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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. --

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[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. --

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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. --

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[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: --

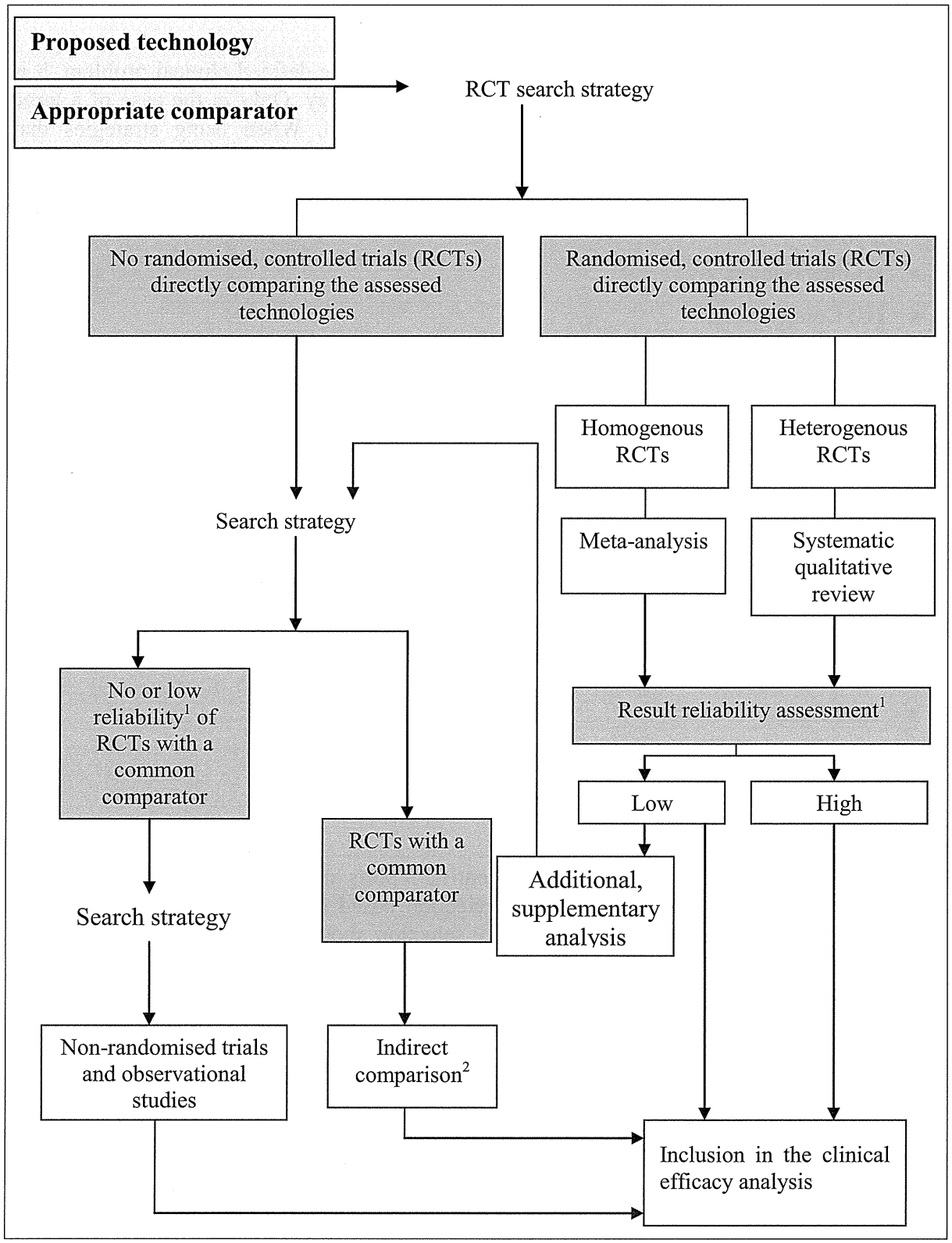
- key words and descriptors used for the search; --
- used elements of Boolean logics; --
- used filters; --
- the time span of the search. --

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

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[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). --

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[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. --