



Guidelines on how to conduct pharmacoeconomic analyses

In force from 1st March 2012
Norwegian Medicines Agency
(Statens legemiddelverk)

PREFACE

The Norwegian Medicines Agency administers the regulation of 28 June 2007 No. 814 regarding benefits for the coverage of expenses for essential drugs (Reimbursement regulations) § 2. The Norwegian Medicines Agency (NOMA) evaluates whether the expenses related to treatment with certain drugs should be covered by the national reimbursement scheme (pre-approved or general reimbursement), on application from the marketing authorization holder. The Regulations define four criteria that must be considered when assessing general reimbursement:

- a) the medicine is used to treat serious diseases or risk factors that will in all probability lead to or aggravate a serious illness,
- b) the disease or risk of disease referred to in letter a) leads to a need or risk of re-treatment over a prolonged period,
- c) the medicine has a scientifically well-documented and clinically relevant effect in a defined, relevant patient population, and
- d) the cost of the medicine is in reasonable proportion to the therapeutic value and the costs associated with alternative treatment(s).

Whether a medicine fulfills the above mentioned criteria is assessed on the basis of a reimbursement application. NOMA has the obligation of counselling the applicants before and after the application is submitted, although it is the applicant who has the burden of proof. The reimbursement application must contain a cost-effectiveness analysis of the medicine, performed by the applicant, except when the application involves a generic product, a new strength, formulation or package size which is no more costly than the relevant reimbursed product.

NOMA assesses the submitted analysis with regard to all main clinical outcomes, resource use and assumptions, as well as the final results. NOMA usually does not perform its own pharmacoeconomic analyses. NOMA may occasionally obtain additional information from the applicant or on his own search for updated information and make their own estimation of costs and cost-effectiveness.

All our reimbursement assessments are available to the public at our website (www.legemiddelverket.no).

Index

PREFACE	2
1 INTRODUCTION	3
2 GUIDELINES FOR THE ECONOMIC EVALUATION OF PHARMACEUTICALS	6
2.1 REFERENCE CASE	7
2.2 DESCRIPTION OF THE PROBLEM	9
2.3 DESCRIPTION OF THE POPULATION	10
2.4 DESCRIPTION OF THE INTERVENTION DRUG AND ITS APPLICATION	10
2.5 SELECTION OF COMPETING ALTERNATIVES (COMPARATORS)	11
2.6 DOCUMENTATION OF HEALTH EFFECTS	12
2.7 VIEWPOINT FOR THE PHARMACOECONOMIC ANALYSIS.....	13
2.8 TIME HORIZON.....	14
2.9 METHODS OF ANALYSIS.....	14
2.10 MEASUREMENT AND INDIVIDUAL VALUATION OF HEALTH EFFECTS.....	15
2.11 RESOURCE USE AND COSTS.....	17
2.11.1 <i>Consumption of goods and services</i>	17
2.11.2 <i>Time use</i>	19
2.11.3 <i>Additional considerations regarding costing in pharmacoeconomic analyses</i>	20
2.12 PRESENT VALUE ESTIMATION AND DISCOUNTING.....	21
2.13 MODELLING	21
2.14 UNCERTAINTY.....	22
2.14.1 <i>Sources of uncertainty</i>	22
2.14.2 <i>Handling of uncertainty</i>	23
2.15 PRESENTATION OF THE METHODOLOGY AND RESULTS	25
3 REFERENCES	26

1 INTRODUCTION

NOMA has had guidelines for pharmacoeconomic analyses since 2002. The present document is an updated version. The main objective of the guidelines is to improve the basis for decision making as regards granting of reimbursement for drug expenses in the National Insurance scheme. The purpose of the update is to incorporate into the guidelines both some of the latest developments in the health economics field and the experience NOMA has gathered in recent years when appraising reimbursement applications. The guidelines are meant for decision making at the patient-group level, not at the individual patient level.

The Assessment procedure guidelines by the Norwegian Ministry of Government Administration, Reform and Church Affairs (Utredningsinstruks, FAD 2005) and the guidelines for preparing economic analyses by the Ministry of Finance (Veileder i samfunnsøkonomiske analyser, FIN 2005) explain why economic analyses should be carried out in order to provide a good basis for decision making on public investments in Norway, and describes how these analyses should be carried out. Specialized public bodies/institutions assessing sector specific economic analyses may have their own, more detailed requirements and/or recommendations. A good example of this, are NOMA's present guidelines.

The updated guidelines list some requirements and outline recommendations about how to conduct pharmacoeconomic analyses. These requirements and recommendations apply to the key elements of the analyses, such as analysis perspective, type of costs and health effects that should be included and how these should be estimated. Some of the new recommendations concern both the methods of analysis and methods for measuring the quality of life. Detailed justification for the choices is made here.

The revised guidelines will replace the 2002 guidelines from March the 1st, 2012. However, in a transitional phase starting 1st March and ending 31st December 2012, it will still be possible to send reimbursement applications using the old guidelines.

In addition to the changes in the pharmacoeconomic guidelines, the Norwegian Medicines Agency has also made changes to section 8 of the reimbursement application's template. In the previous version of the template, section 8 stated that:

"8. Disease description and epidemiology:

Description of the disease the drug is indicated for, including impact/consequences of the disease in the short and long term. A description of the most relevant patient population(s), including the current and the expected development of the disease's prevalence/incidence must be provided".

The updated version of section 8 in the template is now:

"8. Disease description and epidemiology:

Description of the disease the drug is indicated for, including the impact/consequences of the disease in the short and long term *in addition to the degree of severity of the illness*. A description of the most relevant patient population(s), including the current and the expected development of the disease's prevalence/incidence" must be provided.

See http://www.legemiddelverket.no/templates/InterPage_16504.aspx

The Ministry of Finance is currently updating its guidelines for conducting economic analyses. Consequently, the need for a further update of the NOMA guidelines may arise.

Finally, NOMA would like to thank for all input through discussions, suggestions and comments from all participants in the Norwegian Directorate of Health's reference working group for the development of guidelines for economic evaluation in the health care sector, in addition to all those who participated in the rounds of consultation. Your contributions have been extremely useful in the updating of these pharmacoeconomic guidelines.

Norwegian Medicines Agency, March the 1st, 2012.

2 GUIDELINES FOR THE ECONOMIC EVALUATION OF PHARMACEUTICALS

In these guidelines, the word **must** is used to express an absolute requirement on the design of the submitted analysis. When there is no absolute requirement on the selection of a method, but nevertheless NOMA recommends one, the word **may/should** is used. **Can** is used when there are several possible methods of which NOMA has no particular preference.

Determining responsibilities

It should be stated in the application who was responsible for preparing the pharmacoeconomic analyses, who collaborated in the making of the analyses and who funded the whole process.

Language

Pharmacoeconomic analyses and their attachments must be presented either in Norwegian, Swedish, Danish or English.

2.1 Reference case

The base case in any pharmacoeconomic analysis submitted to NOMA in connection with a reimbursement application must meet a set of methodological requirements, which together constitute the so-called reference case.

The rationales for establishing such a reference case are:

- First, to make clear which elements of the analyses are important for NOMA, and
- second, to make the results of different reimbursement analyses more comparable.

The table below highlights *some* of these requirements. A detailed description of both the requirements and recommendations of pharmacoeconomic analyses will be presented in subsequent chapters.

<i>Components in the analysis</i>	<i>Base case</i>	<i>Relevant chapter in the guidelines</i>
Choice of treatment alternative (comparator)	The treatment (drug(s) or health program(s)) that the new pharmaceutical will most likely replace.	2.5
Viewpoint for the analysis	Societal viewpoint, but with some limitations	2.7
Time horizon	Long enough to ensure that the analysis captures all the key differences in expected future costs and effects between alternatives	2.8
Method of analysis	CUA	2.9
Health effect indicator	QALY	2.10
Method for the measurement and valuation of health effects	Generic measures of health-instruments	2.10

Productivity effects (gains or losses)	Inclusion of such effects is, when relevant, not compulsory. However, the choice of method must be justified and the results presented both with and without productivity effects	2.11
Inclusion of unrelated medical and non-medical costs in life years gained	No	2.11
Net deadweight costs due to tax funding of treatment	No	2.11
Discounting rate	4% per annum for both costs and health effects.	2.12
Uncertainty	One way sensitivity analyses (presented in the form of tornado diagrams), multi-way sensitivity analyses (mainly scenario analyses) and probabilistic sensitivity analyses (for handling parameter uncertainty)	2.14

2.2 Description of the problem

A pharmacoeconomic analysis must always include a clear description of the problem, e.g. in the form of a question the analysis will try to answer. The issue will include a brief description of the patient population, the intervention under study, the relevant comparator and the outcome measure(s) in the analysis (i.e. PICO).

2.3 Description of the population

The analysis must include a description of the population to be treated with the pharmaceutical under study, especially age, gender, health status, relevant comorbidity and prognosis (both untreated and treated with the most relevant of current treatments, see section 2.5), as well as a description of the incidence and prevalence of the health status to be prevented or treated in Norway.

Separate calculations must be performed for the different sub-populations when/if the intervention is expected to differ significantly in cost and / or efficacy for different groups (e.g. separately for men and women, different ages, different prognosis and/or different risk levels).

The applicant must also specify if the drug is believed to be more cost-effective for a narrower group of patients than those covered by its indication.

2.4 Description of the intervention drug and its application

The analysis must include an accurate and complete description of the intervention drug, including a clear description of its therapeutic advantages. If the drug is part of a treatment sequence, then the sequence must be described accurately.

The description of the intervention drug should include the drug name, its active substance, ATC-code and date of market access approval. Information on the drug and its mode of operation must be based on the SPC or any equivalent documentation submitted with the marketing application.

Reimbursement of drug expenses under § 2 (general reimbursement) is granted only for use that is consistent with the medical approved indication. It should be clearly stated

whether the pharmacoeconomic analysis concerns the whole of the indication, or only one or more subgroups within the indication.

Dosage per day and expected treatment duration must be reported, together with the expected treatment frequency. Information and experiences regarding compliance (defined as the combination of adherence and duration) must be described. Where the drug will be administered (at home, at doctors' offices, outpatient clinic, etc.), how it is administered, by whom (patients, caregivers, healthcare workers) and the expected concomitant treatment must also be described.

Finally, if the treatment is expected to lead to a reduction in the use of other drugs/additional therapy, this should be both highlighted and explained in the analysis.

2.5 Selection of competing alternatives (comparators)

The costs and health outcomes resulting from treatment with the intervention drug must be compared with those of the most relevant treatment options (comparators) within a Norwegian setting.

- i. The main principle is that the most relevant comparators will be those most likely to be partially or wholly replaced should the new medicine attain general reimbursement. This will typically be current established practice (according to the relevant specialist association, for example) and/or the treatment whose use is most widespread, although comparators may also consist of other forms of treatment than drugs (e.g. surgery) and even take the form of prevention, curative treatment, palliative treatment or watchful waiting. Comparison with “no treatment” alone will not be accepted, except in special circumstances.

If there exists several potential alternative treatments and there is great uncertainty about which of them is most likely to be replaced, then the applicant should include all of them.

- ii. *If it is not clear whether the most commonly used treatment alternative is cost-effective compared with other relevant comparators or with no treatment, then all other options should be included.* In principle, one should appraise the cost-effectiveness of all relevant treatment alternatives. However, if there is a great number of potential relevant comparators to consider, then the applicant should only include those expected to be cost effective, along with the most commonly used option.

The following example explains the rationale behind the above recommendations: Let us imagine we have a new treatment option, A, a most widely used option, B, and three other options, C, D and E, where E stands for no treatment. If it is unclear

whether B is cost effective compared with C, D and E, a comparison of A and B is insufficient. Although A is cost effective compared with B, we do not know whether we should instead use C, D or E as comparators. However, if there is evidence supporting the belief that D and E are not cost-effective against B, then the applicant would only need to incorporate B and C as comparators.

- iii. If the most relevant treatment alternative is not the one recommended in the existing national clinical guidelines (e.g. because it is not the most effective), *the analysis should then include the recommended option as well.*
- iv. *It is extremely important to explain whether the new drug replaces all or part of the existing management strategy, or whether it is an additive i.e. used in addition to current management strategy.*
- v. *The comparators must be strictly individual treatment alternatives, i.e. not a combination of two or more individual alternatives obtained using for example a weighted average of effects, costs, etc. If the new intervention displaces more than one alternative, then some or all of the individual alternatives must be included. The reasons for this are several: First, combining treatment alternatives introduces additional uncertainty, especially when these alternatives are not included in a direct comparative study. Secondly, a composite comparison does not reveal whether the new drug is cost-effective with respect to each of the options. This has even the potential to mask extended domination. Alternatives that are extendedly dominated by other options should not be included in the set of feasible treatment alternatives (Drummond 2005 p 329).*
- vi. *Reimbursement application for drugs used as second-, third-or fourth-line treatments should also include a pharmacoeconomic analysis.* The definition of patient population and selection of alternative comparison can be specially challenging in such cases. The applicant should therefore carefully explain and document choices made, using if necessary multiple comparators in the analyses.

When in doubt about the correct choice of comparator, please contact NOMA for further counselling.

2.6 Documentation of health effects

The application must include a description and analysis of the evidence regarding the effect of both the intervention and the comparator(s) for the relevant indication. All methods and parameters used must be described. Adverse events associated with the treatments under study may have a decisive bearing on the choice of therapy; therefore adverse events profiles must as well be described.

A systematic review of studies as regards the effect of the intervention and the

comparator(s), making use of relevant databases (Medline, Embase, Cochrane, etc.) must be carried out. The search strategy used in the various databases must be disclosed and presented. The inclusion and exclusion criteria of studies must be reported in a transparent manner. The efficacy data must be based on evidence of the highest possible quality, cf. hierarchy of evidence (Elwood 2007). Data from randomized clinical trials (RCTs) with adequate internal and external validity are preferred as the main basis for documentation of health effects. Data from observational studies (e.g. cohort and case control studies) may constitute an appropriate supplement to RCT-data or an alternative if such data are not available.

The assessment of data's internal and external validity must be done using checklists (see e.g. Norwegian Knowledge Centre for Health Services, 2009).

Effect data used in the pharmacoeconomic analysis should preferably be on hard endpoints (such as number of heart attacks, stroke, deaths, etc.), although data for intermediate endpoints (such as cholesterol or blood pressure) may be used. The causal relationship between intermediate endpoints and hard endpoints must nevertheless be well-documented.

Efficacy data should be the result of a direct comparison between relevant treatments. In the absence of efficacy data from a direct comparison between the intervention and the comparator, an indirect comparison may be accepted. However the lack of available direct comparative studies must be documented by using systematic reviews. Indirect comparisons should be made using a common comparator (a so-called adjusted indirect comparison). In order for indirect comparisons to be deemed valid, it is a prerequisite that the included studies are sufficiently similar in terms of population, intervention (e.g. treatment duration and dose) and outcomes. It must be shown/documentated that the similarity assumption is met. An indirect comparison introduces additional uncertainty in the analysis. This should be taken into account through sensitivity analyses.

When using clinical data from international sources, precaution must be used when assessing the data's transferability to a Norwegian setting. For instance, the applicant must be aware of whether treatment conditions in Norway correspond to the conditions described in the foreign studies with respect to therapy traditions, patient characteristics, comparators, etc. All deviations from the Norwegian setting must be highlighted and discussed separately; preferably, with the assistance of Norwegian experts, and based on the best available data (e.g. clinical and epidemiological expertise).

2.7 Viewpoint for the pharmacoeconomic analysis

Pharmaco-economic analyses should be performed from a societal point of view, but with the following limitations:

- The inclusion of productivity gains and costs due to the treatment effect are not compulsory. Additionally, the choice of estimation method is open. However, justification for choice of method must be justified (see 2.11).
- Costs related to added/extra life years should not be included.
- Deadweight loss due to tax funding should not be included.

Otherwise, all other relevant health effects (see 2.10) and costs (see 2.11) must be included in the analyses including their allocation amongst different groups in society (i.e. the distributional profile of the reimbursement decision).

The analyses must provide an overview of how impacts are distributed among different actors in order to ensure that it is possible to compare results with other analyses that make use of a different perspective.

2.8 Time horizon

The time horizon used in the analyses should be long enough such that all the important differences in future costs and health effects between alternatives are captured. This means that the time horizon for analyses should be long enough to the effect that further extension would not affect the results significantly. If the drug has an effect on mortality then a lifetime perspective should be used. This will usually involve an extrapolation of the intervention's health effects and costs to cover time periods the available efficacy data do not cover (see section 2.13 on modelling).

The requirements on documentation as concerns extrapolation are the same as for all other effect parameters, namely;

- Strong recommendation to use an adequate empirical data, and
- If extrapolation involves the use of quantitative analyses (e.g. survival analyses), then the estimation method and results should be explicitly stated and presented.

Additionally, sensitivity analyses showing how the results are influenced by the choice of different relevant time horizons should be presented (see section 2.14).

2.9 Methods of analysis

1. Cost-per-QALY analysis (CUA) is the recommended method of analysis for cost effectiveness evaluations. An important reason for this is based on the benefits measure of such analyses, namely, quality-adjusted life years - QALY (see 2.10). If the intervention under study affects survival, then the cost per extra life year gained should be separately accounted for.
2. Cost Benefit Analysis (CBA), an analysis method where the effect of the intervention under study is measured in monetary terms. This method is generally not recommended due to the ethical and technical challenges associated with setting a monetary value on health improvements (see for example Drummond et al. 2005, Olsen 2009).
3. Cost-effectiveness Analysis (CEA) is not recommended as the sole analysis method (see point above on CUA).
4. Cost-minimization Analysis (CMA). This type of analysis is recommended in certain situations where the use of other methods would appear as wastage of assessment resources. For instance, such situations arise when it is reasonable to assume that health effects (including side effects) are approximately similar between competing alternatives whilst costs differ.

However, it is essential that there is good enough documentation showing that the competing alternatives have approximately identical effect before using a cost-minimization analysis. CMA cannot be used if there is evidence from non-inferiority studies showing that the intervention under study is not non-inferior.

5. Cost-value Analysis (CVA) can be used as part of an additional analysis. See Nord (1999) and Nord et al. (1999) for a detailed description.

2.10 Measurement and individual valuation of health effects

The Quality adjusted life year (QALY) is the recommended measure for health effects in pharmacoeconomic analyses.

This is not because the QALY-methodology does not present shortcomings (see e.g. Brazier 2007), but because of lack of better instruments in addition to the following important features (Olsen 2009):

- A. It allows for comparison across different diseases.
- B. It includes life years and quality of life in the same measure and
- C. It is based on preferences for health states

There is disagreement about what the QALY is intended to be and to what extent the QALY methodology meets the theoretical assumptions it is based upon. Some consider QALY exclusively as a measure of health, while others increasingly see it as a measure of individuals' expected utility of health. For the latter to be true, it requires among other things that the value of a QALY is the same regardless of the size of the QALY gain and that the trade-off between time and quality of life remains constant. Empirical research shows that it is questionable whether these conditions are met (Gyrd-Hansen 2005, Olsen 2009, Desser 2010, Kvamme 2010). It is also important to note that the QALY does not measure society's valuation of health improvements because it does not take into account the degree of severity of the disease or other priority considerations (Nord 1999).

The main rule is that QALY-outcomes are to be calculated using multi-attribute utility (MAU)-instruments that evaluate both the physical and psychological condition of the patient as well as his/her social functioning. Some examples of such MAU-instruments are EQ-5D, SF-6D and 15D.

It is well documented that most of the existing generic MAU-instruments yield different QALY-results when applied to patients with the same health condition. We refer here to Brazier 2007, Culyer and Newhouse 2000. Since it is difficult to give precise recommendations in such situations, NOMA allows the applicant to freely choose generic MAU-instrument as long as the choice is well justified. For example, SF-6D and 15D are considered to be more sensitive than EQ-5D in the upper part of the value scale due to the possibility of a "ceiling"-effect on results when using EQ-5D (Brazier 2007). However, it is also been demonstrated that the use of SF-6D may yield results where a "floor"-effect is present (Brazier 2007).

The pharmaeconomic analysis must be based on Quality of Life (QoL)-data of highest possible quality. In order to collect such relevant data, it is compulsory to perform a systematic literature review and report the results. The quality assessment of the QoL-data should be done according to established criteria (see e.g. Brazier 2007, Table 8.11). This will ensure that the reasons for choosing a particular QoL-data set are clearly stated. The analyses must account for all direct and indirect value-instruments, methods and perspectives used in the calculation of QoL-values.

If data used in the pharmaeconomic analyses comes from clinical studies that also include relevant quality of life data or data that can be translated into quality of life scores using MAU-instruments (e.g. SF-36 data), then it is required to use these data. Any deviation from this rule must be justified.

When no data from relevant MAU-instruments are available then data from studies where the relevant health states have been valued by means of time trade-off or standard gamble

techniques can be used. If this type of data does not exist, then mapping the available health state valuation data over to MAU-instruments is allowed. The mapping method should be of an adequate quality though. There are several available approaches for this (see Brazier 2007, chapter 8.2 for further details). Additionally, weaknesses of the method used and their effects on the results of the analysis must be discussed and estimated.

If the QALY-weights used in the analyses are obtained from a non-Norwegian population, then the applicant must account for its transferability to a Norwegian setting, due to the fact that the use of weights estimated abroad may present challenges.

The probability distribution assigned to QALY-weights and their associated parameters should be based on all available information. This will help to reflect uncertainty around QALY-weights as accurately as possible when conducting sensitivity analysis.

2.11 Resource use and costs

As is common in most cases, adoption of a new treatment will have an impact on resource use, primarily consumption of goods, services, time and use of physical capital. All resources deployed in the provision of each of the included treatments in the analyses must be identified and valued before comparisons are made.

When reporting resource use, market prices should be used as proxies for unit costs / calculation prices (see FIN 2005). The size of the resource and calculation price used must be presented and justified separately.

2.11.1 Consumption of goods and services

The valuation of intermediate goods and services must, to the greatest extent possible, reflect market prices and exclude VAT (although taxes that correct for externalities such as environmental taxes must be included, if relevant).

There are however, many goods and services (drug treatments, visits to the doctor, hospitalizations, day care at a nursing home, laboratory services, etc.) that are traded in markets with imperfect competition and where the public is heavily involved in their production and/or funding. In such cases an equilibrium price that can balance supply and demand and that reflects both the willingness to pay of the consumer and the opportunity cost of production, does not exist.

It may then be more appropriate to use the marginal cost as calculation price. On the other hand, marginal costs may often be calculated only in a local context, while reimbursement decisions are not linked to a local context - but many local contexts: Most reimbursement applications include the use of medical and/or hospital resources across the country. Due to differences in workload between treatment units, the use of a representative marginal cost relevant for all of them may prove difficult. We therefore recommended the use of average costs instead of marginal costs.

There are several potential candidates for use as proxy estimates for average costs. NOMA recommends the following:

- *Hospital services:* The cost can be calculated using an ISF-reimbursement rate of 100% instead of the reimbursement rates hospitals operate with (most often, under 100%). The Norwegian Directorate of Health can be contacted for more information about the ISF-system.
- *Physician and specialist services:* The cost may be calculated by multiplying the relevant fee stated in the official tariff lists, by two (x2). This is because the true cost of providing medical and specialist services (e.g. consultations) is covered both through fees (i.e. the sum of the reimbursement rate and patient co-payment) and government grants (basic subsidies to general practitioners, operating subsidies to specialists). This represents a rough approximation of the true cost, but it is assumed that the cost estimate would become closer to the true average cost of providing the service than when not doing so. The Norwegian Medical Association and the Norwegian Health and Care department can be contacted in order to obtain a copy of the official list of fees and grants.
- *Outpatient laboratory and radiology services:* As with physician and specialist services, the unit costs for outpatient laboratory and radiology services can be calculated as the sum of the reimbursement fee per consultation and patient co-payment, multiplied by two (x2), so that the basic grant to the Regional Health Authorities is taken into account. For a copy of the official list of tariffs, user fees and grants, please contact the Norwegian Directorate of Health and/or HELFO
- *Nursing home services:* It is recommended to contact SSB (KOSTRA) and the Norwegian Directorate of Health for access to reliable estimates of the average cost of nursing home services.
- *Psychiatric care:* It is recommended to contact the Norwegian Directorate of Health for reliable estimates of unit costs in the mental health service.
- *Pharmaceuticals used in in-patient treatment of cancer:* It is recommended to contact the Norwegian national register for cancer drug treatment to get data on

drug costs associated with cancer in-patient treatment.

Proxies for average costs will generally reflect both fixed and variable costs. In some cases it may be most relevant to only use variable costs. This is in cases where treatments are believed to affect only the variable cost estimates and not the fixed costs. In such cases the fixed costs should be calculated and then subtracted from the proxy estimates.

2.11.2 Time use

Time is a scarce resource, and as such it has an opportunity cost. In health economics the use of time is considered both as an input to a treatment and as an output of the treatment (Drummond et al. 2005). Below we present these two different perspectives.

2.11.2.1 Time as an input to treatment

All treatments require that patients, and possibly their relatives/caregivers too, spend time when treatment administration is required (travel time and treatment period). When comparing different treatments, it may be that one treatment alternative saves/requires more time as compared to others. In such cases, the difference in time usage must be estimated, and the results of the model reported both with and without the inclusion of those accrued time costs.

To calculate the value of the differences in time use, the applicant must consider the most probable alternative use of that time by the patient/caregiver (FIN 2005):

- If the alternative use of time is more/less working hours, then the calculation method per hour should be the average hourly wage in Norway including income tax, employer's contribution to social security and other social costs. This type of information is provided by Statistics Norway.
- On the other hand, if the alternative use of time is more/less leisure, then the calculation method per hour should be the average hourly wage in Norway after tax. This calculation method applies for both employed and unemployed patients and their relatives/caregivers, irrespective of age.

2.11.2.2 Time use as a result of treatment outcome (productivity effects)

New treatments usually allow patients to experience more time in good health. If this time is spent working (getting back to work after a sick leave, or working more hours if currently working part-time), we say there are productivity gains. On the other hand, when patients experience less time in good health and that time was going to be spent working, we say there are productivity losses.

Whether and how to include the productivity effects in health economic analyses are a controversial issue (Drummond 2005). Nevertheless, when evaluating treatments whose main purpose is to increase the probability of workers remaining or returning to the labour market and therefore avoiding sick leaves, productivity effects are of the highest relevance. Besides, it is also true that productivity effects are included in economic evaluations in other sectors. This is why NOMA is open to the inclusion of such effects in the analysis.

The applicant may include productivity effects in the standard analysis where applicable. This is not required, but if productivity effects are eventually included then the results of the analysis must be shown both with and without these effects.

Applicants are free to choose method for the calculation of production effects, but their choice must be justified. See Drummond et al. (2001) for an overview of available methods and the advantages and disadvantages associated with them.

2.11.3 Additional considerations regarding costing in pharmacoeconomic analyses

- i. In the standard analysis, the viewpoint is a societal one with limitations (see 2.7). From that point of view, payment of Social Security benefits, pension benefits, VAT and other transfers of purchasing power between economic agents within society are not included in the analysis as they are not considered to be costs (FIN 2005).
- ii. Capital costs associated with treatment are usually already included in physician fees, DRG-weights, outpatient clinic fares, grants to nursing homes, etc. If any of the treatments under study is associated with additional capital costs then this must be discussed and incorporated into the analysis.
- iii. The discount rate required in these guidelines is a real interest rate (see 2.12), meaning that neither prices nor wages in the analysis should be adjusted for inflation.
- iv. The potential for generic competition must nevertheless be incorporated when forecasting future drug prices. This is because the prices of drugs drop sharply when generic competition is introduced. In Norway this is regulated by the stepped pricing system. Generic competition may affect both the comparator(s) and intervention, hence affecting cost-effectiveness results significantly. There is often considerable uncertainty associated with the future evolution of drug

prices, especially as regards patent expiration and estimations about how much prices will drop. There is however no obstacle for handling uncertainty around prices in the same way as uncertainty around other important variables in the model. *It is therefore required that the likely price paths for all drugs included in the analysis are forecasted, taking into account the onset of generic competition and the stepped-price system. The profile of the price paths must be justified and the uncertainty surrounding these discussed and illustrated. Stepped-prices are to be used in the base-case when at the moment of sending the reimbursement dossier to NOMA, a marketing access application regarding generic products for the relevant active ingredient is already been registered.*

Information about registered market access applications for generic products can be found on NOMA's website.

- v. Resource use and costs for treating the same patient group may vary considerably between countries. A pharmacoeconomic analysis conducted abroad can be of little relevance in a Norwegian context due to differences in clinical practice, health care system capacity, organization, and reimbursement systems. *Therefore special care must be given when adapting costs from abroad to a Norwegian setting.*
- vi. The Norwegian Knowledge Centre for Health Services started in 2011 a project aimed at defining and collecting important unit costs to be used in health economic evaluation. NOMA's guidelines may then experience changes as the project is completed.

2.12 Present value estimation and discounting

In order to compare and summarize health effects and costs that take place in different years, the annual health outcomes and costs must be converted to a present value. In a present value calculation, both health effects and costs are discounted at a rate equivalent to the one recommended by the Ministry of Finance for public projects with moderate systematic risk, currently at 4 % per year. This rate is used due to the fact that most projects in the health sector are assumed to have moderate systematic risk. The discount rate is a real interest rate so that prices in the pharmacoeconomic analysis must not be adjusted for inflation (FIN 2005).

NICE (National Institute for Health and Clinical Excellence) recommended earlier different discount rates for health outcomes and costs, but then in 2004 it changed its recommendation and proposed the use of the same discount rate. This triggered debate in central pharmacoeconomic journals which is not yet closed (Brouwer 2005, Claxton 2006, Gravelle 2007, Nord 2011, Claxton 2011). NOMA's recommendation when it comes to discounting may change as a result of the on-going debate and/or new knowledge.

2.13 Modelling

Pharmacoeconomic analyses will often make use of modelling, even when using resource and efficacy data collected as part of a clinical randomized trial. Modelling is necessary in enabling analyses to cover the entire relevant time horizon and/or integrate data from different sources. This helps to shed light on effects of the treatment that are not measured in randomized clinical trials.

There are various approaches available when building a pharmacoeconomic model, such as decision trees and Markov models. The choice of approach should be justified. It is very important that the assumptions made and data used in the model are well documented. If the consequences of the treatment are spread over a long period of time, it is compulsory to make projections about the future evolution of key variables such as mortality, quality of life, treatment options and costs. Models should be carefully validated in order to check whether the calculations done are both accurate and consistent (internal validity). Furthermore, model results in terms of predicted clinical events must, whenever possible, be compared to independent sources (i.e., against data that is not used as input in the model), such as e.g. epidemiological studies.

Models developed abroad can be used when applying for general reimbursement in Norway, but they must be adapted to a Norwegian setting in terms of clinical practice, costs and possible health effects. It must be clearly stated which adjustments were made to adapt it to a Norwegian setting. When no adjustments are made, then the impact due to such lack of adaptation should be calculated and presented in the results.

2.14 Uncertainty

Uncertainty present in the analyses must be examined and discussed. In the following section the main sources of uncertainty in health economic evaluation are presented and discussed, as well as the preferred methods for handling uncertainties. This section will also address other relevant issues regarding uncertainty.

2.14.1 Sources of uncertainty

In modern health economics literature it is common to distinguish between different sources of uncertainty (Briggs 2001, Drummond 2005). Four of them are discussed below:

1. *Methodological uncertainty*

This kind of uncertainty arises when there is no agreement in the academic world about how to handle certain issues in health economic evaluation. One example of this is the on-going discussion regarding the choice of discount rate, an issue that involves a good number of ethical, political and economical aspects.

2. *Parameter uncertainty*

The true value of many important variables used in the analyses such as costs, utilities and treatment effects are in most cases unknown so that the only available data are estimates from samples. These estimates are then treated as random variables and the uncertainty around them is given by their variance and the amount of available sample data.

3. *Model and structural uncertainty*

When building a model, some assumptions and choices are made about the model's structure in order to balance the need for precision with the need for keeping the model as simple as possible. In some cases there may be disagreement about which assumptions and/or choices are most plausible. This may in turn cast doubt on the results.

4. *Generalization uncertainty*

This kind of uncertainty arises especially when PICO (Patient-Intervention-Comparator-Outcome) in the health economic analysis do not correspond with the relevant ones from a Norwegian viewpoint. For example, when the data used in the model come from a population that is different to the relevant one, when the setting of the treatment or the dosage is different to the ones used in Norway, etc.

2.14.2 *Handling of uncertainty*

Uncertainty in the results of analyses must be examined and discussed using deterministic and/or probabilistic sensitivity analysis.

2.14.2.1 *Deterministic sensitivity analysis*

This type of analyses can be carried out in the form of one-way and multi-way analyses (Drummond et al. 2005)

- One-way analyses: Here estimates for each parameter are varied one at a time in order to investigate the impact of each on the results. In order to get a first impression of which parameters and assumptions have greatest influence on the results, it is compulsory to carry out a one-way sensitivity analysis for the most relevant parameter/assumption candidates. One possible way of conducting this kind of analysis is to assign the parameter under study three different values: Its average, and the values representing the lower and upper boundaries of the confidence interval. The results for all one-way sensitivity analysis must be presented in a Tornado-diagram.
- Multi-way analyses: Here estimates for several parameters are varied at the same time to investigate the aggregate effect on the results.

- Scenario-analyses. Here a series of scenarios are constructed representing a subset of the potential multi-way analyses. Typically, the scenarios include a base case scenario (best guess) and the most optimistic (best case) and most pessimistic (worst case) scenarios.

The usefulness of one-way, multi-way and scenario analyses can in some cases be limited: One-way analyses fail to give information about how the results depend on the correlation between parameters or on the joint parameter uncertainty, while multi-way analyses involving a great amount of parameters may result in very many value combinations such that it becomes difficult to draw any conclusions. Additionally, neither one-way, multi-way nor scenario analyses give information about the likelihood of the different outcomes of the analysis.

This is why univariate and multivariate sensitivity analysis are the preferred methods for handling methodological, model, structural and extrapolation/generalization uncertainty, while probabilistic sensitivity analysis (PSA) is the preferred method for handling parameter uncertainty.

2.14.2.2 Probabilistic sensitivity analysis (PSA)

In this kind of analyses a relevant set of variables are defined as random variables with an associated probability distribution to reflect their full uncertainty. However, the choice of variables to include in the PSA and their associated probability distributions must be discussed and justified. Distributions' most important moments (in many cases, the expected value and the variance) must be as far as possible based on empirical data.

If no adequate empirical data are available to inform the choice of distribution, the analyst may freely choose one based on the nature of the random variable. However, one should have in mind that only some types are considered to be relevant in modern health economics literature (e.g. Briggs 2001 and 2006)

As stated above, PSA is the preferred method for handling parameter uncertainty. Model and structural uncertainty may as well be examined with the help of PSA, by assigning probabilities or distributions to the different assumptions and choices under consideration. The results from the PSA should preferably be presented in the form of scatter diagrams of the simulations on the cost-effectiveness plane, CEAC (for comparisons between two or more treatments), the CEAF and histograms of the Incremental Net Benefit-results (Fenwick et al. 2001, Drummond et al. 2005 and Briggs et al. 2006).

2.14.2.3 *Some additional moments when handling uncertainty*

- If systematic bias is detected in the available empirical data the analysis is based on, then this should be dealt with when characterizing the uncertainty around the relevant estimates.
- The impact patient heterogeneity (i.e. differences in patient features) may have on the results should be examined through sub-group analyses, and not through uncertainty analyses.
- When both clinical and costing data are collected as part of a clinical study, uncertainty may be handled through statistical analyses (Briggs et al. 2006). It is also possible to model effects, costs and relationships which are not fully covered in the study.
- Decisions based on existing information will be uncertain, and there will always be a chance that the alternative with the highest Incremental Net Benefit eventually is not the chosen one (i.e. one makes a wrong decision). The expected cost of uncertainty is determined jointly by the probability that a decision based on existing information will be wrong and the consequences of a wrong decision (Briggs et al. 2006).

The expected costs of uncertainty regarding a reimbursement decision should be examined with the help of Incremental Net-Benefit (INB) analysis (Fenwick et al. 2001), Expected Value of Perfect Information (EVPI) analysis and Expected Value of Perfect Information for Parameters (EVPPI). The results from the EVPI-analysis may be used to examine the value of conducting further research rather than making a decision immediately (Briggs et al. 2006, Guttormsen et al. 2010), while the results from the EVPPI-analysis may be used to find out what type of additional evidence would be most valuable to collect (Briggs et al. 2006)

2.15 Presentation of the methodology and results

Methods, assumptions and included data must be accounted for and presented (including references) so that the various steps taken in conducting the analyses can be easily followed and reproduced if need be for example under alternative assumptions.

In addition, results of the analyses must be presented both at an aggregated level and broken down into categories for both costs and health effects:

- Costs: drug costs, hospital costs, care costs and any costs associated with the production effects.
- Health effects (QALY and LYG)

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