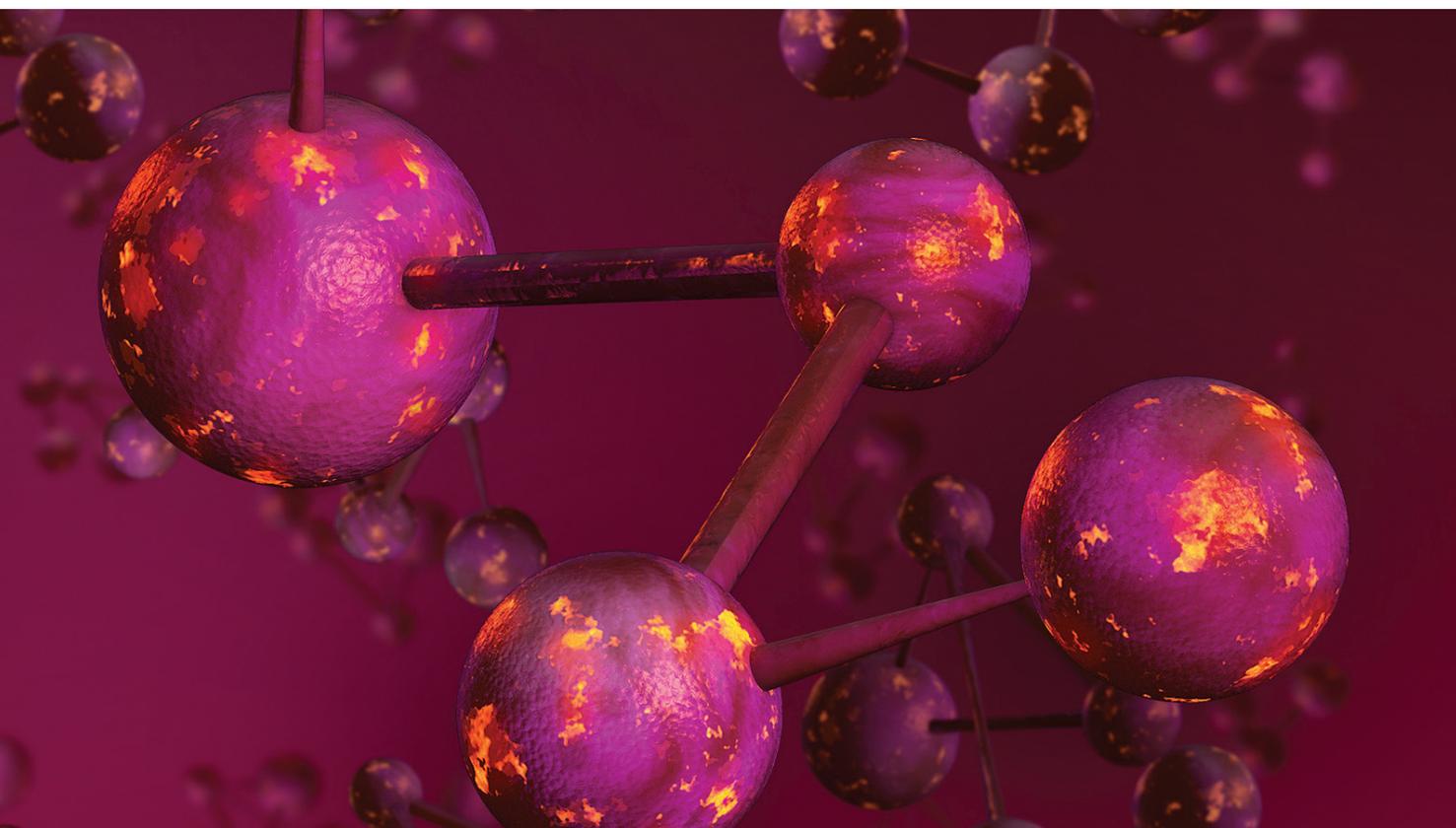


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Dear Reader,

The aim of health technology assessment is to inform professional and political decision makers in an efficient and transparent manner, based on relevant evidence, in order to facilitate the efficient allocation of available resources. The updated professional guideline of 2017 (its official title in English: "Professional healthcare guideline on the methodology of health technology assessment") serves to provide help for this purpose.

During the process of updating the Guideline, the main consideration was to develop and validate it with the involvement of a range of professionals as wide as possible. The incorporation of European and world health technology assessment trends, as well as their adaptation to the domestic environment with the help of renowned, independent experts and organisations, commissioned by the National Institute of Pharmacy and Nutrition, ensure that the Guideline meets present-day, high standards.

Special thanks are extended to the Hungarian Health Economics Association for their productive help.

II. Foreword

Evidence-based healthcare professional guidelines support decisions made by healthcare experts and other users in set healthcare environments. Healthcare professional guidelines, created and applied with systematic methodology, supported by scientific trials, enhance the quality of healthcare provision. The set of recommendations in professional healthcare guidelines are formulated taking into consideration the scientific results of the highest level, clinical experiences, the perspective of patients as well as the particularities of the Hungarian healthcare system together. In the guidelines, recommendations are formulated in a sector-neutral manner. Although the recommendations of professional healthcare guidelines represent best practices, which are based on the latest evidence available at the publication of the professional healthcare guidelines, they cannot replace

the decisions of healthcare experts in all cases, therefore, in justified cases, they can be overruled with documentation. The present guideline is of a methodological type, and differs from diagnostic and therapeutic procedural rules in many aspects. It assumes the availability of scientific evidence on the efficacy and effectiveness of the examined healthcare technologies, but it also supplements it with the costs of the healthcare technologies, the comparison of the costs and the results and the comparison of the technologies included in the analysis. In this regard, it serves as an important link between diagnostic and therapeutic procedural rules and financing procedural rules, although, for this guideline, not all aspects of the framework created for the presentation of diagnostic and therapeutic procedural rules are applicable or relevant. ■

III. Abbreviations

BNO:	International Classification of Diseases, ICD(betegségek nemzetközi osztályozása)	NNH:	number needed to harm (minimum number of treated patients needed to effect adverse events)
CBA:	cost-benefit analysis	OENO:	International Classification of Procedures in Medicine (orvosi eljárások nemzetközi osztályozása)
CCA:	cost-consequences analysis	PICO:	population, intervention, comparison, outcome
CEA:	cost-effectiveness analysis, cost-efficacy analysis	PRISMA:	preferred reporting items for systematic reviews and meta-analyses
CEAC:	cost-effectiveness acceptability curve	PSA:	probabilistic sensitivity analysis
CMA:	cost-minimisation analysis	REA:	relative effectiveness assessment
CUA:	cost-utility analysis	QALY:	quality-adjusted life year
DALY:	disability-adjusted life year	SAVE:	saved young life equivalents
DSA:	deterministic sensitivity analysis	SF-36:	Short Form (36) Health Survey ■
EQ-5D:	EuroQol five dimensions questionnaire		
EUnetHTA:	European Network for Health Technology Assessment		
GDP:	gross domestic product		
HBCs:	Diagnosis Related Group, DRG (homogén betegségcsoport)		
HCSO:	Hungarian Central Statistical Office		
HYE:	healthy years equivalent		
HTA:	health technology assessment		
ICD:	International Classification of Diseases		
ICER:	incremental cost-effectiveness ratio		
NNT:	number needed to treat (minimum number of treated patients needed to effect positive changes)		

IV. Introduction

Professional guidelines for health economic evaluations are necessary so that health economic evaluations may be appraised in a uniform manner using appropriate methodology and on a professional level, to a high standard.

In Hungary, the first health technology assessment guideline was published in 2002. This marked the first country in the Eastern Central-European region to take the principle of cost-effectiveness into consideration in reimbursement decisions on health technologies. The guideline was first revised in 2013.

In Hungary, various legal regulations state that efficacy, efficiency as well as cost-effectiveness need to be taken into consideration in healthcare provision. According to Paragraph 9 in Section 11 of Act LXXXIV of 1992 on social insurance financial funds and on their budgetary management, "the fiduciaries of social insurance funds are obliged to manage the social insurance funds in an economical, efficient and cost-saving manner which serves the insurance payer's interests".

Act LXXXIII of 1997 requires the preparation of economic evaluations as a mandatory element for the social insurance inclusion of healthcare capacities. Legal regulations of recent years on the social insurance inclusion of healthcare technologies also require health technology assessments and the preparation of cost-effectiveness studies as an essential element. Such legal regulations are, for example, Gov-

ernment Decree 180/2010 on the principles, conditional framework and detailed rules of social insurance inclusion decisions of healthcare technologies, Decree 28/2010 of the Ministry of Health as well as Decree 32/2004 of the Ministry of Health, Social and Family Affairs.

The goal of the guideline is to facilitate the preparation of health economic assessments, inclusive of health economic evaluations, based on a uniform, correct methodology and up to a proper professional standard, thereby supporting rational and transparent decision making and the efficient allocation of available resources.

The guideline, in general, serves as a methodological tool and guidance for professionals that create health economic evaluations and for professionals that make use of the analysis results. Among the target group of users, participants of the health technology assessment procedure are of special emphasis, for whom the guideline provides professional, practical health economics guidance for their day-to-day work. Furthermore, the contents of the guideline also provide guidance for creating various health economic scientific studies. Analyses that are completed taking the contents of the guideline into consideration enable decision makers to arrive at decisions that are rational and effect the efficient use of available resources. Therefore, applying the contents of the guideline in creating financing procedural rules is of special importance. ■

V. Professional explanation of the recommendations

1. Presentation of the submitted technology, general description of the epidemiology, indication, disease, healthcare provision and therapies

RECOMMENDATION 1

It is necessary to give a detailed presentation of the need for a healthcare service and of the demographics, epidemiology and possibly the social and economic situation of the patient group corresponding to the indication of the curative-preventive procedure to be analysed. It is required to present the course, outcome and epidemiology of the disease

in both domestic and international contexts, as well as a summary on the healthcare technology to be analysed and the routinely applied interventions at present in the indication relevant to the scope of the given analysis. The current therapeutic practice should be presented in a retraceable manner, if possible, supported by competent medical experts or the competent medical professional college. In addition, the presentation of the domestic financing and legal conditions as well as the exact determination of the submitted technology is also necessary.

The characteristics and indication of the curative-preventive interventions are defined by the previously com-

Continued on page 6. →

pleted (or ongoing) clinical trial or trials, as well as the marketing authorisation and summary of product characteristics that are based on these trials. If the indication is different from this (e.g. off-label use), then an explanation is necessary. The introduction must include a thorough presentation of the indicators describing the most important demographical and epidemiological characteristics of the patient population corresponding to the indication that already exists or that is requested to be created based on the submission. The introduction, in addition, must include the situation of the technology (the age group in question and its social, economic situation, the incidence and prevalence of the disease, the gender distribution, the number of patients to be treated, the number of patients currently receiving treatment or care, the ratios of patients with mild, moderately severe and severe disease etc.). It is also important to present the trends of the recent 5-10 years regarding the disease and the patient population.

If national data is not available, it is recommended that the incidence and outcome of the given disease in Hungary should be estimated and modelled based on international literature, if possible, on European data. However, international literature data is not in all cases suitable for local use without adaptation, as there may be differences in the population covered by the technology, in the healthcare environment and in legal and cultural characteristics.

When citing expert estimates, it is necessary to present detailed information on the number, qualifications, place of employment and position of the experts asked.

In addition, it is important to present the fundamental data on the course, outcome of the disease [onset time of the disease (age), its average time course, prognosis for the different patient groups, differences by gender, frequency of relapses, ratio of spontaneous healing cases, mortality, median survival time, more frequent comorbidities etc.] in the light of the clinical trial(s). Furthermore, it is necessary to present the currently used therapy for the disease, the level of healthcare provision (primary healthcare, hospitals, home healthcare), the relevant service data for the currently used therapy (outpatient care statistics, number of hospital admissions etc.) and the trends. Within these aspects, it is important to discuss as to what need is not or only partly covered with the usage of the current, routinely used diagnostic and therapeutic procedures (e.g. early detection, low cure rate, therapy resistance, adherence, severe side effects etc.) and which technology/technologies can be supplanted or complemented.

2. Presentation of the curative-preventive technologies to be compared and the reasons for their selection

RECOMMENDATION 2

For the base-case comparison, the technology/technologies routinely used and reimbursed in the indication must be chosen which may be supplanted by the healthcare technology examined in the analysis.

If comparison is reasonable with further technologies besides the primary comparators defined for the base case, it may be presented in a supplementary analysis.

If the primary comparator defined for the base case is not available as a publicly funded service, a comparison may be possible with other technologies if it is professionally relevant and supported by facts.

a) General considerations

Health economic evaluations always compare two or more curative-preventive technologies that are comparable to each other, with regard to costs and consequences. For a comprehensible and professionally well-founded analysis, it is necessary to present the curative-preventive technologies to be compared.

For useable and generalisable results, it is necessary to precisely describe the authorised and examined indications of the analysed curative-preventive technologies and present their relative and absolute contraindications.

The results are only relevant for the patient groups (subgroups) in the case of which the therapeutic indications and contraindications make it possible.

RECOMMENDATION 3

Under ideal circumstances, the comparator is the reference technology:

- ▶ the routine use of which is supported by data/evidence,
- ▶ which is defined based on the up-to-date, operative and quality guidelines on European and international clinical practices,
- ▶ which is supported by quality evidence on efficacy, effectiveness and safety published in the professional international medical literature, and
- ▶ which is authorised and reimbursed in the indication and therapeutic line that is the subject of the analysis.

Table 1. Presentation of the healthcare technologies (possible comparators) used in the therapeutic field

Name of the comparator technology	Market share of the technology in the therapeutic area	Source	Type of the available evidence for the comparison of the examined technology and the comparator	Source

If these conditions do not apply and another comparator is selected, an explanation must be provided.

b) Point of time for determining the comparator

It is reasonable to choose the appropriate comparator already in the preparatory stage of the analysis, in the course of determining the healthcare technology and the endpoints.

c) Sources used and participants in determining the comparator

When determining the comparator, the clinical guidelines and the (international) methodological guidelines must be taken into consideration.

Participants in determining the appropriate comparator may be: the manufacturer or the owner of the marketing authorisation of the technology, the organisation carrying out the assessment, clinical experts, the payer as well as patient organisations.

d) Considerations in choosing the appropriate comparator

As the basis of the comparison, the technology/technologies routinely used for the given patient group must be selected which may be supplanted by the healthcare technology examined in the economic evaluation.

It is necessary to support the claim that the technology is routinely used. The evidence for that may be as follows, in order of preference:

- ▶ list of reimbursed products, statistics on prescription purchases and other healthcare statistics,
- ▶ market research,
- ▶ consultation with clinicians, patient organisations, registers,
- ▶ local clinical protocols that are in effect,

- ▶ if the above data is not available: internet search results, especially from professional sites.

It is recommended to present all possible comparators within the indication according to the aspects (Table 1).

If more technologies are available which are demonstrably of the same efficacy and used frequently, then the most frequently used technology beside the one with the lowest cost must also be selected for the purposes of the calculation.

If not the most widely used technology or the one with the lowest cost serves as the basis of the comparison, a detailed explanation must be provided, with supporting evidence. The selection of the comparator needs to be in accordance with the perspective of the analysis. In the case of the payer perspective, i.e. analyses completed for the purposes of reimbursement inclusion decisions, only technologies already reimbursed can be regarded as primary comparators, if such are available.

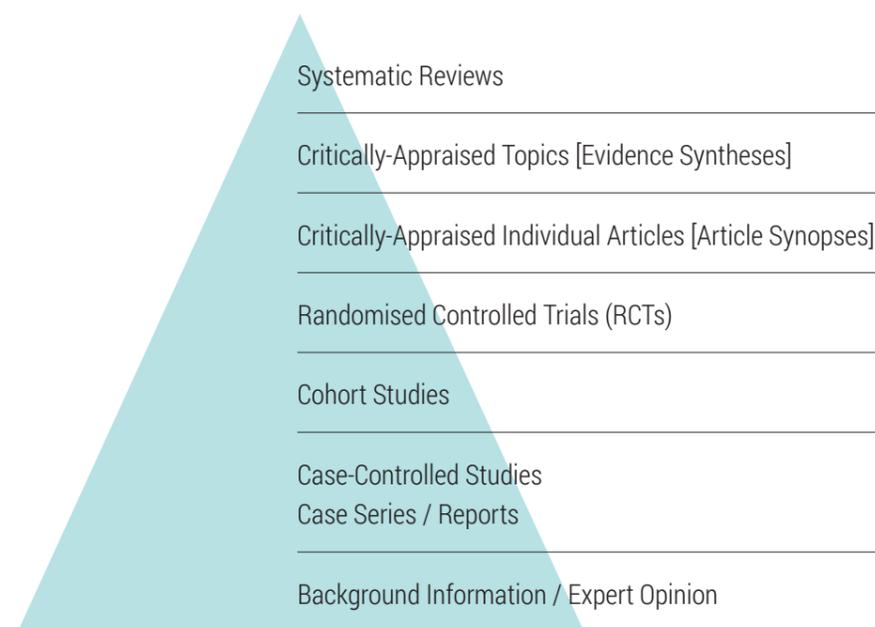
I. MEDICINES OR OTHER TECHNOLOGIES

A comparison between different types of technologies (e.g. medicines, surgical intervention, psychotherapy) is necessary if the comparator of the new curative-preventive technology is a different type of technology.

II. DOSE AND ADHERENCE

In the case of medicines, the authorised dosage regimen and potency of the comparator, as written in the summary of product characteristics, need to be taken into consideration. In some cases, it is possible that the dosage regimen used in the clinical practice is different from the one included in the summary of product characteristics. In such cases, it is necessary to present the analysis based on both the dosage regimen in the summary of product characteristics

Continued on page 8. →

Figure 1. The evidence pyramid

Source: Based on Sackett 2000, EBM Pyramid and EBM Page Generator [5, 6]

as well as on the dosage regimen used in real life practice. Guidelines on the clinical practice and real-life data (e.g. prescriptions redeemed) may be useful in determining the right doses of the comparator.

For the base-case analysis, it is supposed that the adherence of the compared technologies is the same. In case a statistically significant difference between the adherences is supported by the relevant clinical study, an additional analysis may be prepared to present the impact resulting from the difference. In the case of other, non-drug technologies, considerations concerning dosage regimens/utilisation need to be addressed based on an evidence-based methodology, according to the instructions in the user manual.

III. AUTHORISATION STATUS OF THE TECHNOLOGIES

In the case of medicines and medical aids, the analysis of the technology may concern the indication approved and included in the summary of product characteristics currently in effect, or a narrower indication within it.

In the case of other technologies, the analysis may concern the indications recommended by Hungarian or international diagnostic and therapeutic guidelines or, in the lack thereof, by the medical professional college or the Medical Research Council.

In the base case, the comparator may only be an authorised technology: in the case of medicines, a marketing authorisation, in the case of non-drug healthcare technologies, a CE marking is necessary.

It may be the case that a routinely used technology does not have a marketing authorisation. In such cases, the technology without a marketing authorisation can also be regarded as a comparator, provided that the fact of the routine usage is supported by data/evidence.

Results of economic evaluations are only valid for the priority identified indication(s) and patient group(s).

IV. LEVEL OF NECESSARY EVIDENCE ON THE NEW AND THE COMPARATOR TECHNOLOGIES

Under ideal circumstances, blind, randomised, controlled, direct comparative studies (if not available, then indirect studies) are necessary for the comparison of the comparator and the new technology.

However, it is to be noted that this is not feasible in all cases (e.g. the method of administration, side effects can affect the blind design of the study, the side-effect profile can apparently favour one patient subgroup). In the case of the comparator, practical, pragmatic studies, observational studies or registers can serve as suitable evidence,

provided that they are of good quality and statistically well-founded.

The level of reliability of sources of evidence is described in the evidence pyramid. (Figure 1.)

V. NUMBER OF COMPARATORS

If a single, well-definable comparator is not available, it is recommended that the analysis should be carried out using a comparison to more comparators at the same time.

The case of the so called add-on therapies is to be noted, in the case of which the simultaneous use of the routinely utilised and the new technologies is more effective than their separate use. In such cases, the comparison of all authorised alternatives is recommended (e.g. psychotherapy by itself, pharmacotherapy by itself and psychotherapy and pharmacotherapy together).

VI. THE THERAPEUTIC INDICATIONS OF THE NEW AND COMPARATOR TECHNOLOGIES WITH REGARD TO PATIENT SUBGROUPS

Under ideal circumstances, the therapeutic indication of the new and the comparator technology is the same in terms of the patients to be treated.

However, the new technology may have a wider therapeutic indication: it may cover various therapeutic lines and it may be applicable in various grades of severity and disease stages. In such cases, the use of more than one comparator may be necessary, according to the treatment of the various subpopulations.

3. Perspective

RECOMMENDATION 4

The perspective of the economic evaluation must be clearly presented. It is reasonable to choose the perspective of the economic evaluation according to the target patient group. As a primary choice, the payer perspective is recommended. Besides that, if possible, a comprehensive societal perspective should be aimed for, depending on the given technology.

As a general principle, the perspective of the analysis should be in line with the goal of the analysis. If the goal is to influence the public financing of the examined technology, then, in the base case, the analysis must be carried out according to the payer perspective. Besides that, however, it is recommended that the analysis results of the

societal perspective are presented, depending on the given technology. In other cases, the analysis can be carried out using other (e.g. service provider, societal) perspectives. It is important that the perspective chosen for the economic evaluation should determine the scope of the costs (direct and/or indirect) occurring and included in the analysis as well as the type of the end results.

RECOMMENDATION 5

The results of the different perspectives need to be presented distinctly separated from each other.

In analyses carried out using the payer perspective, for the purposes of reasonable decision making, it is recommended (but not mandatory) to present the results calculated using the societal perspective. The reason for this is that an optimal allocation of resources on a societal level is the "higher" goal, and the cost-effectiveness analysis can provide information about that if the results of the societal perspective are also presented. It is important to point out that in analyses supporting the efficient allocation of available resources, other (e.g. service provider, societal etc.) perspectives presented beside the payer perspective cannot be substitutes for the payer perspective in the given health economic evaluation.

In analyses using the societal perspective, all benefits and costs (direct and indirect costs within and outside of the healthcare system) emerging in the whole of society, in connection with the therapy must be taken into consideration. This is especially important for technologies in the case of which the societal perspective gives a better account of the benefits and costs (e.g. in the case of vaccines).

Apart from the two perspectives recommended above, it is possible to carry out the analysis based on another (e.g. service provider) perspective, but this is a possibility that may be provided in a supplementary analysis, separately from the base case analysis.

4. The type of health economic evaluation

RECOMMENDATION 6

From the six basic types of economic evaluations that are also used in the international practice (cost-effectiveness analysis, cost-efficacy analysis – CEA, cost-utility analysis – CUA, cost-benefit analysis

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sis – CBA, cost-minimisation analysis – CMA and cost-consequences analysis – CCA), the one must be selected which corresponds best to the health problem that is to be analysed. The basic types of health economic analyses differ in the effectiveness of the compared technologies relative to each other and in the comparability of these technologies. In general cases, in order to present the results of the analysis, the preferred methodology to be selected is the cost-utility analysis, complemented with the cost-effectiveness/cost-efficacy analysis. For all other cases, it is necessary to provide a rationale for the selection of the type of methodology.

Health economic evaluations are basically differentiated between based basically on the measurement method of the health benefit.

► The **cost minimisation analysis (CMA)** is the method to be chosen in cases when, based on the available and reliable scientific results (e.g. randomised controlled trials with adequate numbers of study participants or meta-analyses based on systematic literature reviews), the health benefits gained by the compared procedures (life years gained, improvements in quality of life) are the same, or there are no significant differences in the controlled or routine curative activities. In other words, the generated benefits (health benefits) and damages (e.g. side effects) are the same (there is no statistically significant difference). In such cases, the study must focus on the comparison of costs.

► The **cost-effectiveness analysis and the cost-efficacy analysis (CEA)** measure expenses in costs and outcomes in so called natural units (e.g. physiological parameters, side effects emerging, number of asymptomatic days, lives saved, life years gained, indices on patient satisfaction etc.). Furthermore, studies qualify as cost-effectiveness/cost-efficacy analyses which measure health benefits using disease-specific or general quality of life questionnaires that are based on scores independent of utility values as well as on measuring the occurrence of clinically quantifiable changes. From the two analysis types, the cost-effectiveness should be the primary choice, but, in the lack of effectiveness data, the cost-efficacy analysis can be an acceptable choice, provided that the analysis must be revised after a certain amount of time, for which the organisation responsible for health technology assessment makes recommendations.

► The **cost-utility analysis (CUA)** measures health benefits in life years weighted with health states, expressing them in utility values. In case a cost-utility analysis is used, it is recommended that health benefits be measured in QALY measurement units. It is recommended to determine utility values with the use of utility-based, health-related quality of life questionnaires. It is also recommended that cost-effectiveness/cost-efficacy analyses should be prepared in addition to (simultaneously with) cost-utility analyses, if the necessary data for that is available or can be generated.

► The **cost benefit-analysis (CBA)** expresses the value of health improvements in money. Some international guidelines accept the use of the cost-benefit analysis as a possible type of economic evaluation for the preparation of decisions on the allocation of public funding sources, while other international guidelines do not recommend its use in the area of healthcare. In Hungary, the use of cost-benefit analyses for reimbursement inclusion submissions is not recommended.

► The **cost consequences analysis (CCA)** presents costs and consequences and can be used only if there is no acceptable information available on the health benefits.

If the methodology of the analysis differs from the methods described above, it is necessary to present the method of the analysis in detail, explain the selection of the methodology and provide rationale for the exclusion of the above methods.

5. Health benefit: the measurement of the health benefit related to the applied curative-preventive procedure: the calculation of the denominator of the incremental cost-effectiveness ratio

a) Efficacy and effectiveness

RECOMMENDATION 7

As far as possible, health economic evaluations should aim to measure (long-term) clinical results achieved in routine practice, instead of efficacy under controlled circumstances (health benefit in strictly defined and controlled clinical trials).

Table 2. Clinical trials in the therapeutic area of the submission

Healthcare technology (e.g. substance)	Number of trials (pc.)

Table 3. Clinical trials of the analysed healthcare technology (in every indication)

Trial name/number	Indication	Starting time of trial	(Estimated) completion date of trial	Current stage of trial

The efficacy of healthcare technologies (e.g. medicines) achieved in clinical trials, under „optimal” circumstances does not in all cases match the efficacy of therapies applied in the circumstances of real therapeutic practice (effectiveness). Decision makers are interested primarily in the effects of the given healthcare service under real-world circumstances, therefore analysts must seek to base the analysis on (long-term) clinical results achievable in the real world (effectiveness) and not on efficacy determined in the course of controlled clinical studies.

Nonetheless, especially in the case of new curative-preventive procedures (e.g. medicines), only efficacy-related clinical trial results are available many times, which may under- or overestimate the health benefit achievable by using the examined curative-preventive procedure under routine circumstances. In such cases, it is advisable to examine how the end result of the cost-effectiveness changes if the efficacy results, for both the examined and the comparator technologies, are projected out to routine practice. In these cases, it is recommended that the analysis of the examined technologies should be revised based on effectiveness data. This should be achieved through the marketing authorisation holder providing effectiveness data, together with making available the information necessary for the validation of the collected data.

There can be significant uncertainties about health economic evaluations based on trial results of early phases (before phase 3). In order to handle these uncertainties, it is advisable to reassess the given technology (by making use of the most up-to-date evidence).

b) Literature searches; considerations in the selection of relevant clinical trials

The quality of the health economic evaluation depends considerably on which clinical data it is based on.

RECOMMENDATION 8

In health economic evaluations, the clinical results on achievable health benefits must be sought out, evaluated and presented according to the internationally accepted methodological recommendations of evidence-based medicine and systematic literature reviews.

A rationale must be provided for the selection of the studies utilised in the analysis. The methodology of the literature review, including the strategy for the literature search must be presented in the analysis. The use of PubMed, Cochrane Library and ClinicalTrials.gov is recommended.

It is necessary to present the clinical trials of the given technology in table format, according to the data of ClinicalTrials.gov. If the given technology is/was examined in more therapeutic areas, the trials must be aggregated by therapeutic areas first (Table 2).

Every identified study concerning the therapeutic area of the analysis must be listed, independent of the therapeutic line, stage of the disease etc. of the submission. In the case of literature not utilised for the analysis, the reasons for the exclusion (methodological mistakes, clinically not relevant endpoints etc.) must be precisely indicated (Table 3).

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Table 4. Trials conducted with the analysed technology in the relevant (submission) indication

Trial name/ number	Starting time of trial	Completion of trial	Methodology	Population	Intervention	Comparator/ comparators	Endpoint/ Endpoints

Fundamental information on trials conducted with the given technology in the relevant indication (therapeutic line, disease stage etc. of the submission) must also be presented in detail (Table 4).

c) Hierarchy of scientific evidence

The level of reliability of scientific evidence is demonstrated by the evidence pyramid shown in Chapter 2. The most reliable results concerning health benefits are from large-scale, direct comparative (head-to-head), randomised clinical trials done under circumstances according to routine practice and from the meta-analyses and systematic literature reviews of such trials.

In case a randomised clinical trial is not available, this must be indicated clearly. In this case, it is recommended that non-randomised trials (possibly observational studies) should be presented and detailed rationale should be provided for the selection of the trial utilised for the analysis. Expert opinions may play a substantial role in health economic evaluations, e.g. in designing the decision trees in the analysis, in the possible estimation of resource use, or in the interpretation and critical appraisal of clinical results, but by no means can be substitutes for scientific results.

If the results on health benefits are from aggregating the results of more trials, then the method used for the statistical aggregation must be presented in detail.

When measuring health benefits, the authors of the analyses may either gather evidence themselves utilising their own trials, or they may incorporate results from trials conducted by others into their own analyses. Both approaches are acceptable, but a reasoning must be provided for the choice between them. The chosen methodology must be presented in detail, and the limitations for the chosen approach must be indicated.

d) Indirect comparisons

In case there are no direct comparative randomised clinical trials available, or systematic literature reviews, meta-analyses based on such trials, then it is necessary to prepare indirect comparisons. In indirect comparisons, such clinical trials should be utilised which compared the procedures in the comparison to the same procedure. If only trials are available in which the procedures of the comparison were not compared to the same technology, then the network meta-analysis or other internationally accepted methodologies may be applied to prepare an indirect comparison.

In many cases, comparators from direct comparative clinical trials cannot be applied as comparators in health economic evaluations. For example, randomised controlled trials of adequate quality and with suitable endpoints may not exist for the given technology if such trials are not mandatory requisites for the routine application of the given technology (in the case of certain surgical procedures, medical devices, diagnostic procedures, medical nutritional formulas). In other cases, the comparator used in the clinical trial for the registration may not be used anymore in routine practice, because a more modern procedure has supplanted it since the completion of the trial, or, quite to the contrary, the technology used as a comparator in the clinical trial is still not reimbursed domestically in the given indication and therapeutic line.

In such cases, the evaluation of the efficacy can be based on the indirect comparison with the relevant comparator. If the examined technology of the analysis has been directly compared to the comparator of the health economic evaluation in clinical trial(s) of adequate quality, then the results from such trials must be taken primarily into consideration. Therefore, it must be explained as to why the utilisation of the results of direct clinical comparative trials is not possible. A justification must be provided for the use

of the selection criteria of the considered clinical trials in indirect comparisons.

Such clinical trials should be used which have examined the procedures of the comparison to the same procedure (e.g. placebo). An indirect, corrected comparison must be applied, which must be prepared according to international methodological recommendations (e.g. the Cochrane recommendations, the EUnetHTA Guideline, the ISPOR Good Research Practice).

The meta-analysis utilised must be presented in detail, it is not sufficient to present the conclusions based on the meta-analysis.

It is especially important that the indirect comparison be prepared according to internationally accepted methodological recommendations if there are only single-arm non-controlled trials available for the completion of the indirect comparison.

e) Presentation of clinical trials and results

The quality of the results of clinical trials depends on their external and internal validity, therefore these must be assessed and presented in table format, according to published methodological recommendations (e.g. Cochrane recommendations, EUnetHTA checklist, etc.).

I. ASSESSED ENDPOINTS

The data on the health benefit must relate to the long-term, clinically relevant effect (mortality, morbidity, quality of life assessed by patients in the various stages of a disease) of the curative-preventive procedure, instead of the exclusive use of surrogate outcomes.

The three domains of clinical endpoints are mortality, morbidity and the quality of life associated with health. Clinical endpoints must be relevant, sensitive, valid and reproducible. In relative effectiveness assessments (REA), the hierarchy of the endpoints is to be determined (primary and secondary endpoints). The choice depends on the target population, the main characteristics of the given disease/condition (life-threatening versus non-life-threatening) and on the goal of the treatment. In the case of a life-threatening disease, mortality as an endpoint or survival endpoints are the primary endpoints and morbidity and/or quality of life are secondary endpoints. In the case of non-life-threatening diseases, morbidity and quality of life endpoints are preferred.

- ▶ The use of surrogate outcomes is acceptable in case hard endpoints are not available and the correlation between surrogate and clinical endpoints is supported by evidence.

- ▶ The use of non-validated surrogate outcomes may become necessary if neither clinical endpoints nor validated surrogate endpoints are available. A rationale must be provided for the use of non-validated surrogate endpoints.

- ▶ A condition for the use of composite outcomes is that every component endpoint meets the criteria of validity, reproducibility and clinical relevance.

II. PRESENTATION OF THE RESULTS OF CLINICAL TRIALS

The results of the utilised clinical trials must be presented separately in table format which includes the main characteristics of the trial (e.g. completion date, methodology, number of patients, patient population characteristics, the measured clinical variable, the extent of the change, level of statistical significance and the 95% confidence interval). If there are more clinical variables, it is advisable to show these in separate tables. If the statistical analysis was not completed according to the intended treatment goal, this must be indicated. In the presentation of the results, the clinical significance of the measured change(s) must also be presented.

For the generalisability of the results and the comprehensibility and reproducibility of the studies, it is important that the results of clinical trials be indicated precisely and in a traceable manner.

It is advisable to aggregate the results in table format. In the table, it is recommended to indicate the completion dates of and references for the trials, the main characteristics of the analysed patient population, the number of patients, the measured clinical variable, the extent of the change (reduction of relative and absolute risks), the 95% confidence interval, the NNT, the NNH and the level of statistical significance.

If there are more clinical variables, then it is advisable to present these in separate tables. If the statistical analyses have not been conducted according to the intended treatment goal, this must be indicated.

In the case of rates, both the numerator and the denominator values must be presented.

If a study has measured health benefits using more parameters, then a rationale must be provided as to why the health economic evaluation is based on the chosen parameter.

III. QUALITY-ADJUSTED LIFE YEAR (QALY)

In case a cost-utility analysis is used, it is recommended to measure health benefits in QALY measurement units.

The QALY is a measurement unit which combines health

Continued on page 14. —▶

benefits in life expectancy and (utility-based) quality of life. It is recommended to determine utility values with the use of utility-based, health-related quality of life questionnaires.

An adaptation suitable for Hungary must be applied. As long as population surveys are not available which cover the value preferences of the population of Hungary concerning various health states, it is recommended to use international data (preferably originating from other European countries).

In order to determine the utility values of the various health states, both general and disease-specific quality of life questionnaires may be used. As far as possible, preference-based quality of life data should be used. This can either be done using utility weights based on the preferences of the domestic population for possible health states in general quality of life questionnaires (e.g. EQ-5D, SF-36), or converting the results of disease-specific questionnaires into utility weights using mapping methods. This way, it is feasible that the QALY value achievable with the use of the given healthcare technology represents the preferences of the domestic population.

The calculation method for the utility values of the various health states must be explained in detail, precisely indicating also the source of the data used (utilised quality of life questionnaire, utility measurement method – with the indication of the country and geographical region). In the case of calculations using derived data, the mapping algorithm must also be presented.

If the healthcare interventions concern diseases in the case of which the dimensions (e.g. pain, physical functions) of quality of life questionnaires do not adequately follow the changes in patients' health states (e.g. psychiatric diseases), direct utility measurement methods (the visual analogue scale, the time tradeoff and the standard gamble methods) can also be applied in order to determine the utility values of patients. As the values determined this way are not based on societal preferences nor are they methodologically well-founded, QALY values based on quality of life questionnaires, if possible, age- and gender-specific, must be used in all other cases.

Also in the case of adapting foreign studies to Hungarian circumstances, the methodology for determining QALY values (measurement, calculation) must be presented in detail. If quality of life results are adapted with the use of Hungarian data, then the results need to be presented with the original QALY values.

The use of alternative measurement units used in cost-utility analyses – DALY (disability-adjusted life years), HYE

(healthy years equivalents), SAVE (saved young life equivalents) – is not recommended, but in certain cases can be useful in secondary analyses.

6) Cost – The measurement of costs related to interventions: the numerator of the cost-effectiveness ratio

RECOMMENDATION 9

The perspective of the cost calculation and that of the analysis must be in line with each other. The perspective of the analysis determines the scope of costs that can be covered in the analysis. The price of the healthcare technology examined in the analysis must be its total price.

It is a fundamental rule that the perspective of the cost calculation must be aligned with that of the analysis, and that the various cost elements must be presented in detail. The data sources used must be indicated in all cases.

If a healthcare technology is intended for reimbursement inclusion, then the submission analysis must be prepared from the payer perspective. When determining cost data, the data should be derived from the most up-to-date data sources, as far as possible.

In the case of the payer perspective, the costs of healthcare services need to be presented indicating the OENO and HBCs list price values (outpatient and inpatient care cost values) currently in effect, whereas in the case of medicines, non-drug technologies and medicinal bath services, indicating the total price accepted as the basis of reimbursement (i.e. the sum of the amount reimbursed by the payer and the amount paid by patients, the gross consumer price). For drugs purchased in public procurement procedures, the use of the gross retail price is recommended, for devices, medical aids and other, auxiliary materials, the use of the prices of procurement procedures. The main reason behind using data from payer databases is that these are the relevant costs from the perspective of the payer. In case data from payer databases is made use of, the detailed methodology of the data query must also be presented.

If the calculation is based on a price different from the submission price, this must be clearly indicated and a rationale provided. In case the manufacturer price is modified after the submission has been filed, the results based on the new price must also be presented.

In the calculation of costs, the price in effect must be assigned to the various medical resources and it is the vol-

Table 5. Cost items

	Costs (Ft/cycle)			
	The health states in the analysis			
	Health state or event	Health state or event	Health state or event	Total (Ft)
New technology	Cost item 1 Cost item 2 Cost item 3			
Comparator technology	Cost item 1 Cost item 2 Cost item 3			

ume-weighted average prices which must be taken into account as the prices of the resources used. From the costs paid by patients, the fee necessary for patients' access to the services must be taken into account. For any other choice, a rationale must be provided.

In case the payer perspective is used, all societal costs can be taken into account for the calculations.

If the payer or manufacturer finds that the costs generated by the use of the technology examined in the analysis, and/or its comparator vastly differ from the fees set in legal regulations (e.g. the public and the real prices of the technology are different), then it is possible to complete a health economic analysis with calculations based on these costs, separately from the base case, in an additional analysis. The sources of all costs must be precisely cited. However, attention needs to be paid that all healthcare technologies in such additional analyses are compared at real "prices". (The realness of prices is to be ascertained by the authority assessing the healthcare technology, with the involvement of the payer.)

RECOMMENDATION 10

In economic evaluations of healthcare technologies, the costs closely connected to the given health service and the costs avoided by means of the new technology can be taken into account.

In the case of the payer perspective, from the possible costs emerging in the scope of economic evaluations, costs

closely connected to the given health service (direct costs) and direct healthcare costs avoided by means of the new technology (direct costs) can be taken into account. Costs generated due to diseases not related to the given health service, costs emerging in the life lengthened by the therapy but not due to the disease examined in the analysis, or other indirect costs cannot be presented, or, in justified cases, can be presented in additional analyses. Non-healthcare costs emerging in the course of the lengthened lifetimes (e.g. costs of living, healthcare gratuity payments, productivity costs etc.) must be disregarded.

RECOMMENDATION 11

It is recommended to take direct healthcare costs and direct non-healthcare costs into account in cost calculations.

Direct healthcare costs are the healthcare costs associated with the utilisation of technologies. Such costs are the costs of home care, general practitioner care, medical specialist care, psychotherapy, outpatient care, hospital care, mental institution treatment, health visitor services, physiotherapy, medicines, medicinal bath services, ambulance, diagnostic tests, surgeries, disposable equipment, transfusion, oxygen, treatment costs of complications, vaccinations, medical aids, co-payment of patients etc. Indirect healthcare costs are the non-healthcare costs emerging with the application of the therapy (travel costs). These must be presented separately.

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RECOMMENDATION 12

Taxes, including VAT, must be taken into account in the cost calculations.

In the analysis, the total of the costs emerging in health-care must be taken into account. Therefore, if necessary and reasonable, these can include, in the case of human resources, taxes and social security contributions, premiums, allowances in kind and, in the case of products used, the value added tax paid.

RECOMMENDATION 13

The resources used by utilising the technology and their price must be indicated separately. Furthermore, cost items registered by the payer pertaining to the various patient routes/health states are to be presented in a detailed manner, in listings, with their units (e.g. HBCs, BNO, OENO codes – inpatient, ICD, outpatient codes) and in their monetary value. In the presentation of costs, table formats should be used (Table 5).

Resources pertaining to the compared technologies (e.g. visits to doctors, number of diagnostic procedures) and the corresponding unit prices must be indicated separately, in table format. This helps in achieving verifiable and comprehensible results.

RECOMMENDATION 14

In the analysis, the costs and savings emerging in the various healthcare budget types must be indicated in a separable manner.

The transition between the various healthcare budget types is not unlimited and the allocation between them is not possible in all cases. For example, antibiotics rapid tests can burden the outpatient budget and/or hospital budgets, however, they can reduce the expenditures of the medicine budget. Therefore, in economic evaluations, it is required that the costs and savings generated in the various budget types must be indicated in a separable manner. This helps in achieving prudent decision making and taking into account the additional expenditures or savings emerging due to the later reimbursement inclusion

decisions of the new, cost-effective technologies, by the various budgets separately.

RECOMMENDATION 15

If the cost analysis takes the real institutional costs into account, then the methods and depth of gathering cost items, the calculation method for proportionately dividing indirect costs (implementation of internal rules, other provisions) must be presented in detail.

In the case of new technologies applied in hospitals and clinics, it may be the case that a separate code for the given intervention has not been determined, therefore the new technology falls into the same HBCs (inpatient care) code as the chosen comparator. This effects that the real difference in the costs of using the technologies does not become manifest in the analysis, which can distort the final conclusion. If the analysis uses the currently reimbursed fees as a basis for the determination of costs, then actually the technology could be ever so expensive and still its cost would be the same as that of the comparator. In order to address this problem, when assessing technologies used in hospitals, which receive reimbursement based on their HBCs (inpatient care) code cost values, it is preferable that the analysis uses the real institutional flat cost or applies the micro-costing method when presenting the costs of the examined and the comparator technologies.

RECOMMENDATION 16

If the data on the resources used is from international clinical trials or health economic evaluations, then it is recommended to compare the foreign clinical practice with that of Hungary, and, in case of differences, to complete the calculations based on resource use data from foreign clinical trials, in addition to calculations based on Hungarian resource use data.

If the results on the resources used are from clinical trials, then it is important to differentiate between what is only required by the trial protocol (arrangements in trials, tests etc.) and what is also used in the course of routine practice. The international (foreign) and the domestic routine practice can differ in terms of the resources used, both upwards

and downwards (e.g. the number of visits to doctors, the length of hospital care). In such cases, the differences must be discussed in additional analyses.

7) Time horizon of the analysis, discounting**RECOMMENDATION 17**

When determining the time horizon of the analysis, the time frame should be sufficiently long in order to encompass all the clinical and cost effects of the examined technology, but, at the same time, it should also be adjusted to the life expectancy of the Hungarian population, taking the disease-specific mortality into account. The time horizons of the modelling and the clinical trial must be presented in all cases, as well as the mean age of the modelled population. If the time period covered by the analysis encompasses several decades and/or the complete life span of patients, cost-effectiveness results must be presented in a sensitivity analysis for a shorter, proportionately relevant time horizon (e.g. a time horizon relevant for the disease specific life expectancy).

The analysis must cover a time period so long that all (considerable) short- and long-term effects on state of health and costs, directly attributable to the technology (e.g. life years saved, gains in quality-adjusted life years etc.) are taken into account in it. In order to do so, the clinical trial results may need to be extrapolated to a time period possibly exceeding the timeframe of the clinical trials by a considerable extent. In such cases, the use of modelling is preferred. The method for modelling must be clearly presented, and the effects of the uncertainties arising from the extrapolation method and the chosen time horizon must be investigated in scenario analyses (e.g. completing the calculation also with the use of different extrapolation methods or shorter time horizons). The model/models form constituent part(s) of the analyses. The maximum of the examined time horizons within analyses that can be presented is age 100 for the examined patient populations of the analyses. It is required to take also domestic, disease- and age-specific mortality data into account. Only health economic evaluations can be assessed that are submitted in a complete and verifiable manner based on the formal and contentual requirements.

RECOMMENDATION 18

Prices used in the cost calculation must be converted into a given point in time after inflating or deflating them.

In the cost calculations of health economic evaluations, it may be the case that data from several years are used when taking the resources and their prices into account. In such cases, prices, and with that, costs must be converted to one point in time (as far as possible, to the present point in time). In cost-effectiveness analyses, the consumer price index published by HCSO (the Hungarian Central Statistical Office) must be taken into account, regardless of whether the costs (and savings) pertain to the technology examined in the analysis or emerge outside of the health-care system. The basis of the conversion must be the annual consumer price index (inflation, aggregate value category) published by HCSO.

RECOMMENDATION 19

If the effects examined in the analysis concern more than one year, then time preferences and opportunity costs of resources must be taken into account by discounting. In the base case, both costs and health benefits must be discounted by 3.7%. In the case of the discount rate, it is recommended to prepare sensitivity analyses using 2-5% intervals for costs and 0-5% intervals for health benefits or, in justified cases, moving discount rates may be used.

Many technologies have impacts on costs and health benefits longer than a year. In such cases, the method applied in general economic evaluations, namely discounting, must be made use of. The idea behind discounting future costs to present value is that the same amount of money is more valuable today than in a later point in time (as the money available at the present is certain and can be increased in the future). Therefore, for investments and, in this case, for curative procedures, attention needs to be paid to take later expenditures with lesser weights into account. Thus, when discounting, future values are converted into present ones. However, the value of the discount rate is debated in the health economics literature. The value of the discount rate is a choice of preferences, generally dependent on the characteristics of countries (the degree of economic development, or general treasury recommendations) and

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Table 6. The presentation of the ICER value

Technology	Total		Incremental		ICER (Ft/QALY)
	Cost (Ft)	QALY	Cost (Ft)	QALY	
Comparator					
New technology					

varies between 0% and 5% for the base case and between 0% and 10% for the sensitivity analysis in international recommendations. In line with the calculations based on domestic empirical data, the calculated discount rate in Hungary is 3.7% [7].

There is also debate about whether health state values (e.g. QALY) should be discounted as well beside costs. In the base case, it is recommended to discount costs and health benefits to the same extent. Furthermore, it is recommended to complete a sensitivity analysis also on discount rates, using 2-5% in the case of costs and 0-5% in the case of health benefits for the calculations. This makes comparability with the analyses prepared in various countries possible. The use of moving discount rates in sensitivity analyses may be reasonable in preventive-type health technologies the health benefits of which are spread out over a time horizon of several decades. Moving discount rates can be used based on the modification of the discount rate, using the following calculation:

$$\frac{1}{n} * \left[\frac{1}{(1+r)^t} * [n+1-t] + \sum_{t=1}^n \frac{1}{(1+r)^t} \right], \text{ if } t=n$$

$$\frac{1}{n} * \sum_{t=1}^n \frac{1}{(1+r)^t}, \text{ if } t > n$$

n=Life expectancy
t=The length of the modelled timeframe
r=Societal discount rate

8) Detailed presentation of the results, examining the accuracy and generalisability of the results

RECOMMENDATION 20

The incremental cost-effectiveness ratio must be presented, as shown in Table 6.

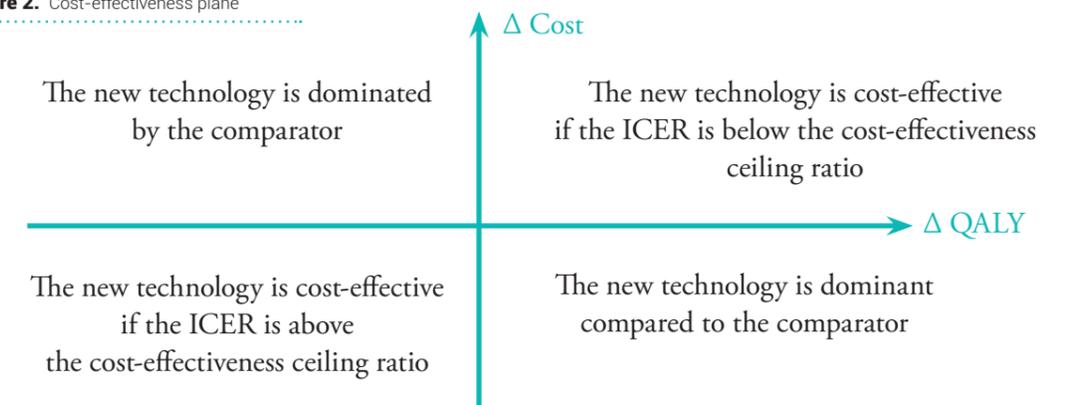
This ratio is the fraction of the difference in costs between the alternative technologies (diagnostic tests, preventive procedures or therapies) and the difference in health gains generated by these technologies. The importance of this ratio is that it indicates at how much of a cost increment a unit of health benefit can be achieved (can be “bought”), or how much of a saving the foregoing of a unit of health benefit generates when changing to a therapy with better efficacy.

RECOMMENDATION 21

Cost and health benefit results must be presented separately, in detail, also in tabular format. Costs generated throughout the whole time horizon must be presented in a detailed breakdown, also shown in tables or displayed in diagrams, by health states.

In order to facilitate understandability, comprehensibility and future use, it must be separately indicated as to how much total cost and health benefit the two (or more) compared alternative technologies will generate, and what the sources of these costs and health benefits will be. The presentation of the average or the incremental cost-effectiveness ratios is indispensable but not sufficient. The presentation of

Figure 2. Cost-effectiveness plane



the results directly related to the effectiveness, efficacy and costs of the technology is required.

RECOMMENDATION 22

The presentation of incremental cost-effectiveness ratios is required also in the case of dominant strategies.

It can be stated as a general principle that a technology is definitely cost-effective if it is more efficacious and generates a lower amount of costs (a dominant alternative, see Figure 2). If the efficacy of the two technologies under controlled circumstances as well as their clinical results under routine circumstances (effectiveness) are the same, then the less costly alternative is the cost-effective. If a dominant therapy exists, the presentation of the cost-effectiveness ratios is still necessary. If the sensitivity analysis indicates that the procedure is not dominant in certain cases, it is recommended to present an incremental cost-effectiveness ratio also for the worst-case scenario.

RECOMMENDATION 23

In case the examined technology provides additional health benefits at a higher price in comparison to the comparator technologies, an informative type of cost-effectiveness ceiling ratio can be established in order to estimate the cost-effectiveness.

In base case, technologies cannot be regarded as cost-effective which have an incremental cost-effectiveness ratio (Ft/QALY) greater than three times the gross domestic prod-

uct (GDP) per capita value, based on the latest available domestic data in the database of the Hungarian Central Statistical Office (cost-effectiveness ceiling ratio).

The cost-effectiveness ceiling ratio established this way is for informational purposes only and must be taken into consideration together with the other results, also bearing in mind the status of the technology in the curative-preventive procedure. Some technologies are not cost-effective at this ceiling value (e.g. (orphan) therapies for the treatment of rare diseases). However, cost-effectiveness is one of the aspects in reimbursement decisions (e.g. efficacy, effectiveness, equity, budget impact) and needs to be considered together with these other aspects.

RECOMMENDATION 24

The effect of uncertain factors on the end results of the cost-effectiveness analysis must be tested using sensitivity analyses, the modified parameters and the extent of the changes must be indicated, and the results must be presented in detail, both quantitatively with textual explanations and graphically.

Analyses are rare in which the exact value for every parameter is known with absolute certainty. The purpose of the sensitivity analysis is to examine, in the case of the uncertain parameters, how the end result of the cost-effectiveness changes, i.e. in what interval the end result values of the analysis take place, if various assumptions are made about the parameter values. This way, the risk of error in the decision making

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Table 7. Distributions recommended for probabilistic sensitivity analyses

Parameter	Distribution
Probabilities	Beta (binomial), dirichlet (multinomial), lognormal (survival), depending on the type of data
Relative risks	Lognormal
Costs	Gamma or lognormal
Utility decrements	Gamma or lognormal

Source: Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford University Press, 2006. pp. 108. [8]

can be reduced. If modelling was used in the analysis, then, in order to check the robustness of the model, both a deterministic sensitivity analysis (DSA) with reasonable limits (e.g. +/-10%) and a probabilistic sensitivity analysis (PSA) is necessary. A multivariate and a probabilistic sensitivity analysis can provide a more thorough analysis about the uncertainties of all model parameters. Such sensitivity analyses can address the correlation between parameters. This way, it is much more probable that the end results will be undistorted, which can lead to a more reliable, optimal decision making.

In the case of the deterministic analysis, which can be either univariate and/or multivariate, the modified parameters, as well as the extent of the modification must be presented in detail. Results must be presented with textual explanations and displayed in tornado diagrams.

In the case of the probabilistic analysis, the parameters included in the analysis and their distributions must be presented in detail. The choice between distributions is recommended as follows (Table 7)

Utility values can be lower than 0, whereas their maximum value, by definition, is 1. In order to prepare the sensitivity analysis, it is recommended to complete a transformation (decrement = 1 – utility), so that the calculated decrement is easier to include in the analysis [8].

Beside the textual explanation of the PSA results, the cost-effectiveness acceptability curve (CEAC) must be displayed. Furthermore, the results must be displayed in a scatterplot diagram on the cost/QALY plane, on which the base-case ICER value of the submitted technology must be indicated. In addition, the explicit cost-effectiveness ceiling ratio (3 X GDP per capita) currently in effect must also be indicated on the scatterplot diagram.

RECOMMENDATION 25

Subgroup analyses may be justifiable if the achievable health benefit or the cost-effectiveness is considerably different in the particular patient subgroup (e.g. high-risk patients).

A particular amount of money can provide the most health benefit if the technologies are used by the ones that can profit from them the most. Subgroup analyses help the purchasers of services in utilising available finite resources in an efficient way and in making financing rules that give incentives to efficient resource use. Cost-effectiveness analyses based on subgroup analyses are only recommended in case both statistically and biologically/clinically significant differences can be ascertained between the subgroups [8].

RECOMMENDATION 26

It is recommended to compare the results of the analysis with the results of previous international/domestic analyses.

The reliability of the results is supported if other health economic evaluations that compared the same or similar technologies arrived at similar results. In case previous studies produced different results, it is recommended to present the possible reasons behind the contradiction in detail. In order to facilitate comparability, it is recommended to convert the results of previous international/domestic studies at the exchange rate used by the given study and with the consumer price index published by the Hungarian Central Statistical Office. If the relevant year for the

Table 8. Expected changes in the therapeutic area following the years of the reimbursement inclusion decision of the new technology

Technology	Market share of the technology in the therapeutic area	Source	Impact of the introduction of the new technology on the development of the market shares of the given technology	Source

calculation of costs is not indicated, it is recommended to take the third year backwards from the publication of the study into account, as a reference year.

9) The effects of the introduction and reimbursement inclusion of the examined technology on healthcare expenditures: the budget impact analysis (BIA)
a) Effect on the healthcare or central budget

RECOMMENDATION 27

It is necessary to present the effects of the reimbursement inclusion of the technology examined in the analysis on public expenditures (gross and net budget impact) for the 3 years following the completion of the analysis. The budget impact analysis needs to be completed without discounting.

Terms

- ▶ Concerned patient group – the total patient population that is concerned in the given disease/health state;
- ▶ Target population – the part of the concerned patient group in which the new technology is intended to be used.

Knowing the concerned patient group, it is necessary to estimate, based on the size of the target population and on the expected rate of its spread of use, how great a budget expenditure, or, more generally, how great an increase (decrease) in public expenditures the reimbursement inclusion will effect in total.

If the new technology supplants another technology (technologies) widely used until now, then the expected savings must also be presented, along with what effect this will have on total public healthcare expenditures.

The increasing or decreasing effect of the reimbursement inclusion of the new technology on the various allocated healthcare budgets (e.g. costs emerging in the medicines budget, outpatient and inpatient care, the curative-preventive budget, etc.) must be presented separately.

The suggested time horizon of the budget impact analysis is 3-5 years. As the budget impact analysis must be presented in a breakdown by years, from the perspective of the decision maker responsible for the given budget type, therefore it is unnecessary to convert the expected expenditures into present value, i.e. the budget impact analysis must be prepared without discounting. In case an expert opinion is used, it is required to indicate the names of the medical experts, the questions asked in the interviews as well as the received answers.

Based on the above, the recommended structure of the budget impact analysis is as follows:

- a. Determination of the target population (in case it is different from the one in the cost-effectiveness calculation);
- b. Listing of the types of services and budgets that are impacted by the change in expenditures and presentation of the direction and nature of the impacts;
- c. Presentation of the time horizon;
- d. Presentation of the model of the budget impact calculation;
- e. Presentation of the calculations and deductions, if necessary, calculation of more budget impact scenarios (for example, depending on the prevalence and reimbursement amount of the new technology);
- f. Presentation and interpretation of the results.

It is recommended to present the development in market shares in the below tabular format (as far as possible, electronically, in MsExcel), both in a breakdown by technology and in an aggregate form (Table 8).

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b) The examined patient population

The size of the target population needs to be determined taking the authorised and examined indications into consideration.

The target population means the entirety of individuals in the case of whom the application of the examined technology can be advantageous in the examined time horizon. It is to be noted that this group of patients constitute an open cohort, meaning that, with the passage of time, certain patients might exit the group and others might enter it, thereby reflecting real-life characteristics. (This is generally different from patient cohorts used in health economic evaluations.) If needed, it is recommended to identify biologically reasonable subgroups based on supporting clinical and cost-effectiveness evidence.

It is to be emphasised that determining the size of the target population needs to be based on the medical background parts of the submission.

I. EPIDEMIOLOGY, DEMOGRAPHICS

In order to determine the demand for the new technology, it is necessary, based on the epidemiological data, to accurately determine the disease/condition and to estimate the size of the total patient population affected by the given disease.

If possible, the use of Hungarian data is necessary. If the analysis is not based on Hungarian data, this needs to be justified. So that the change in the size of the concerned patient group can be estimated accurately, the epidemiological characteristics of the disease/condition need to be presented as follows: prevalence, annual incidence in the examined time horizon and mortality.

In order to accurately estimate the size of the concerned patient group, the characteristics of the population need to be determined based on the latest available data. The demographics (age, gender) of the concerned patient group and the target population need to be presented in a proper level of detail.

II. DETERMINING THE DEMAND FOR THE NEW TECHNOLOGY

The target group may be identified according to the authorised and the examined indication.

Depending on the data available, the extent of the demand can basically be determined in two ways:

- ▶ estimating the annual number of patients includable in the treatment based on epidemiological and demographic data, which is the aggregation of prevalent and incident cases minus the cured cases and deceases, taking the annual evolution of the numbers into account,

- ▶ aggregating the annual numbers of patients switching to the new technology and newly treated patients starting the technology (e.g. based on the prescription sales data of the comparator technology).

In the budget impact analysis, it is necessary to take the spread of use of the new technology as well as the changes in demand into consideration in the examined time horizon.

The estimation of the growth of market share must be established appropriately (e.g. published forecasts on the population, disease/condition). For this purpose, international data may be needed from locations where the examined technology or a similar technology is already in use. In the lack of suitable data, an expert opinion may be provided to support the assumptions.

The size of the market must be estimated based on the number of prevalent and incident cases, taking into account the forecasted changes occurring due to the introduction of the new technology.

III. SUBGROUPS

The chosen subgroups must be identified and determined according to precise conditions, based on priorly definable, biologically and clinically well-established criteria.

The aspects for determining the subgroups can be, for example, the given therapeutic line of treatment or the severity of the disease.

The analysis of the same subgroups is necessary for the economic evaluations and for the budget impact analysis.

10) Other aspects

In the health technology assessment process, other aspects beside cost-effectiveness must also be taken into consideration. The alignment of the new technology with health policy priorities as well as the clinical value and societal impact of its use is to be examined. It is recommended to present also the ethical aspects considered in the analysis

a) Alignment with health policy priorities

The alignment with health policy priorities includes various aspects:

- ▶ Whether the implementation of public health goals described in national programmes is facilitated;
- ▶ How the new technology is in line with policy priorities; e.g. presenting whether it improves the efficiency of the healthcare system.

b) Presentation of the clinical value

In the presentation of the clinical value, the following are to be examined:

- ▶ The extent of the unmet medical need, i.e. whether an alternative is present in the given indication or a clinically unmet need exists;
- ▶ The nature and extent of the clinical effect (e.g. curative, clinically relevant, moderate, uncertain clinical relevance).

c) Societal aspects

The consideration of societal aspects cannot be distinctly separated from other aspects; it may be closely connected to effectiveness, ethical, safety and organisational issues. The basic question to be answered is what impact the use of the new technology may have on the lifestyles and work capacities of patients and of individuals in their environments.

d) Equity

RECOMMENDATION 28

It is recommended to present the impact of the reimbursement inclusion and of the financing method of the new procedure on fairness and equity.

In the analysis, it is necessary to examine the impact of the financing method (conditions) of the new healthcare service, curative-preventive procedure on equity in the health-

care system: e.g. equal opportunities in access, accessibility, inequalities in the utilisation of healthcare services or in the health condition.

It is worth to be noted if the cost-effectiveness of the curative-preventive procedure differs significantly from the average in the case of certain defined socio-economic groups (patient groups) or regions.

It must be noted if the given patient group is at the same time also a socially disadvantaged group.

e) Ethical aspects

RECOMMENDATION 29

It is recommended to present the ethical considerations concerning the health economic evaluation.

The ethical analysis is an integral part of the full scope health technology assessment process. In the ethical analysis, values presently prevailing, accepted by society and relevant to the health technology assessment, other than efficacy, effectiveness, efficiency or equity, are taken into consideration. These values, moral principles and societal rules, together with the legal regulations in effect in the given country, constitute the fundamentals of social life.

VI. BIBLIOGRAPHY

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