost examination must be identical to the time horizon and the perspective of assessing clinical results. The choice of a perspective and a time horizon are strictly correlated to the following stages, where the categories of examined costs are identified and the method of their measurement and assessment is defined. --

4.7.1. Cost categories --

The analysis should differentiate the following: --

1. direct medical costs, --
2. direct non-medical costs, --
3. indirect costs. --

All the above-listed cost categories are accounted for in the case of the social perspective. The results accounting for the direct and indirect costs and the results accounting exclusively for the costs incurred by the public payer in the health care system should be presented separately.

4.7.2. Identification of used resources

Identification of used resources involves the need to determine, which resources are appropriate for an examined problem (illness, intervention). It is recommended first to describe a given technology in detail, to identify the resources to be accounted for in the analysis. Then it is proposed to decide which elements should be measured and assessed separately. Sensitivity analysis should be carried out, in order to identify the resources with the highest impact on the total and incremental cost. The sensitivity analysis is also used to identify the costs, which should be measured and assessed separately in detail (by the micro-costing method[40], and the costs, which can be sufficiently analysed by the gross-costing method[41]. --

[40] The micro-costing method is based on detailed data on all resources used in a given intervention and is often associated with the collection of original data.

[41] The gross-costing method is based on the more aggregated data about the used resources. The characteristics of gross-costing include: simplicity, practicality and (intended) resistance to details specific for site or patient characteristics.

4.7.3.Measurement of used resources --

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.

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

- research perspective, --
- share of a given component in the total or incremental cost, --
- data availability, --
- equilibrium between internal and external reliability. --

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 trial protocol. Secondary data, e.g. from national registers, are characterized by a generally high external reliability. However, they may turn out to be incomplete, as such databases do not cover all types of resources. --

Both the micro-costing method and the gross-costing method, differing in the precision of used resources assessment, can be used to measure used resources. Both methods can also be used in a single analysis. The higher the impact of a given cost component on the total or incremental cost, the higher should be the precision of its assessment. Thus, the micro-costing method is better suited to the interventions and events occurring at the present moment. The method of gross-costing is acceptable, when the implementation of the more accurate microcosting method shall have no significant impact on the analysis results. Precision is usually of less importance in the calculations of costs to be incurred in the future. --

4.7.4.Determination of unit costs --

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

- use the list of standard costs, --
- use the formerly published research, --
- use local scales of charges, --
- direct calculation. --

The choice of the monetary method of assessing units of used resources should be conditioned by the choice of the method of measuring the used resources[42]. --

When using a list of standard costs (if it was published) 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 particularly recommended to use local scales of charges, when an examined intervention is available only in a health care institution of a certain type. The list of charges covers a large

[42] 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.

number of procedures and services; the data are available to researchers without additional amount of labour or costs. 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 profitability analyses carried out from the perspective of a public payer. In other cases, the analyst should determine the relation between charges and the actual costs of examined interventions. --

The direct calculation of unit costs is the most labour-intensive method. It is used in the assessment of units of resources, which have special impact on the total or incremental cost, and in the cases, when no data from other sources are available. --

When deciding to carry out the direct calculation, the researcher should select: --

- a specific environment, --
- a calculation method (either "top-to-bottom" or "bottom-to-top"), --
- a method of cost allocation (e.g. costs from other hospital wards, buildings, the cost of general purpose equipment and fixed costs). --

As unit costs may vary with different service providers, the cost calculation is highly influenced by the choice of a centre. It is recommended to collect data on unit costs from a sufficient number of centres which provide a given type of services with varying level of referentiality (or from all the centres that provide a given type of service). A sensitivity analyses should also be performed based on the identified cost differences. Cost presentation should include both the central tendency measure and the measure of scatter for total results and for particular reference levels. --

When calculating unit costs by the "top-to-bottom" method, the financial and administrative data of a service provider are used as the primary data. The method can be implemented in the case when services of a given ward are characterized by a high degree of uniformity. Then, it can take advantage of the data obtained directly from the financial department, concerning the cost of personnel, medical materials and the annual number of man-days at a given ward, in order to calculate the cost of a single man-day. The "bottom-to-top" method is more suitable if the services at a given ward are heterogeneous. In this case, the unit cost of a service is determined on the basis of the measurement of the actual consumption of materials and equipment, and of the work time needed for the personnel to provide a given procedure to a single patient. The disadvantage of the "bottom-to-top" method consists in the fact that it is time-consuming and a researcher is not always able to carry out direct and detailed measurements. In practice, a combination of both methods is implemented. --

The allocation of costs from other hospital wards, buildings and the cost of general purpose equipment and fixed costs should be realized by the direct allocation method[43]. --

It is recommended to use standard values for the calculation of certain unit costs[44]. Their use may reduce the differences in the assessment of these costs. --

The loss of productivity caused by illness or premature death is recommended to be assessed by means of the human capital method (e.g. on the basis of average wages)[45]. --

[43] The method consists in identifying the wards providing direct services to patients (such as a surgery ward) and auxiliary wards (such as the kitchen, the financial ward), in ascribing the costs of auxiliary wards first to the wards providing direct services, and then in allocating costs between the products of these wards.

[44] Examples of standard values: the number of work days per year and the average annual wages, the annual number of work hours of persons employed in this health care sector and their annual wages, the average distance from the hospital (used to calculate the cost of transport), the rate of discount, the inflation rate.

4.8. Discounting

The assumed rate of discount is equal to: --

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

4.9. Data presentation --

All data should be presented with scatter measures, in a clear manner, in table form, and identified by the data source. The input variable distribution should be defined and justified in probabilistic analyses. The methods 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 clinical results and, separately, total costs of compared technologies, --
- incremental cost-effectiveness ratio (in the case of domination or extended domination). --

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

The results of the analysis of particular population sub-groups should also be presented if such analysis has been carried out. It should indicate whether and how much can the examined technology be more cost-effective in the sub-groups than in the entire analyzed population. --

4.11. Sensitivity analysis and result uncertainty assessment --

The sensitivity analysis — tackling the problem of uncertainty of the results of clinical and economic assessments — is an indispensable element of the presentation of economic analysis results. Result uncertainty is due to absence of certain data, insufficient precision in value assessment, and to methodology-related controversies. The sensitivity analysis allows to tackle the problem of generalizing analysis results, i.e. it examines whether and to what extent the results based on measurements in a given sample population of patients and/or in a specific context are true for the entire population and/or in other contexts. --

The sensitivity analysis should address first of all those input data for which the scatter measures and estimation uncertainty are the highest. --

The sensitivity analysis is indispensable due to the uncertainty of the results of the economic analysis. The simple sensitivity analysis assesses the impact of a change in the value of one

[45] According to www.aodgp.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pubs-pharmpac-glossary-glossh.htm.

variable[46] or several variables[47] on the final conclusion. The threshold analysis requires the critical variable values, leading to a change in the final conclusion, to be calculated. The extreme values analysis assesses the impact of the situation, when one or several variables assume minimum or maximum values (the analysis of the most pessimistic or the most optimistic scenarios). The probabilistic sensitivity analysis accounts for the probability of the appearance of particular values from the scope of variability of a given parameter. --

It is necessary to carry out at least a simple one-way and multi-way sensitivity analysis. --

The sensitivity analysis should: --

- identify uncertain parameters (subject to assessment error), --
- define the scope of variability of uncertain parameters, --
- calculate the analysis results, assuming a determined variability of uncertain parameters. --

The scope of parameter variability should be determined on the basis of a review of publications, experts' opinions or on the basis of confidence intervals around the average value. One can also assume a probable scope of parameter variability. The variable distribution implemented in the assessment of uncertainty of input parameters should be defined and justified in probabilistic analyses. --

It is recommended to present sensitivity analysis results in table and graphical form. --

4.11.1. Result uncertainty assessment --

The uncertainty of the incremental coefficient for cost-effectiveness or cost-utility should be estimated using the appropriate statistical methods. --
A probabilistic analysis can be performed using the analytical methods or using the Monte Carlo method. The distribution of variables which are the model parameters should be defined and justified. If the effect of some uncertainty parameters on the result is ignored, it should be justified. --
The distribution of the possible results of the model, which is the result of the probabilistic analysis, should be presented graphically in the cost-effectiveness, cost-utility coordinate system. Based on this distribution, if possible, the mean and confidence intervals ICER (e.g. 95%) should be determined or it should be presented in another way, e.g. using an acceptability curve or incremental *Net Monetary Benefit* (NMB)[48]. --
The selection of methods should be described and justified, and their assumptions should be tested[49]. --

[46] One-way sensitivity analysis.

[47] Multi-way sensitivity analysis.

[48] Net Monetary Benefit (NMB) is an additional effect obtained owing to the use of the new therapy, expressed in monetary units, minus the additional cost associated with the new therapy.

(1) Stinnett AA, Mullahy J (1998) Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 18:S68–S80

[49] (1) O'Brien BJ. Briggs AH , 2002], Analysis of uncertainty in health care cost-effectiveness studies: An introduction to statistical issues and methods. Statistical Methods in Medical Research. Vol 11(6) (pp 455-468).
(2) Briggs AH, Mooney CZ, Wonderling DE. 1999, Constructing confidence intervals for cost effectiveness ratios: an evaluation of parametric and non-parametric techniques using Monte Carlo simulation. Statistics in Medicine; 18:3245-62.

It is recommended to present the results of the uncertainty analysis in the form of appropriate charts and diagrams.

4.11.2. Areas of possible divergences between the clinical and the economic parts --

4.11.3. Health outcome presentation method --

Sometimes, in the studies included in the clinical part based on the predefined inclusion criteria, no solid endpoints (e.g. cerebral stroke risk) are assessed but e.g. blood pressure reduction. In these cases, in the economic part it is recommended – taking into account that the analyses should refer to the measures common for all medical technologies such as the quality of life or survival – to convert the data regarding the surrogates to the probabilities of clinically significant endpoints (provided a reliable conversion method exists). --

The studies concerning efficacy have the highest internal reliability. Therefore, these reports are usually included in the systematic review. It should be emphasised that actual efficacy is in most cases lower than experimental efficacy. The adoption of different assumptions in the economic analysis requires a rationale based on scientific evidence of consistent logical reasoning. In the case of the economic part of the report, a significant importance is attributed to the practical effectiveness studies (post-marketing studies, phase IV, patient registers). Therefore, to minimise the divergences between the analyses, it is recommended to perform a systematic review also for these studies in the clinical part. However, attention should be paid to keep the review of studies of the highest reliability as the crucial part of the analysis. -

4.11.4. Data presentation in time --

It happens that in the studies included in the clinical part based on the predefined inclusion criteria the observation period is short (which is often the case for the studies of the highest internal reliability), and extrapolation from a short horizon of clinical trials is unreliable or may be associated with a significant error. In these cases, it is justified to perform an additional systematic review of observational studies with a longer time horizon in the clinical part of the report, and in the economic part, a discussion should be included regarding the limitations associated with the use of the two methods, with a rationale for selecting one of them. --

4.11.5. Scope of data used for result presentation --

If the economic analysis consists in the adaptation of an existing model, it should be noted that the data on which the model is based may be unavailable in the systematic review. To ensure the possibly highest reliability, it is therefore recommended to perform a systematic data search for the crucial parameters of the model. --

4.12. Limitations and discussion --

The limitations and discussion should be clearly separated. --

4.12.1.Limitations

In the part concerning limitations, all characteristics of the analysis and the available initial data, as well as the scope of analysis in the context of the specific decision problem, should be discussed. All phenomena that significantly affect the degree of uncertainty of the obtained results and the conclusions should be described. --

4.12.2.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 report. 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. Results of other analyses of the same problem should also be presented and used as a background for discussing the obtained results, justifying possible differences. --

4.13. Final conclusions and summary --

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

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. In the economic analysis, the results should refer to the profitability limits and the significance of differences in the profitability of the compared options.--

5. Analysis of impact on health care system --

The analysis of the impact of a decision to finance the examined medical technology or not assesses all the principal, possible and probable consequences of the decision for the health care system in Poland. --

The analysis of impact on the health care system covers the budget impact analysis and the assessment of organizational consequences for the heath care system, and possibly the assessment of possible ethical and social implications. --

5.1. Budget impact analysis --

The budget impact analysis determines the financial consequences of the introduction of the assessed health technology in the Polish health care system. --

If there are no precise data for Poland, the most important input data should undergo multidimensional assessment. --

5.1.1. Population --

In the budget impact analysis, the examined population is constituted by all patients, who can be subjected to a procedure realized by means of a given medical technology. The examined population is defined on the basis of the indications registered for a given technology. Local restrictions concerning the possibility of implementing a medical technology outside the scope of registered indications should be respected, and the induced demand (e.g. a certain percentage of patients, hitherto "untreated", shall use the technology, as it is more efficient and characterized by a better safety profile), as well as the degree of implementation of the new technology in the reviewed time and the change in the degree of usage of the hitherto implemented methods, should be considered. In contrast to the clinical efficacy and effectiveness and the economic analysis, where the examined population is closed (a cohort of patients is defined at the start and all the included patients remain in the examined population within a given 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 using a closed population. --

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

- identify the prevalence of a given condition, --
- assess the number of persons, who would be advised to take advantage of the technology, --
- assess the market position of the technology, as advised on the basis of particular indications, and do so on the basis of the estimation of: --
    - 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 expected abandonment of currently used technologies in favour of the examined new technology and the scope of implementation of the current technologies and of the new one. --

The technology impact should be assessed through the construction of alternative scenarios: the most probable, the optimistic and the pessimistic one. The scenarios should be constructed on the basis of the factors that can have the greatest impact on technology implementation and of various assessment of the condition prevalence. The dissemination of the new technology, the replacement of current technologies with the new one and the expected degree of new technology over-implementation should be considered. The impact of the legal regulations in force should also be taken into account[50]. --

5.1.2. Perspective --

The budget impact analysis should be carried out from the perspective of a public payer, who finances health care services. --

5.1.3. Time horizon --

The budget impact analysis involves an assessment of impact of a given medical technology on the annual health care budget during the next years after the introduction of the new technology. Usually the time period sufficient for the market to reach the state of equilibrium is used, or at least 2 years since the date when a given medical technology was started to be financed from public means. --

5.1.4. Compared scenarios --

The budget impact analysis compares scenarios defined rather by a set of interventions than by specific interventions. The "existing scenario" and a "new scenario" are taken into consideration. The "existing scenario" is a set of interventions, currently used in a given population. The "new scenario" is a scenario of expected developments after the introduction of the new technology which may be added to the existing ones, or else it may replace all or some of them. The analysis should describe and justify the assumptions concerning the "existing scenario" and the expected changes, related to the accessibility of the new medical technology. --

5.1.5. Parameters taken into consideration --

The parameters for the budget impact assessment comprise: --

1. the size and characteristics of the examined population, --
2. the scenario presenting the "existing practice", --
3. the scenario of expected developments after the introduction of the new technology (the "new scenario"), --
4. the costs of the above-mentioned scenarios. --

[50] Such as the regulations concerning reimbursement of therapeutic products.

The type of relevant data varies, depending on the considered parameters. Data sources are highly differentiated and cover: published and unpublished epidemiological research, national statistical data, market research, registers, various databases, experts' opinions. The following aspects should be presented: advantages and disadvantages of the above-mentioned data sources, criteria for the selection of data sources, methods of collecting and analysing primary data. --

5.1.6. Budget outlays and receipts --

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

The budget impact analysis should focus especially 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, as this can have practical implications for planning the organization of the health care system. --

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, to prepare new clinical guidelines or to change the diagnostic principles, and to describe the related costs in a specific time period. --

The actually implemented medical technologies should be identified. --

A separate assessment for particular types of outlays should be prepared[51]. --

Based on the determination of both the effect on the population and the results of cost-effectiveness analysis, the incremental net changes in public expenditures as regards health care as a result of the decision concerning the appraised technology should be estimated. --

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

- the outlays related to the new technology, --
- the cost of additional outlays in the health care system, related to the implementation of the new technology, --
- the reduction of outlays related to the reduced use of the current technologies, in case the new technology takes over, --
- the reduction of costs related to the savings in the domain of other services (e.g. reduction of the number of inpatients), --
- the analysis of the possibility of actual reduction of outlays in the domains of expected savings. --

5.1.7. Discounting

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

[51] E.g. drug reimbursement, hospital treatment expenditures, specialist outpatient care expenditures.

5.1.8. Presentation of results --

For each year within the examined time horizon, both the total and incremental impact on the budget should be presented. Consumption of resources and outlays should be presented in separate tables to show the changes in particular years within the time horizon. The impact on health care results in particular years can be presented in an analogous manner. --

5.2. Impact on the organisation providing health care services --

If a positive decision about the appraised technology could cause significant consequences for public expenditures in sectors other than health care, then such effect should be analysed separately. In particular, it refers to expenses for sickness benefits and pensions, as well as other expenses incurred as part of the public social insurance. 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, to prepare new clinical guidelines or to change the diagnostic principles, and to describe the related costs. --

Sometimes the quality of results obtained by means of the technology in question depends on the experience and skill of the providers and the centre. In this case, particular emphasis should be placed on the need to ensure high quality of services by the health care organizers. -

5.3. Ethical and social aspects --

It should also be considered, whether the positive decision concerning the technology in question shall have an impact on the costs or results concerning other persons, than those taking advantage of the technology (external impact). --

The following issues should be taken into consideration: --

- which groups of patients, if any, may be favoured as a result of the adopted assumptions of 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, a small benefit, or is the benefit to be of general character, --
- does the technology constitute a response to the hitherto unfulfilled needs of the group of the socially handicapped, --
- does the technology constitute a response the group of persons with the highest health care needs, who are not offered any available treatment method at the moment. --

It should be considered, whether a positive decision concerning the assessed technology can lead to 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 stigmatization, --
- can it lead to anxiety, --

- can it lead to moral dilemmas, --
- possible sex- or family-related problems. --

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

- is in contradiction with the legal regulation currently in force, --
- results in a need to introduce changes into the law/regulations, --
- has an impact on the rights of a patient or on human rights. --

It should be determined, whether the procedure of technology implementation imposes special requirements, such as: --

- the need to inform a patient in detail or to obtain his/her consent, --
- the need to provide a patient with convenient environment, --
- the need to allow for individual preferences, the need for a patient to participate actively in making a decision on the method of treatment. --

Summing up the social and ethical impact, as well as the organizational impact, one may prepare a SWOT analysis of financing the technology in question from public means, as compared to the existing circumstances[52]. In this section, it is also advisable to identify potential followers and opponents of the relevant decision, while assessing the expected degree of their involvement in supporting or criticising the decision. --

5.4. Final conclusions and summary --

The basic conclusions drawn from the analysis of impact on the health care system should be synthesized. The report should contain a summary presenting the analysis of impact on the health care system. --

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I, Jolanta Szadkowska, sworn translator of English at the Ministry of Justice in Poland, entered onto the List of Sworn Translators under no. TP/1713/05, hereby confirm the accordance of the above translation with the original drafted in Polish.

Piaseczno, 17th June 2009

[52] 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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