

Annex 6 to Article 35, paragraphs

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(Repealed, SG No 92/2014, effective 07.11.2014; new - SG No 26/2019, effective 01.04.2019)

Guidance on requirements for the contents of the health technology assessment analysis

The analysis may contain other data and sections that are necessary to provide the information specified in the scope of the assessment.

The main sections that the analysis should contain are as follows:

1. Introduction.
2. Clinical evaluation of the efficacy, therapeutic effectiveness and safety.
3. Pharmaco-economic evaluation.
4. Budget impact analysis.
5. Specific requirements for health technology assessment for rare diseases or specific patient groups, such as subgroups identified based on genomic information, etc.
6. Information on the moral and ethical aspects of the use of the health technology (if any).
7. Summaries and reports (attached) of decisions and evaluations by government institutions for purposes of other national healthcare systems.
8. Evidence from the references used.
9. Description of the references used.

Information to be provided in the above sections:

1. Introduction:

1.1. Health issue:

Description of the health problem based on reliable sources of information, as well as clear positioning of the health technology in the diagnostic and therapeutic processes for the analyzed disease. Information on the definition of the disease according to the International Classification of Diseases (ICD) shall be provided. If the assessment relates to a specific target population (e.g. with a specific stage of the disease), a brief description of the disease shall be provided, followed by detailed information regarding the particular stage of the disease.

The principles and criteria for diagnosing the disease shall be described, as well as the examinations and studies (laboratory and other) needed to make the diagnosis, identifying the relevant reliable sources - preferably clinical recommendations and guidelines based on a systematic review of scientific evidence, including such published within the Bulgarian healthcare system. If specific scales or tests are used for the purpose of diagnosis, they should be indicated, as well as which ones are financed by public funds in Bulgaria.

1.2. Epidemiological data, medical and social gravity of the disease:

Up-to-date epidemiological data, including incidence and morbidity, shall be provided, with preference given to data on the Bulgarian population, as well as information on the gravity and severity of the disease, its public relevance and the characteristics of the patients to be treated, should be provided depending on the disease, e.g. chronic disease, rare disease, disease in patients of active age.

1.3. Clinical picture, natural course of the disease, complications and prognosis:

The natural course of the disease, the prognostic factors associated with the course of the disease, and its impact on the quality of life of patients shall be described. The role of the new health technology in the natural course of the disease and its impact on its change and quality of life shall be emphasized.

1.4. Therapeutic standards:

The current treatment shall be described based on international recommendations and guidelines. The treatment algorithm according to clinical practice in Bulgaria shall be then described, followed by the relevant stages of the disease, with emphasis on the stage at which the health technology will be used.

Indicate whether the new technology is included in pharmacotherapeutic guidelines or other European therapeutic guidelines.

Information shall also be included on alternatives that are reimbursed in Bulgaria for the respective therapeutic indication.

1.5. Target population:

The population in respect of which the health technology will be applied shall be described. If the health technology is to be applied to a specific population of patients diagnosed with a certain disease (for example, those with a specific mutation), the criteria for determining that subpopulation must be clearly stated. When defining the target population, data on Bulgaria shall be used, and methods for determining them shall be described. Indicate whether the necessary clinical and other tests will be paid for with public funds.

1.6. Description of the health technology:

1.6.1. Key features of the new technology:

INN	
Trade name	
Marketing Authorization Holder	
Therapeutic class	
Active ingredient / active ingredients	
Pharmaceutical form / pharmaceutical forms	
ATC code	
Mechanism of action	
Pharmacodynamics	

Pharmacokinetics	
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1.6.2. Route of administration and dosage:

Route of administration	
Dosage	
Frequency of dosing	
Duration of treatment	
Interval between treatment courses established	
Number of recurrent courses of treatment established	
Dosage adjustment	

The technology being assessed should be described in detail. It should be specified whether it is authorized for use in Bulgaria, when it was first authorized and where, in how many other countries it was authorized (in the event of no centralized marketing authorization in Europe) and what specific therapeutic indications the authorization was issued for. If the assessment is for a new therapeutic indication in respect of which it has not been applied so far, this should be indicated.

The following information should be made available: type of technology (diagnosis, prevention, therapy), its main characteristics, various indications, contraindications and risks already known and described in the literature.

The following specific information should obligatorily be included:

- authorization to use the relevant health technology, including special conditions, if any, and period of validity;
- mechanism of action, therapeutic group, ATC code - for medicinal products;
- conditions under which the health technology will be applied (for example, in primary outpatient care, in specialized outpatient care, for hospital treatment, or others).

The place of the health technology in accordance with current clinical practice shall be described, as well as which therapy, including other health technologies, will be partially or completely displaced by the new technology.

In the case of a favourable decision, the following should be described: reimbursement status of the health technology in Europe, therapeutic indications, restrictions and level of reimbursement, summary of the reimbursement recommendations, whether the reimbursement concerns all therapeutic indications or only specific therapeutic indications in other countries.

1.7. Selection of comparative alternatives:

When there is a number of therapeutic approaches (including non-drug therapies and absence of treatment), these should be listed. Therapeutic approaches used as comparative alternatives should be selected based on commonly used or first-line therapy. In order to ensure international comparability, it is advisable to refer to what is perceived as the "best standard treatment" as the definition for a comparative alternative.

The following alternatives may also be used: treatment used in the current clinical practice; most commonly used therapy; most commonly used alternative medicinal products; reimbursed therapies with the same or equivalent therapeutic indication, the product most likely to be displaced or complemented by the new technology. If the new health technology belongs to an existing pharmacotherapeutic group, the comparative product should be the most commonly used product in the group or one that is most likely to be impacted by the introduction of the new technology. If the new health technology belongs to a new pharmacotherapeutic group, the comparative product should be the most commonly used medicinal product for the same therapeutic indications.

The dose and duration of treatment with the alternatives should be according to the information in the summary of product characteristics and the pharmacotherapeutic guidelines. Non-drug therapies and lack of treatment are acceptable alternatives only, if most commonly used in therapeutic practice or when there are no other alternatives for the treatment of the target patient group.

The added value of the therapy with the new health technology, such as improved safety, improved adherence to the therapy compared to alternatives, as measured using specific clinical indicators against existing alternatives, must be clearly justified.

2. Clinical assessment of the efficacy, therapeutic effectiveness and safety:

2.1. General data.

The following sources are considered as sources of evidence as concerns the efficacy, therapeutic effectiveness and safety of new technologies:

- clinical trials that are part of the manufacturer's research program and are included in the dossier for authorization for use and / or approval of the health technology (those published in scientific journals should be indicated);
- post-registration and post-marketing tests published in the scientific literature; - other tests outside the two specified groups; - systematic reviews and meta-analyses.

Test results of trials should be presented in tabular form containing the following information:

- trial identification data (registration number and bibliography of the publication);
- country in which the test was carried out (all countries should be indicated for multinational tests);
- number of participants (description of the number and demographic characteristics of patients, as well as specific patient subgroups, if sample or post-hoc studies are available);
- type of trial (randomized, non-randomized, case-control, case-by-case, cohort, post-marketing, etc.);
- intervention carried out;
- comparative alternatives;
- a description of the results;
- results obtained (data on the results may contain information about possible errors and limitations of the studies).

Each of the above study groups should be described in a separate table.

It is recommended that the limitations of literature be discussed and studies of lower quality identified.

2.2. Reasoned systematic analysis to identify and select relevant clinical trials and literature.

2.2.1. Criteria, methods of identification, selection and databases that ensure that all relevant randomized trials are included in the clinical assessment. Selection strategy for clinical trials.

The main objective is to identify all randomized trials which compare the new technology with the main alternative. If no direct randomized comparisons are found, randomized trials should be sought that will allow for indirect comparisons. If it is not possible to make indirect comparisons, a search for nonrandomized trials should be conducted. Any use of indirect comparisons and the inclusion of non-randomized trials must be substantiated.

Recommended databases that can be used to identify trials of the health technology being assessed are as follows:

Database	Specifid Search Period (from - to)	Search results
PubMed		Keywords and number of results obtained
Cochrane Library		Keywords and number of results obtained
ClinicalTrials.gov		Keywords and number of results obtained
European Union Clinical Trials Register		Keywords and number of results obtained
Other sources		Keywords and number of results obtained

A complete list of identified trials including the applicant technology (regardless of the comparison group) and all trials including the primary means of comparison (regardless of the comparison arm), systematic reviews and meta-analyzes should be provided.

2.2.2. Description of trials

Clinical trial	Country / countries	Participants	Type of study, duration	Intervention	Comparative alternatives	Results
Registration number or bibliography for the publication	List of the countries where the trial was conducted	Number, subgroups	RCP (number of arms, blindness, etc.), postmarketing, etc.	Description of the exact stage of the disease and characteristics covered	Description of alternatives to the indicators above	Description of the results and their main values

In addition to tabulating each of the subgroups of trials - clinical, post-marketing, systematic reviews and meta-analyzes, information on the criteria for inclusion and exclusion in the selection of clinical trials is also required: the main demographic and clinical characteristics of the participants in the trial; treatment scheme, dose details, route of administration and duration of treatment. Indicate whether the dose or the treatment scheme, including the use of concomitant treatment, is supported by the information provided in the summary of product characteristics. Justify where the determined dose differs from the recommended dose according to the summary of product characteristics.

For each trial, present data on co-medication taken (if any) and discuss its relevance to the clinical efficacy and safety data obtained.

Indicate whether the health technology is undergoing further testing for other indications or combinations and list the relevant trials and the time limit for their completion.

2.3. Comprehensive description of the results of each clinical trial and the methods for measuring them.

Notwithstanding the results given in the tabular review of the trials in this section, all results thereof, as well as systematic reviews, meta-analyzes and other types of studies, should be illustrated and clarified in detail. The illustration may contain additional tables, figures (for example - survival) and more. The results reported in the trials are:

- primary results;
- secondary results;
- final results.

Clinically relevant outcomes that are critical to a given disease or intervention should be a priority in assessing the health benefits of the technology. Clinically relevant are three main groups of results that should be noted:

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

Events and side effects (classified by gravity and frequency) are also clinically relevant. The reported results should:

- be defined and explained in terms of the health problem being addressed;
- be co-related to the disease being evaluated and its course;
- reflect the most important aspects of the health problem and, at the same time, make it possible to identify possible differences between the technologies compared;
- be important for clinical decision making (critical points for the health problem under consideration).

When reporting the results, describe the methods used to achieve long-term results in the absence of data (e.g. extrapolation for survival, etc.).

Therapeutic outcomes should be analyzed for as long a period as possible. Assessment of short-term treatment is appropriate for acute illnesses or illnesses entailing long-term consequences. In chronic diseases, long-term results are higher in value, but in some cases, assessment of the therapeutic effect due to long survival may also be obtained by extrapolating short-term follow-up results.

For the survival analysis, it is recommended to report the overall survival rate, as well as providing clear data on the possible crossover effect. Progression-free survival rates may also provide useful information for some diseases.

When evaluating clinical efficacy based on surrogate endpoints (intermediate, short-term results), the clinical analysis should demonstrate their relationship with clinically relevant outcomes. The validation of surrogate endpoints must be carried out in accordance with the underlying health problem.

In certain cases (e.g. analysis of a specific subpopulation), it is permissible to report the results of a post-hoc analysis, but these results should be interpreted only with respect to the subgroup concerned and not generalized. The post-hoc analysis should differ from the analysis of subgroups of patients with differing initial prognosis for the evolution of the disease.

The use of generalized endpoints is only recommended if these have been previously defined at the trial design stage. Complex endpoints are not recommended in the post-hoc analysis. If the population subgroup analysis is predetermined, the results may be more relevant than in the post hoc analysis. When summarized endpoints are reported, separate results for each component should be provided even when they do not achieve statistical significance.

Where results are obtained through a scale of questions, information on their clinical relevance must be provided. In the case of conversion of continuous or ordinal variables, or dichotomous variables (e.g. healthy-sick), the cut-off point should be specified.

Data on the results should also contain information about possible errors and limitations of the trials.

When using network meta-analyses or indirect comparisons, the results should be considered in terms of the reliability of the data and their applicability in making decisions in the healthcare system. For each meta-analysis, the results of the homogeneity test must be reported according to the methods in the Cochrane Handbook.

The efficacy and effectiveness data, as well as those from meta-analysis or clinical trial generalizations should be discussed separately.

2.4. Outcomes reported by patients.

Patient-reported outcomes are an important part of evaluating both clinical effectiveness and health-related quality of life. Patient-reported outcomes include general and / or condition-specific data (e.g. respiratory conditions, depression, arthritis), quality-adjusted life year scale from 0 (death) to 1 (full health) / recovery), symptoms or functions.

The analyses should indicate when and how outcomes reported by patients are assessed.

Provide the chart according to which patient-reported outcomes have been assessed (e.g. reported by participants, QALY, visual-analogue pain scale, visual acuity test, 6-minute walking test, etc.). All outcome measures reported by the patient should be indicated (e.g. EQ5D, HUI).

The effects of tested health technology on quality and life expectancy of patients in actual clinical practice need to be assessed.

2.5. Safety analysis.

A summary of the safety considerations, including important identified risks, important potential risks and missing information, relevant to the technology being assessed, shall be provided.

The product safety monitoring plan for the product should be summarized, listing any additional safety monitoring methods, if required at the time of marketing authorization or subsequent regulatory review. The category of post-marketing safety studies conducted should be defined.

Approved and implemented measures to minimize the risk in using the product should be presented and analyzed in the context of a possible increase in public costs for their implementation. For example, the requirement for periodic monitoring of hepatic impairment to avoid hepatotoxicity is a cost-increasing action, while the dissemination of training materials or signal cards is a risk-minimizing action that does not overburden the public and the patient's budget.

The cycle of submitting periodic safety updates for the medicinal product should be presented along with summary information on the cumulative marketing period of the product and summary exposure data.

The incidence and severity of adverse reactions should be reported according to the latest approved Summary of Product Characteristics, specifying the date of approval.

The positive benefit / risk ratio should be subject to regulatory assessment and a prerequisite for a valid marketing authorization. Any additional change to the benefit / risk ratio, whether additional benefit or additional risk, should be presented objectively and accompanied by clarifications as to whether the new information has already been submitted for inclusion through a change in the marketing authorization or, if not submitted, whether there is a plan to apply for a change.

The latest periodic safety report should be presented as an annex.

The comparative analysis of the safety profile of the evaluated health technology and the comparative alternatives should be presented in tabular form.

All adverse events of clinical or economic relevance (e.g. affecting patients' quality of life, mortality, adherence to therapy) should be included in the analysis, paying particular attention to cases where significant differences between technologies being compared exist.

The following categories of adverse events should be described:

- all adverse events;
- any adverse events leading to participants dropping out of the trial;
- all serious adverse events;
- all adverse events leading to death;
- all adverse events with a frequency or severity that stand out between the groups.

They should be presented in tabular form and the data obtained should be summarized.

Clinical trial identification					
	Observed adverse events				
Alternative	Number of patients	Absolute number of adverse events in the group	Number of patients with adverse events	Frequency of serious adverse events	Frequency of all adverse events
New technology					
Comparative alternative					
Comparative alternative					
Placebo					

A list of and supporting material from references used should be provided.

3. Pharmacoeconomic assessment.

3.1. Description of pharmacoeconomic analyses conducted using the health technology being assessed in other countries.

Where health-economic assessments or pharmaco-economic analyzes have been conducted using the assessed health technology for the purposes of other healthcare systems, these should be described. A tabular type for the description and detailed written information is recommended.

The following data should be clarified in tabular form:

- source of the study;
- purpose of the study;
- method (s) used in the study, including used modeling (if any);
- compared alternatives;
- outcome measures (clinical indicators, quality of life, long-term results, etc.); - results of the analysis (e.g. value of incremental ratio, etc.); - conclusion by the authors.

The results obtained should be commented on and correlated with the assessment of the current health technology. The more singular results or the interpretation of data and results should also be clarified in a textual form.

3.2. Description of published assessments of the health technology performed by government institutions for the purposes of another national healthcare system.

Data must be provided for all countries where the technology has been assessed where the technology has received at least one positive rating from a government institution in the United Kingdom, France, Germany and Sweden.

Data on the assessments carried out should include the following information:

- the institution which carried out the assessment;
- point of view of the assessment (public funds, special funding systems, society, etc.); - the indication for which the assessment was carried out;
- affected population;
- alternatives being compared;
- assessment methods applied;
- where patient access schemes are included, these should also be indicated;
- decision reached (including limitations associated with that decision);
- clarify whether the decision taken is conclusive or whether the technology will be subject to further monitoring.

All decisions made by public institutions together with relevant references and the document containing the final assessment and conclusion should be attached.

3.3. Analysis used.

The analyzes used should reflect the Bulgarian therapeutic practice and treatment standards, as well as sources of cost data and therapeutic outcomes.

Purpose of the analysis	Specify the purpose of the analysis
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Comparative alternative	List the alternative / alternatives identified according to the guidelines in point 1.7 and used in the clinical assessment.
Perspective analysis	The paying institution's perspective on health benefits and costs and, if applicable, the public perspective shall be specified.
Time horizon	Long enough to ensure that all important future cost differences and outcomes between alternatives are identified.
Methods used	Cost-effect analysis (CEA). Cost-utility analysis (CUA). Cost-minimum analysis (CMA). Cost-benefit analysis (CBA).
Outcome measurers	QALY, LYG, HRQoL or intermediate results.
Discounting	3.5 per cent per year in both cost and performance for a period longer than one year.
Modeling the evolution of the disease or therapy	Specify the type of model applied ("Decision Tree", Markov model, epidemiological, simulation, discrete choice model, etc.).
Method of assessing the uncertainty	Deterministic Sensitivity Analysis (DSA), Probabilistic Sensitivity Analysis (PSA).

Purpose of the analysis.

The stated objective must be clear and specific and be consistent with the financing institution.

3.4. **Comparative alternative.**

When conducting a pharmaco-economic analysis, comparative alternatives must take into account the recommended alternatives from the presentation of clinical trials, namely: - the alternative most likely to be replaced by the new technology;

- alternatives from conducted systematic reviews and meta-analyzes; - alternatives that are included in standard therapeutic guidelines; - alternatives from randomized clinical trials.

The assessed medicinal products for reimbursement should be oriented following this sequence of alternatives - the higher in the hierarchy of comparative alternatives used in the analysis, the higher its reliability.

The choice of any of the comparative alternatives should be substantiated from the viewpoint of Bulgarian therapeutic practice.

3.6. **Perspective.**

The analyzes should reflect the perspective of the paying institution.

The public perspective is recommended for the assessment of vaccination programs, screening programs, and prevention programs.

3.7. **Time horizon.**

The time horizon for the analysis should be long enough to ensure that all important future differences in costs and outcomes between alternatives are identified.

The choice of the time horizon for the analysis should be justified in terms of life expectancy for the population concerned and long-term therapeutic results should be taken into account.

3.8. **Methods used.**

The main economic method used in the health technology assessment must include at least a costutility analysis (CUA) or cost-effect analysis (CEA). More than one analysis may be carried out where appropriate.

A cost-minimum analysis (CMA) can be used for comparative alternatives with no superiority of therapeutic results, as well as for the assessment of combined medicinal products when the therapeutic result is compared with that of the monoproducts. The cost-benefit analysis (CBA) method can be used for the assessment of vaccination programs, health programs, equipment, organizational measures in health care (e.g. screening programs, etc.).

The choice of analytical method should be justified from the viewpoint of the paying institution, the time horizon and the evidence regarding the therapeutic results.

The main theoretical recommendations, as well as those of the Good Research Practices should be observed in using the methods.

3.9. **Costs of the health technology being assessed.**

The cost of each unit of the technology being assessed and the alternatives should be reported as a unit price, the cost of a course of treatment within one year, as well as other costs required for its implementation (where necessary).

The sources of all unit prices and costs should be indicated to enable a comparison. For prices of medicinal products, the registers of the National Council for Prices and Reimbursement of Medicinal Products (NCPRM), where available, should be used; for health care prices - the National Framework Agreement and the regulations issued in connection therewith. Other types of prices of services not covered by NHIF may be derived from tariffs of hospitals and other sources and these should be indicated. In such cases, we recommend to use more than one source and calculate an average cost.

The costs of treatment should be presented in tabular form - the cost of a course of treatment for one patient and for all potential patients to whom the medicinal product will be administered.

The cost of drug therapy should be calculated for the ceiling price at retailer level including value added tax (VAT). If the product applies for 100 per cent reimbursement in Annex No 1, the costs should be

calculated for the price at wholesaler level including VAT. In the case of applying under Annexes 2 and 3, the costs should be calculated for the price at wholesaler level including VAT.

In cases of reimbursement at less than 100 per cent, the costs for NHIF and the patient should be calculated in a separate table for the price at wholesaler level including VAT.

The costs of treatment with comparative alternatives should be presented in tabular form - the cost of a course for one patient per month and per year. Costs based on the wholesaler or retailer prices, depending on the level of reimbursement, should be presented. Costs for all clinically comparable alternatives to the assessed product should be included, as well as such for the treatment accepted as standard under the therapeutic guidelines or national standards. It is important to identify the medicines that are most likely to be replaced by the health technology being assessed.

Where it is required to value the work of medical and other specialists, the minimum social security standards should apply.

Direct medical costs should be presented as the sum of the costs of the technology, its implementation, the additional procedures, the costs of other health care activities, the costs of treatment in cases of adverse events and / or complications, as well as the investment and management costs. Other types of costs that may be relevant to the health technology may be added.

Indirect costs should be calculated only where significant social and economic benefits from the introduction of the new technology result, which go beyond the health benefits. In calculating indirect costs, the human capital method is recommended. Indicate what kind of indirect costs are valued - losses from incapacity to work due to temporary absence from work, losses from permanent incapacity to work, reduced working capacity, early retirement, premature mortality or others.

Indirect costs should be reported and estimated separately from direct medical costs.

All costs are presented in tabular form, indicating the type of units being assessed, their number, the scheme of application, the costs for each unit and the total costs.

3.10. Discounting.

3.5 per cent per year for both costs and results when presenting the costs and results for a period longer than one year.

3.11. Outcome measures.

Analytical techniques should be applied in compliance with the recommendations for outcome measures expected for the implementation of the health technology. Long-term outcomes (life years gain (LYG), quality-adjusted life years (QALY), followed by intermediate results (changes in clinical parameters and disease progression) should be preferred.

The choice of outcome measure should be justified from the point of view of the type of disease, the expected duration of treatment and changes during treatment.

In reporting the QALY indicator, the source of data on changes in quality of life and whether these are data from clinical trials conducted for the applicant health technology or from databases with published studies (these must be indicated) or expert assessments by medical professionals, or other sources should be indicated.

3.12. Cost-outcome ratio modeling.

Modeling should be applied where the available clinical and non-clinical data are not sufficient to determine the cost-effectiveness ratio. The structure of the model should be presented. The complexity of the model and the modeling methods should be commensurate with the complexity of the health problem.

It is recommended that the models be as simple and transparent as possible while maintaining their detailed implementation to enable the assessment of the difference in efficiency of the compared technologies. The assumptions in the model should be clear, well-founded and tested through a sensitivity analysis. Models should be developed using standard tools in order for them to be tested and verified.

In cases where no statistically significant difference in the clinical efficacy of the alternatives exist, modeling is not required. If the model includes key data for the changes of which there is no uncertainty, only those for which there is a statistically significant difference should be tested through the sensitivity analysis. The rest of the parameters should be excluded from the model or considered neutral with respect to the model.

When presenting the cost-outcome ratio, modeling may be applied, such as the Decision Tree, the Markov model, the epidemiological model, or other scientifically accepted modeling techniques. The modeling should include the following data:

Subject of analysis	Principles of good practice	Critical assessment questions
Model structure		
Health status	The structure of the model should be as simple as possible, but at the same time it should correspond to the health problem, the knowledge of the course of the disease, the causal link between the variables. The lack of data is not a reason to eliminate a health condition.	Are the health problem, the subject of the assessment and the alternatives clearly defined? Are the stages important for the course of treatment described? Are the assumptions in the model described and justified? Is the selection of health conditions justified? If so, are they consistent with the existing knowledge of the disease? Are there missing health conditions?
Comparative alternatives	The model must comply with the comparative alternatives described above.	Are comparative alternatives described? Are alternatives in line with the recommendations for their selection?
Time horizon	The time interval should be sufficient to assess the long-term cost differences and results of the alternatives being compared.	Is the time horizon defined? Is it appropriate for the situation being analyzed?
Cycle duration (using models with cyclic structure)	The duration of the cycle should be the shortest period in which changes in the studied parameters of the disease progression process are observed.	Is the cycle duration defined in the model? Does it correspond to the evolution of the disease?

Model inputs		
Identification of input data	The model should use the best available data (epidemiological, clinical costs) relevant to the knowledge and situation in Bulgaria. Input data must be obtained from objective sources. Key data include the following: -effectiveness and safety for the interventions being compared, -benefits for the health conditions, - variables for which even small changes in value have a significant impact on results. Data sources can be from clinical studies, non-clinical, economic	Are the data sources in the model represented? Is an appropriate data search method implemented? Is the data variation parameter specified? Does anything suggest that the data is being used selectively? Is there data based on an expert opinion (if yes, how are the experts selected, number, method of gathering information, conflict of interest)?
	databases, systematic reviews, etc. The sources must be indicated and justified.	
Data modeling	Data modeling should be carried out using conventional statistical methods.	Are the methods used described? Are they compatible with conventional biostatistic and epidemiological methods?
Inclusion of data in the model	Units, time intervals and population characteristics should be mutually comparable throughout the model. A half-cycle correction method may be used to standardize or eliminate the effects of time.	Are units of measure, time intervals, population characteristics described, and are they comparable to the alternatives? Is a half cycle adjustment method applied?
Sensitivity analysis		
Sensitivity analysis	Each model should have a sensitivity analysis of the key parameters and the same should be justified. The sensitivity analysis involves deterministic analysis of key parameters or probabilistic analysis. The lack of sensitivity analysis should be justified.	Has a sensitivity analysis been conducted for all uncertain parameters? Are the variation check intervals defined? Has a probabilistic or deterministic sensitivity analysis been conducted? Is the lack of probabilistic sensitivity analysis justified?

3.13. Presenting the results of analytical method applied.

When the analytical technique used is cost-effectiveness or cost-utility, the results should be presented as a cost-effectiveness ratio or an incremental cost-performance ratio.

When presenting results, the generally accepted rules for ranking alternatives in ascending order of results should be followed and the incremental cost ratio (ICER) for each of the therapies with respect to the respective comparative alternative presented in the following table should be calculated:

Alternative	Total costs	Total number of years of life	QALY's total	Additional costs	Life years gained (LYG)	QALY gained	ICER vs. respective alternative or (QALY's)	NHB net health benefit (Net Health Benefit)
Alternative 1								
Alternative 2								
Alternative 3								
.....								

Where the analytical technique used is a minimum cost, evidence of equivalence of therapeutic results should be provided and the overall health costs for the selected prospect of the funding institution should be compared.

Where the analytical technique used is cost-benefit, the cost-benefit ratio, the net health benefit and other applicable indicators shall be presented.

3.14. Subgroup analyzes.

Data indicating that the efficiency and/or costs associated with the health technology differ across subgroups, if available, should be provided. If so, and there is an indication of cost-effect in the treatment of these subgroups, indicate whether the subgroups have been identified before the clinical trial is conducted or after the results of the trial have been obtained; the characteristics of the subgroups should be described and the model results for those subgroups should be indicated.

3.15. Interpretation of analysis results.

The results should be interpreted with respect to the perspective of the analysis, with respect to the cost-outcome ratio or the incremental ratio.

The possible limitations of the analysis used and the factors that which can have an impact but are not included in the analysis should be analyzed.

3.16. Comparison with other analyzes performed.

Indicate whether the results of the analysis are in line with the results of similar analyzes already published and, if not, indicate possible reasons for the differences.

4. **Budget impact analysis.**

The budget impact analysis (BIA) is an important part of the overall economic assessment, used to determine the financial changes in public health spending after the introduction of new health technologies.

4.1. **BIA Perspective.**

The budget impact analysis should be conducted from the perspective of the paying public institution. In the case of sharing the costs with the patient, it is recommended that the patient's average cost be presented. Only in duly justified cases can a budget impact analysis be conducted from another perspective.

4.2. **Time horizon.**

The budget impact analysis should include an assessment of the impact of the health technology being assessed on the annual public health budget within a few years of the introduction of the new technology on, or the withdrawal of available alternatives from, the market. The budget impact analysis should be presented for a period of 5 years.

4.3. **Elements of the budget impact analysis.**

The budget impact analysis includes the following elements:

- numbers and characteristics of the target population;
- current therapeutic practice;
- new therapeutic practice after the introduction of the new health technology / abandonment of the current one;
- costs of the current and new health technology;
- presentation of results;
- sensitivity analysis.

4.4. **Data sources.**

Possible data sources for the budget impact analysis can be: published epidemiological studies, national statistics, market surveys, data from registers. To this end, the search strategy, data selection criteria and methods of analysis need to be presented, as well as the strengths and weaknesses of the sources used.

It is advisable to use epidemiological data for the Bulgarian population, while the use of data from other countries should be justified. When using data from unpublished sources (e.g. expert opinions, marketing studies, patient organization data), it is mandatory to declare a conflict of interest.

The estimated actual cost of the payer associated with the new health technology and comparative alternatives should be presented.

4.5. **Numbers and characteristics of the target population.**

When preparing the budget impact analysis, it is imperative to assess the size of the target patient population and the distribution of any characteristics related to it that may have a budget impact. Once the target population is defined, the percentage of patients diagnosed and treated, and the severity of the disease should be determined. Usually, more restrictive inclusion criteria are applied in this regard to accurately calculate the population of patients who are reliable with regard to the new health technology. In assessing the size of the target population and the severity of the disease, it is important to anticipate the change in these

parameters over time with and without the new health technology. Such changes can alter the budget impact of new health technology. Data from clinical trials or registers should be used to evaluate these changes. The analysis should also include published data or expert assessment on any additional opportunity to determine the target population (such as the use of diagnostic tests, for example) that may increase the size of the population or change the severity of the disease.

The target population should be defined according to the following criteria:

- incidence of the disease;
- assessment on patients who are appropriate for the new health technology;
- estimate of the presumed market share of the new technology due to the target population relative to the population that uses the comparative alternatives for the given indication.

4.6. **BIA scenarios.**

The budget impact analysis is based on two scenarios - "A world without the new health technology" and "A world with the new health technology". The "world without the new health technology" scenario describes the current therapeutic practice, while the "world with the new health technology" scenario reflects the impact on the market after the introduction of the new technology (which may be added to existing ones or may replace some or all of them). Assumptions about both scenarios should be detailed and substantiated in the analysis.

4.7. **Costs.**

The cost analysis in the scope of the budget impact assessment should be consistent with the perspective of the analysis. The methods used to estimate costs must be clearly described and justified. The cost analysis should be based on the actual cost of acquiring the new health technology by the paying institution and on the additional costs associated with the health technology being assessed, with the calculations being presented at the level of wholesaler including VAT, or at the level of retailer including VAT.

When presenting public expenses, it must be ensured that these are actual costs or savings for the payer.

Depending on the type of the new health technology, it is important to describe the possible costs associated with its implementation, including, if necessary, training medical professionals or the patient, as well as changes in diagnostic principles or other functional changes in the healthcare system.

In the budget impact analysis, costs are not discounted.

When estimating total additional costs, account should be taken of the following:

- costs associated with the new health technology;
- additional costs within the healthcare system related to the implementation of the new technology;
- cost reductions associated with reducing the use of existing alternatives, if the new technology replaces the current ones;
- cost reductions associated with savings, such as fewer hospitalizations, etc.

4.8. **Sensitivity analysis.**

In the budget impact analysis, two types of uncertain data are expected: uncertainty in the values of input data and structural uncertainty related to the assumptions made. It is recommended that the sensitivity analysis be conducted in a way that allows changes in the values of the selected input parameters and structural assumptions, aimed at forming plausible alternative scenarios.

4.9. **Presentation of results.**

Table 2

Table 1

Numbers or proportion of patients, if new technology is reimbursed						Numbers or proportion of patients, if new technology is NOT reimbursed					
	Year 1	Year 2	Year 3	..	Year X		Year 1	Year 2	Year 3	..	Year X
New technology						New technology					
Alternative 1						Alternative 1					
Alternative 2						Alternative 2					
Alternative 3						Alternative 3					

Costs (Annual cost per patient * number of patients per year)						Costs (Annual cost per patient * number of patients per year)					
	Year 1	Year 2	Year 3	...	Year X		Year 1	Year 2	Year 3	...	Year X
New technology						New technology					
Alternative 1						Alternative 1					
Alternative 2						Alternative 2					
Alternative 3						Alternative 3					
Total costs						Total costs					

The budget impact represents the difference between the two scenarios in each of the respective years of analysis. Year 1 is the first full calendar year after making a decision to introduce the new technology.

Budget impact	Year 1	Year 2	Year 3	...	Year X
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(+) Costs, if the new technology is reimbursed					
(-) Costs without reimbursement for the new technology, i.e. the current situation					
(-) Costs paid by the patient during outpatient treatment					
Total added cost					

The results obtained should be clearly stated and the limitations of the analysis should be indicated.

5. Assessment of health technologies for medicinal products designed for specific disease groups.

When assessing health technologies for orphan drugs, information should be provided regarding efficacy and therapeutic effectiveness.

The health technology assessment for orphan medicinal products should meet the following additional criteria:

- presenting, over a period no longer than one year, additional evidence of the benefits from administering the medicinal product;
- presenting models (Markov model, etc.) which track the course of the disease;
- assessment based on the severity, gravity of the rare condition; existence of an alternative; what would the cost to the patient be, if the medicinal product is not reimbursed;
- moral and ethical considerations;
- an economic evaluation and an overall budget impact assessment should be presented for orphan drugs that are of great social benefit, are not cost effective, and their use is indicated for serious conditions for which there is no effective alternative therapy.

6. **Information on the moral and ethical aspects of the use of the health technology (if any).**

7. **Summaries and reports (in annex) of decisions and assessments by government institutions for the purposes of other national healthcare systems.**

8. **Evidence from references used.**

9. **Description of references used.**