1. Introduction

Pharmacoeconomic evaluation i.e. economical analysis of pharmaceutical products is a method which in clear and precise way defines “added value” that the product contributes to the health of society. The overall objective of pharmacoeconomic analysis is to provide reliable information that can support the decision making process in order to achieve efficiency in resource allocation. Pharmacoeconomic analysis aids the decision-making process in terms of enhancing the information on which decisions are based, allows decision-makers to make informed choices based on evidence, and contributes to an efficient resource allocation.

Sine qua non condition in use of pharmacoeconomic evaluations in health care decision making is their high quality and ability to compare them against each other.

The above leads to the necessity to elaborate guidelines which will define:

1. objective, use of pharmacoeconomic evaluations and their status (compulsory or voluntary)
2. methodology followed in pharmacoeconomic evaluations
3. ethical principles while conducting pharmacoeconomic evaluation and when making publication of it.

The Polish pharmacoeconomic guidelines should be of use for those who conduct such evaluations and those who evaluate their results and/or use the results in their professional practice. Pharmacoeconomic analyses should be performed in line with Polish guidelines. The general recommendations included in guidelines set quite specifically the methods of evaluation to be selected and therefore maximise the ability to compare such evaluations as well as reduce significantly the possibility of misleading conclusions. Nevertheless they do not block potential progress in methodology and are not meant to restrain scientific freedom in this domain.

2. Objective, use of pharmacoeconomic analyses, responsibility in their conduct and target audience
2.1 Objective

Economic evaluation of health care interventions relies on comparison between costs and effects of two or more alternative methods of treatments. If economic evaluation relates to pharmaceutical products the term of "pharmacoeconomic evaluation" should be used even if the existing alternative is no treatment at all or non-pharmacological treatment.

The objective of pharmacoeconomic evaluation is to provide evidence-based information to be used in reimbursement decisions, but will not replace the reimbursement decision. A pharmacoeconomic evaluation allows to define whether a given product has got additional economical benefit (superior to existing alternatives) that would justify a reimbursement or change the level of existing reimbursement status. Argumentation raising from this evaluation is important, however it is not the only element in the complex decision making process.

2.2. Use of pharmacoeconomic analyses

Pharmacoeconomic analysis can be performed on all pharmaceutical products for which an application for reimbursement is submitted, except:

- pharmaceutical products with the same active ingredient as in a pharmaceutical products for which reimbursement has already been granted, including generic pharmaceuticals, parallel-imported preparations and preparations in new packaging
- pharmaceutical products for which a new formulation quite clearly does not change the costs and health effects of treatment.

Pharmacoeconomic analysis is especially useful for decision making, concerning pharmaceutical products with earlier not reimbursed indications or belonging to a new therapeutic class of products, which were earlier not reimbursed.

2.3. Responsibility

Responsibility for the preparation (financing and conduction) of pharmacoeconomic evaluations rests with the reimbursement applicant.

Pharmacoeconomic evaluation can be conducted at any phase of drug development provided adequate data exist to support a robust analysis, nevertheless it is recommended to perform it after introduction into the market.

Pharmacoeconomic analyses, including appendices, must be written in Polish.

2.4. Target audience

In Poland the Minister of Health decides as to whether a pharmaceutical product will be reimbursed. For this decision there is a need, in addition to a pharmacoeconomic analysis, insight into the consequences for the costs classified by type of benefit. This can be provided by financial analysis. The financial analysis is not a part of the pharmacoeconomic analysis.

3. Methodology of pharmacoeconomic evaluation
3.1. Definition of outcome objectives

The health care problem, which will be addressed by pharmacoeconomic evaluation should be carefully defined. The problem must be worded in a way showing the issues it aims to respond to. In order for the analysis to appear credible and transparent, its assumptions, parameters and limitations must be clearly stated.

3.2 Definition of the pharmaceutical product and its use.

The analysis must include data on the preparation’s name, ATC classification, date of approval for use in Poland, information of efficacy and safety and based on the accepted SPC. The approved indication must form the basis for the performance of the pharmacoeconomic analysis. It must be specified in the indication description whether the indication in its entirety or only parts of the indication is or are most relevant for reimbursement and which parts of the indication the analysis concerns. It must be described daily doses and expected treatment period, as well as anticipated frequency of repetition of treatments, if relevant. It should be stated which other drugs or forms of medical treatment can be expected to be used concomitantly. If the treatment is expected to result in a reduction in the use of other drugs or additional therapy, this should be specified and reasons given.

3.3. Population under evaluation

The analysis must contain a description of the illness for which the pharmaceutical product in question is to be used and a profile of the patient group(s) who is/are the target group(s) for the drug. The anticipated number of patients in Poland who will use the new drug should be estimated (prevalence and incidence figures). Estimates should also be made of discontinuation and death among patients. If drug is regarded as being more cost-effective for a narrower patients group than the one covered by the indication, this should be specified.

The target population is selected along with the registered indication for pharmaceutical product(s) in query. Pharmacoeconomic evaluation must be conducted on defined population as a whole and also in sub-groups which can be defined in study the protocol based on potential variance in efficacy, costs and/or preferences.

3.4. Comparison with alternative treatment – definition & selection criteria

The evaluated drug should be compared to the alternative (or alternatives) which is most likely to replace this drug in real practice. Such alternative(s) could be another drug or method of treatment i.e. surgical procedure or no treatment (placebo). The other relevant treatments are known as comparators or reference alternatives. The treatment which is chosen as a basis for comparison is of great influence on the economic evaluation study. In any case, the reasons for selecting the reference alternative must be clearly stated. It is a prerequisite that the reference alternative chosen be relevant for the same patient group and indication as for the calculation alternative.

Whereas, typically, the most prevalent medical treatment or first line therapy is recommended as the reference alternative, the following criteria may apply in the selection of an intervention as the reference alternative:

- most frequently used (current practice)
- most effective (most effective clinical practice)
- least expensive (minimum clinical practice)
“Current practice” can mean only one currently most used practice (if there is one predominant practice) or combination of 2 or more currently used practices taking into account their share in overall treatment practice.

“Most effective practice” means the alternative of treatment which if most effective clinically based on results of clinical trials conducted for this alternative.

“Minimum practice” means a practice which has got lowest cost and is more effective than placebo.

“Current practice”, “most effective practice” and “minimum practice” are illustrated in the following example:

Let’s assume that we may introduce to the market new product X, where we already have 4 existing products (A, B, C & D) with identical indications. Features of these products are presented in the table below:

Table 1.

Features of products with identical indications which exists on the market

<table>
<thead>
<tr>
<th>Product</th>
<th>Efficacy</th>
<th>Price</th>
<th>Sales</th>
<th>Market share</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>70%</td>
<td>500</td>
<td>200 mln</td>
<td>40%</td>
</tr>
<tr>
<td>B</td>
<td>80%</td>
<td>600</td>
<td>80 mln</td>
<td>16%</td>
</tr>
<tr>
<td>C</td>
<td>60%</td>
<td>300</td>
<td>60 mln</td>
<td>12%</td>
</tr>
<tr>
<td>D</td>
<td>60%</td>
<td>250</td>
<td>160 mln</td>
<td>32%</td>
</tr>
</tbody>
</table>

“Current practice” (one predominant treatment): A

“Current practice” (costs and efficacy is multiplied by percentage market share) :

\[0.4 \times A + 0.16 \times B + 0.12 \times C + 0.32 \times D\]

“Most effective practice”: B

“Minimum practice”: D

Comparison with “no treatment” is accepted, where this is the only relevant alternative offered to patients. This involves a treatment form without direct medical treatment of the disease in question, but symptomatic treatment as well as other types of care and nursing. The costs of this form of treatment must therefore also be calculated. If “no treatment” is the most prevalent option, but not the only medical alternative offered, both “no treatment” and the most prevalent other treatment should be included as two separate reference alternatives. In the practical application of selecting a comparator treatment, a number of problems can occur. Both the prescribing behaviour of doctors and the therapeutic insights can change over time. This means that views on the most suitable comparison treatment can also alter. A well-founded choice of comparison drug
for phase 3 studies may no longer be the most appropriate choice after the research has been completed or by the time that the product is being submitted for reimbursement.

It is also of importance that clinical research on new drugs has a markedly international character. A manufacturer cannot be expected to take into account all possible views and wishes when choosing a treatment comparator. The choice that is than made can deviate from is viewed as standard in Poland. To that end such choice will have to be justified, whilst adhering as far as possible to generally-accepted guidelines and protocols.

3.5. Time horizon

Time horizon means an interval of time between the start and the end of evaluation. The costs and effects must be measured over the same period of time. The time period, in which effects and costs can be expected, depends on upon the aim of the treatment and, thus, on the expected outcomes. The analysis should have the time horizon, which corresponds to the period in which all important economic and health consequences of the therapy are relieved. In view of the fact, that primary data do not provide sufficient insight into the value of the drug in the medium- and long-term, modelled data will have to form an integral part of the application for reimbursement. Short-term and long-term results should be presented separately.

3.6. Evaluation perspective

Pharmacoeconomic analyses are routinely used by public authorities to evaluate the benefits to society and should therefore be made on the basis of a societal perspective, which means, that all costs and all health benefits resulting from this treatment should be taken into consideration, irrespective of fact who pays and who benefits from the treatment in question. It is recommended to show both options of costs – with and without indirect costs – separately.

3.7 Evaluation techniques

A pharmacoeconomic evaluation involves incremental analysis: what is the difference in costs and the difference in health effects when intervention A is replaced by intervention B. In order to be able to place the results of incremental analysis in a broader context, the total costs and effects must also be reported.

In health economic evaluation a number of different techniques may be used:

- Cost-of-Illness Analysis (CIA),
- Cost Minimisation Analysis (CMA),
- Cost-Effectiveness Analysis (CEA),
- Cost-Utility Analysis (CUA),
- Cost-Benefit Analysis (CBA),
- Cost-Consequences Analysis (CCA).

CIA shows the cost of the condition in question to society over a specific period of time. A CIA is a pure cost analysis and health consequences are not evaluated. The total costs are calculated, but not incremental costs. All costs caused by the condition in question are added up. While CIA is useful, it is not suitable in connection with reimbursement because the result only describes the costs of the condition in question and does not show the cost effectiveness of the treating patients. However, such analysis may be used as basis for calculating costs in cost-effectiveness analysis, in which, in turn, can be used in connection with reimbursement application.
CMA should be considered when treatment with new drug and alternative drug have identical outcome ratios. In this type of analysis only costs of both treatments are compared.

In CEA costs of alternatives are compared to results measured in natural units.

It is most advantageous if so called intermediate results - surrogate results (i.e. blood pressure in mmHg, glucose blood level in mmol/l) can be transposed to end results such as life years gained – LYG).

CUA is a variation of cost-effectiveness analysis in which costs are compared to results weighted in quality of life adjusted life years (QALY). Benefit of QALY as measurement of results of health programs is ability to define at the same time the benefits resulting from decrease of mortality (quantitative gain) and from decrease of morbidity (qualitative gain).

CUA should be used when:

- health-related quality of life is an important outcome from evaluated programs,
- programs have variant results and there is a need to find a common denominative unit allowing comparison,
- we compare given program with another one evaluated with CUA method.

CUA should not be used when:

- only intermediate outcomes of given program can be achieved
- efficacy data show that alternative programs are effective at same level (than cost minimisation analysis is recommended) or CEA showed evident superiority of one alternative versus another and introduction of utility value will not lead to variation of result and/or will only confirm the result.
- health-related quality of life is an important element of outcomes, but it can be in one variable measured in natural units easily understood i.e. various methods of treatment of lower extremity fracture can be compared via decrease of number of days with lesser physical activity.

In CBA both costs and outcomes are expressed in monetary units. Thanks to that it is possible to compare completely different health programs. Currently the most adapted variation of CBA while evaluating results is willingness to pay, WTP. The methodology of willingness to pay is still under development. That is why CBA is not currently recommended as the unique method to evaluate health interventions. If the study co-ordinator believes in strong advantage resulting from the use of CBA analysis, than it can be additionally included in the outcomes summary. Nevertheless CEA or CUA has to be included as well.

CCA has been defined as an analysis in which costs and effects are calculated but not aggregated into quality-adjusted years or cost-effectiveness ratio. This type of analysis provides the most comprehensive presentation of information describing the value of a drug therapy or other healthcare intervention, and is also conceptually the simplest. In general, the CCA, by making the impact of the new treatment as comprehensive and transparent as possible, will enable decision-makers to select the components most relevant to their perspective and will also give them confidence that data are credible to use as the basis for resource allocation decision.

The analysis method is chosen in relation to the health outcomes to be identified and valued. The choice of one method does not automatically exclude the use of another method as a supplementary method if this is expedient for the problem in question.
Reasons must be given for the choice of method. In connection with an application for reimbursement, pharmacoeconomic analyses based on CEA are recommended. CUA can also be included. CBA is currently not recommended on the basis of the reasons given above.

3.8. Identification and measurement of costs

The following costs types are defined:

- **direct cost** - resources spent as a result of treatment:
  - direct costs within the health care sector (medical), i.e. work time of medical personnel, costs of drugs, costs of hospitalisation, administrative costs, etc.
  - direct costs outside the health care sector (non-medical), i.e. transport costs, special diet costs, etc.

- **indirect costs** - resources lost as a result of treating a disease:
  - indirect costs within the health care sector, i.e. medical costs which may arise during life-years that have been saved,
  - indirect costs outside the health care sector, i.e. loss of productivity

- **intangible costs**, i.e. pain, suffering. These can alternatively be evaluated as a change in quality of life and be measured as a health outcome.

**Direct costs**

All direct costs (both inside and outside the health care system) are to be included in pharmacoeconomic analysis, regardless of who bears the costs (societal perspective).

**Indirect costs**

The use of indirect costs within the health care sector should only be included in the analysis, if there is a clear relationship with the intervention. Future health care costs, which are not related to the intervention should not be taken into consideration.

For the indirect costs outside the health care sector, the focus is usually upon the costs of production losses. Two approaches for determination of these costs exist: traditional one, called human capital approach (HCA) and newer one, called friction cost method. The first one evaluates potential loss of income (where real loss in productivity might be much smaller). Basis for the second one is the assumption that value of lost productivity due to disease depends on the amount of time necessary to re-establish initial level of productivity. Due to the constraints in gathering necessary data about friction costs it is recommended to use the method of human capital approach (HCA).

Indirect costs outside the healthcare system should be stated separately (two analysis: taking into account these costs and without taking them into account). It must be stated why these costs are considered important and which method has been used to calculate them.

**Intangible costs**
Caution is recommended when taking into consideration intangible costs. Undoubtedly they play an important role in economical evaluation of health programs but methods of their evaluation are methodologically weak.

For each of resources used it is necessary to define unit of measurement (i.e. number of doses of drug, number of days spent in the hospital, etc.). Measurement of units of resources used and their prices have to be presented separately. It is necessary to use latest unit prices and to give the references used.

It is important to distinguish between expenses and costs. In a pharmacoeconomic analysis the costs are calculated. For instance, the existing rates for medical fees are not necessarily the actual cost of the service. Consequently, the expenses for medical fees in accordance with the existing rates do not necessarily reflect the costs. The actual cost may be difficult to arrive at. In such case, expenses are accepted as a substitute. Nevertheless it must be clearly defined what is used.

Only costs, that are relevant to the use of the drug in normal medical practice, are to be included. Costs which not be incurred in normal clinical practice must not be included. Neither should costs which are related to other complaints or conditions which have no connection with the analysed condition.

Estimated consumption of resources and expenditure bases for cost calculations, should reflect Polish conditions.

Total additional expenses for the national insurance system of the introduction of reimbursement for the product in question must be reported (financial analysis).

Transfer costs, such as sickness benefits and VAT are omitted in pharmacoeconomic evaluations, because they are either too difficult to calculate correctly or may result in double calculation. Future health care costs, which are not related to the intervention should not be taken into consideration.

3.9. Identification and measurement of outcomes

Outcomes of health programs are divided into medical and economical outcomes. Medical outcomes are for example: changes in mortality, morbidity and quality of life, while economical outcome are for example: saving resulting from decrease of disease cost or losses due to side effects of analysed programs.

Unit of outcome has to:

- reflect key aspects of health issue,
- be adaptable to alternative health programs which have to be comparable,
- allow to discover potential differences between these programs.

When the cost-effectiveness analysis is used, the outcome should be expressed in natural units, in a case of cost-utility analysis - in QALY. In cost-benefit analysis the outcome should be expressed in monetary units.

If the health-related quality of life is included in the design of the study, then it should be measured and valued in a reliable manner. The reasons to include or omit this part in the study must be presented. When measuring the health-related quality of life, two different sorts of questionnaires are usually distinguished: disease-specific and generic. In general for an economic evaluation study it is recommended that both a disease-specific and a generic quality of life questionnaire are included. The disease-specific questionnaire will
be able to detect the effects sensitively, while the generic questionnaire will be able to provide an impression of the magnitude of the effects. To measure the generic quality of life the SF-36 and EuroQol are recommended.

If a CUA is carried out, than the quality of life must be evaluated by means of a utility instrument, to enable the calculation of QALYs. There are various methods for determining the utility of a state of health. The indirect method is by means of two widely-used generic systems: EuroQol and the Health Utility Index. The most direct method is by means of interview techniques, such as the standard gamble and time-trade-off. A visual analogue scale can also be used, but the results refer to as “value”, not “utility” and allow calculation of risk-neutral QALYs.

Because the social perspective is recommended in economic evaluations of healthcare, the utility of the state of health should derived from the general public (a representative random sample from the population).

In pharmacoeconomic studies end results are important (decrease in morbidity and mortality) rather than the intermediate results (so called surrogate results i.e. decrease in cholesterol level, decrease in blood pressure). If end results are not available, then modelling techniques should be used. All assumptions made have to be endorsed by scientific evidence data.

Ideally pharmacoeconomic studies should be based on results achieved in natural conditions (effectiveness) and not in clinical conditions which differ from reality (efficacy). If no data about effectiveness are available, than relevant models should be built where above assumptions will be clearly presented.

3.10. Sources of outcomes data

Sources of outcomes data can be: experimental or observational studies, in case of lack of such studies – expert opinions may be accepted.

Proposed hierarchy of outcomes data is following:

Experimental studies

I Randomised controlled clinical trials
II-1a Controlled clinical trial with pseudo-randomisation
II-1b Controlled clinical trial without randomisation

Observational studies

II-2a Cohort prospective studies with parallel control
II-2b Cohort prospective studies with historical control
II-2c Cohort retrospective studies with parallel control
II-3 Epidemiological case - controlled studies retrospective

III Studies of “before and after” type
Experts opinions

IV Experts opinions (expert committees reports, descriptive studies)

The value of above mentioned studies depends on one hand on their type but also on the way they have been planned, conducted and analysed. Golden standard in source of outcomes data is randomised, controlled clinical trial however very often it needs to be completed with data from observational trials.

The selection of studies being source of data for analysis needs to be started with review of all related studies (published and also non published being available for drug producer), allowing comparison between the given drug and its alternative (point 3.4). Randomised clinical trials are preferred where direct comparison between given product and its alternative has been studied (head-to-head study). List of studies needs to be complete.

If there is no such studies available it may be considered to compare a set of controlled clinical trials with common reference (placebo or other drug) and conduct an intermediate comparison. List of studies needs to be complete where selected studies must be comparable.

If there is no randomised clinical trial related to given product and/or its alternative to be used in comparison it should noted in the report. In that case non-randomised trials results may be used for comparison as source of data. Types of studies that may be of value are observational trials (cohort studies, case-controlled studies) and trials of type “before and after” with series of cases with historical control, comparison of results of 2 or more one-arm trials. Non randomised studies are not a valuable source of data if products efficacy is measured. They are accepted source of data, if extrapolation of the results is required beyond the frame of trial. Taking into account the fact that data from non-randomised trials may contain false information (confounding) the assumptions based on these trials should be carefully considered.

In certain cases in pharmacoeconomical study a meta-analysis can be useful where several randomised comparative trials can be reviewed. Meta-analysis can increase precision in evaluation of differences between a product and its alternative. It is as well useful when results obtained following trials conducted in similar conditions, following the same protocols are contradictory. Meta-analysis may also discover features of studied product which may not be visible in one randomised trial and which are clinically important. Systematic reviews and meta-analysis should be based on methods from accepted guidelines (for example Cochrane Library). The method chosen for a review of published randomised studies must be described in detail and criteria for inclusion and exclusion of trials must be stated. The country of origin for the clinical trials must be clearly specified.

To enable evidence of the highest scientific rigour to be considered, in same circumstances it may be reasonable to support the key head-to-head trial(s) with evidence from additional randomised trials, for example if only one under-powered head-to-head trial is available. Possible supportive information includes:

- analysis of 2 sets of trials with common reference which include higher number of patients,
- the meta-analysis of all trials related to studied product versus other products widely accepted as equivalent to alternative selected for pharmacoeconomic study,
- the meta-analysis of all trials related to selected alternative in pharmacoeconomic study versus other products widely accepted as equivalent to studied product.
These supportive information should be clearly labelled to distinguish it from information from “key trial(s).

Experts opinion can not replace scientific outcomes. If however such data from randomised or non-randomised trials are not available, than experts opinion may be useful in order to:

- define context for pharmacoeconomic evaluation i.e. definition of place in treatment of given product (main indication, main alternative to compare),
- modification of data on resources used (data from experimental studies conducted in other countries, in other conditions),
- projections which resources and in which quantities will be used to achieve results in randomised clinical trials.

The criteria of selection of experts and method of gathering their opinions should be clearly indicated in analysis.

3.11. Use of data from other countries

Clinical trials from other western countries normally provide an acceptable basis for analysis of conditions in Poland. However, it is worth distinguishing between clinical and economical data. In terms of using clinical data, it may be possible to use clinical data of satisfactory quality that are based on foreign conditions as a basis for further calculations in pharmacoeconomic analysis. It should be taken into account whether the Polish treatment conditions correspond to the conditions in the non-Polish trials in terms of:

- therapy traditions,
- patient characteristics (demography, epidemiology)
- reference alternatives.

In case there is a deviation, this should be taken into account and special mention should be made of this. It is a prerequisite that the drug has been used in line with the approved indication in Poland.

In terms of economic data, the costs of treatment of the same type of patients group may vary considerably from country to country. A health economic analysis performed abroad may be less relevant to the Polish environment because of differences in:

- medical practice,
- relative prices,
- financial incentives to providers of care,
- the way the public health service is organised,
- likely differences in the reimbursement system,
- the actual capacity of the publicly funded service.

This automatically creates the need to replace and/or supplement information on the use of resources obtained from abroad with Polish data to adjust and adapt the analysis to Polish conditions.

3.12. Modelling

If modelling is necessary, it is recommended to present the structure, rationale behind chosen model and as well to present it in graphical way (decision tree, Markov model).
Modelling is not a substitute for ‘real’ data but is an accepted method of conducting pharmacoeconomic analysis of health programs if used in appropriate situations and in proper way. Modelling can be used in order to:

- extrapolate results beyond data received through randomised and non-randomised trials,
- combine intermediate results of clinical trials (surrogate results) with end results,
- generate data from clinical trial into real life conditions and from one country to another,
- provide synthetic direct comparisons if no appropriate studies are available,
- provide information at estimate level if no credible data are available,
- evaluate initially the integrity of planned studies.

Modelling is best available method in following conditions:

- early stage of development of new program where not much data are available,
- when there is no credible way to get relevant information necessary to make decisions.

If it is decided that modelling is best available method in current conditions it is recommended to fulfil following conditions:

- model should be as simple as possible and build in comprehensive way for all users,
- presentation of results should be clear in order to enable the end user of data to distinguish data from reliable source and data of lesser scientific power,
- modelling should aim at clarification of contradictory statements and uncertain results and to compensate them. That is way it is so important to provide the sensitivity analysis to confirm the “power” of outcomes,
- every model should be evaluated in order to estimate the degree of accuracy and compliance with other models or studies related to similar issue and should be verified as new data become available.

When choosing relevant clinical trials for a model analysis, it must be borne in mind that the trials are as similar as possible with respect to patients population, inclusion and exclusion criteria, the problem presented in the trial, the duration of the treatment, etc., so that mutual consistency is achieved.

Non-Polish model analyses may be used, but they should principally be adjusted to Polish conditions regarding clinical practice, costs and, possibly, health outcomes. The adjustments have been made, reasons must be given for this, and the consequences which the lack of adjustments may have for the result must be stated. The results of model calculations are uncertain and should be interpreted with caution.

**3.13. Discounting**

Discounting is conducted in order to bring costs and results to one time point. It is very important in case where implementation of analysed health program is spread across a long period of time. Necessity to discount costs is undoubtful. Only the necessity of discounting the results may be questionable. It is recommended to submit for analysis the results without discounting, after costs discounting and after costs and results discounting. Proposed discounting rate is 5%.

**3.14. Sensitivity analysis**
Sensitivity analysis is conducted in order to examine how results of analysis will be influenced by changing the parameters in key assumptions. It is necessary to conduct at least simple sensitivity analysis: one-way or multi-way sensitivity analysis.

In sensitivity analysis it is necessary to:

- identify “uncertain parameters”, which should be checked through sensitivity analysis,
- define credible range of variations of “uncertain parameters”,
- calculate results of analysis assuming defined variation of “uncertain parameters”.

Credible range of variations should be defined on the basis of available scientific literature, experts’ opinions in the range of credible average. The assumptions and variables may alternatively be changed across a scale that is regarded as probable. For instance, it can be argued that a certain cost may vary from -15% to +25% in relation to the base rate.

Probabilistic analysis may be conducted where probability of appearance of indicated values (i.e. borderline values) is defined.

3.15. Presentation of results of pharmacoeconomic analysis

Results of analysis should be presented in most clear way, possible both in non-aggregated and aggregated form. The manner in which the results are reported will depend on the analysis methods chosen. The result is to be based on principal parameters and assumptions. In the cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) the result is reported as the difference in costs (incremental costs) in relation to the difference in health outcomes (incremental health outcome), i.e. incremental cost-effectiveness ratio (ICER) or incremental cost-utility ratio (ICUR). Results of cost-benefit analysis (CBA) should be presented in form of net benefit.

In addition the total costs and health outcomes should be reported separately. This gives an overview of the total economic consequences and health consequences of the treatment.

The total additional expenses for the national insurance system in Poland should be estimated, if the drug is expected to be reimbursable (financial analysis). For further information on financial analysis, please refer to Appendix 1.

The analysis must contain a discussion of the data, methods and results presented. An evaluation must also be made of the societal consequences of introducing the new therapy in Poland. An account must be given on the transferability of results based on trials to Polish everyday clinical practice (efficacy vs. effectiveness).

The discussion must show, which other published and unpublished, if any, pharmacoeconomic analyses exist in the analysed field or disease in question. This review is to be based on a systematic search/review of the literature, and it must be stated how the search was performed. If the analysis deviates from any of the previous publications, the reasons for the deviation must be discussed. It should also be discussed whether other assumptions and parameters should have been tested in the sensitivity analysis. At the end of the study, there must be a list of references to sources of the data and assumptions of the analysis.

3.16. Plan of standard pharmacoeconomic analysis
4. Ethical code of practice while conducting and publishing results of pharmacoeconomic analysis

Pharmacoeconomic studies can be conducted by scientific institutions, independent experts and representatives of pharmaceutical industry. It is important that personnel conducting above studies dispose of relevant skills to conduct them (knowledge of methodology, high professional ethics).

Analysis should be conducted in accordance to methodology guidelines. It should be clear what relationship is present between the executing partner and order provider. Above all this will be critical for freedom of publication to follow.

Appendix 1

Pharmacoeconomic vs. financial analysis

The purpose of pharmacoeconomic research is to support the process of deciding whether to reimbursed a new drug: the results of this research indicates whether the new drug is cost effective alternative to the existing treatment. For policy-making, apart from cost effectiveness of the drug, the consequences for the macro-costs are also important: for this purpose a financial analysis is used. A financial analysis must provide insight into the financial consequences of the inclusion of the new drug. The are a number of differences between the pharmacoeconomic analysis and the financial analysis, i.e. the consequences for the macro-costs within the insurance system. There is the difference in perspective: while the pharmacoeconomic analysis starting point is a societal perspective, in the financial analysis the insurance system perspective applies. This means, for example, that:
in the financial analysis, only those costs are included which are of importance for the insurance system: costs outside the health care sector (which are of importance for a societal perspective), are now excluded,

in the financial perspective we are concerned with the costs that are declared. The starting point is therefore not the integral cost price, but the existing financing system, i.e. the tariffs and budgets.

Finally another differences with the pharmacoeconomic analysis is that the latter takes the individual as unit of measurement (i.e. costs and effects are weighted up at patient level), while the financial analysis is performed at macro level.

The financial analysis is not a part of pharmacoeconomic research. However, data from pharmacoeconomic research can be useful for the financial analysis.

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The purpose of pharmacoeconomic research is to support the process of deciding whether to reimbursed a new drug: the results of this research indicates whether the new drug is cost effective alternative to the existing treatment. For policy-making, apart from cost effectiveness of the drug, the consequences for the macro-costs are also important: for this purpose a financial analysis is used. A financial analysis must provide insight into the financial consequences of the inclusion of the new drug.

There are a number of differences between the pharmacoeconomic analysis and the financial analysis, i.e. the consequences for the macro-costs within the insurance system. There is the difference in perspective: while the pharmacoeconomic analysis starting point is a societal perspective, in the financial analysis the insurance system perspective applies. This means, for example, that:

in the financial analysis, only those costs are included which are of importance for the insurance system: costs outside the health care sector (which are of importance for a societal perspective), are now excluded,

in the financial perspective we are concerned with the costs that are declared. The starting point is therefore not the integral cost price, but the existing financing system, i.e. the tariffs and budgets.

Finally another differences with the pharmacoeconomic analysis is that the latter takes the individual as unit of measurement (i.e. costs and effects are weighted up at patient level), while the financial analysis is performed at macro level.

The financial analysis is not a part of pharmacoeconomic research. However, data from pharmacoeconomic research can be useful for the financial analysis.

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