Statens legemiddelverk

Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals

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Introduction

The Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals reflect the principles for priority-setting which are described in White Paper 34 (2015-2016) (1), hereafter referred to as the Priority-setting White Paper ("Prioriteringsmeldingen"). The guidelines are based on the Norwegian regulation on Medicinal Products ("legemiddelforskriften") and the Blue Prescription regulations ("blåreseptforskriften") (2).

The Norwegian Medicines Agency (NoMA) has had guidelines for pharmacoeconomic analyses since 2002. These guidelines appear here in an extended and updated form, which is reflected in the new name, "Guidelines for the submission of documentation for single technology assessments (STA) of pharmaceuticals".

These guidelines are to be used in the preparation of documentation for single technology assessments (STA) of pharmaceuticals for public financing under the National Insurance Scheme ("folketrygden") and for the specialist health services ("Nye metoder"). A major target audience for these guidelines is therefore those who will prepare and submit such documentation.

An important aim of this update is to adapt the guidelines to the principles agreed in the Priority-setting White Paper. The new guidelines are more precise in order to clarify the requirements that documentation needs to satisfy. The aim is to make it easier to submit documentation and to limit the need for the Norwegian Medicines Agency (NoMA) to request further documentation. The single technology assessments (STAs) and the relevant guidelines apply at a group level. They are not aimed at the practical clinical level where decisions are made about which treatment an individual patient should be offered.

The guidelines for *single* technology assessments which are presented here specify the documentation required for assessing whether a new pharmaceutical should be publicly financed by the health services in Norway, given the requirements for prioritisation set by the Priority-setting White Paper. The new pharmaceutical will thus be evaluated by comparing it to the established treatment alternative(s) which would be replaced by the new pharmaceutical. Assessing whether a new pharmaceutical should be introduced to replace the current pharmaceuticals(s) or other established methods, is a narrower decision-making context than one which considers a broader perspective (cf Instructions for Official Studies ("Utredningsinstruksen")) or evaluating which alternative methods could remove or reduce the burden of disease for a patient group. If several new pharmaceuticals are to be evaluated against each other, or against other treatment alternatives, then a *full* health technology assessment may be more appropriate.

Health service interventions are to be evaluated against three prioritisation criteria – the benefit criterion, the resource criterion and the severity criterion. The priority-setting criteria are to be evaluated together and weighed against each other. A cost-effectiveness ratio must be calculated which reflects the use of resources in relation to benefit. This is to be done using a health economic analysis, by means of a health economic evaluation, typically involving decision analytic modelling. The cost-effectiveness ratio will be weighed against the severity of the relevant condition/disease. For more severe conditions, a higher cost-effectiveness ratio will be accepted. This is discussed in more detail in the Priority-setting White Paper, together with the reports from the Norheim Commission and the Magnussen Working Group (1, 3, 4). In these guidelines, chapters 2-8 cover the benefit criterion. Benefit is to be measured in Quality Adjusted Life Years. The benefit depends on the relative efficacy of the pharmaceutical on patient survival and on health-related quality of life.

Chapters 9 and 10 cover the resource criterion and calculation of the cost-effectiveness ratio. Chapter 11 covers the severity criterion. Chapters 12 and 13 respectively cover uncertainty and budget implications, two central factors which will form part of the overall discretionary evaluation.

The overall evaluation of an intervention will be based on both the STA and the discretionary evaluation. The latter is primarily linked to evaluation of the quality and the level of uncertainty in the documentation, as well as the budget impact.

In the Blue Presciption regulations ("blåreseptforskriften") § 1b it is stated that national insurance will only provide benefits to cover the expense of pharmaceuticals which are to be used for the treatment of serious disease or of risk factors which are highly likely to cause or worsen serious illness, and where there is a need for or risk of repeated treatment over a long period of time. These criteria must also be fulfilled for a pharmaceutical to be financed under the National Insurance Scheme.

These guidelines describe the requirements and recommendations for documentation of benefit, resource use and severity as well as budget impact. The guidelines describe the preferred methods for the preparation of documentation. Any deviation from these requirements and recommendations must be justified. The guidelines do *not* describe how the Norwegian Medicines Agency will evaluate the documentation beyond what is stated above.

In this document, the words **will** and **must** are used to express an absolute requirement for the documentation to be submitted. **Should** is used when there is not an absolute requirement for submissions to use this choice of method, but the Norwegian Medicines Agency, nonetheless, recommends it. When c**an** is used, this means that there are several methods available, and that the Norwegian Medicines Agency does not prefer any of these in particular.

Small patient groups

There is a requirement that all new pharmaceuticals are evaluated by a health technology assessment before a decision is made about financing the pharmaceutical. This also applies to pharmaceuticals aimed at *small patient groups* and the narrower group of pharmaceuticals aimed at *very small patient groups with extremely severe conditions*. The guidelines in this document therefore also apply to submission of documentation for such pharmaceuticals. In many cases there is limited documentation for pharmaceuticals aimed at small patient groups and very small patient groups with extremely severe conditions. *Submission* of documentation in such cases should, nonetheless, follow the recommendations in these guidelines as far as possible. Pre-meetings with the Norwegian Medicines Agency are recommended before the preparation of documentation to clarify what sort of documentation is possible or appropriate in the individual case.

When *assessing* pharmaceuticals aimed at small patient groups, a lower level of documentation may be accepted, and for very small patient groups with extremely severe conditions a higher cost-effectiveness ratio may be accepted than for other pharmaceuticals (1, 2).

A separate note describes the scheme for pharmaceuticals aimed at very small patient groups with extremely severe conditions[1].

Vaccines, infectious diseases control and prevention and antimicrobial resistance

For STA of vaccines, please refer to policy details outlined in the guidance document "Retningsgivende notat om dokumentasjonsgrunnlag for hurtig metodevurdering av vaksiner"[2]. The guidance document supplements the Guidelines in this document.

For questions regarding how infection control and prevention (ICP) or antimicrobial resistance should be addressed in single technology assessments, please refer to policy details outlined in the guidance document "Smittevern og resistens i metodevurderinger" [3]. The guidance document supplements the Guidelines in this document.

The Norwegian Medicines Agency recommend pre-submission meetings before the preparation of documentation for STAs of vaccines or STAs where ICP or antimicrobial resistance are a key element.

Conclusion

The template for the submission of documentation for single technology assessment (STA) of pharmaceuticals must be used (this is available at www.legemiddelverket.no).

These guidelines may be updated as necessary, for example, if new guidance, new evidence or experience etc suggests it is necessary.

These revised guidelines apply from and including 1 January 2018.

During a transition period, from 1 January until and including 30 June 2018, documentation can be submitted using either the revised or the previous guidelines (valid from 1 March 2012). From and including 1 July 2018, these revised guidelines must be used for the submission of documentation.

From and including 1 January 2018 the *evaluation* of documentation for public financing of pharmaceuticals will be made in accordance with the criteria and principles of the Priority-setting White Paper and the revised Norwegian Act on Medicinal Products ("legemiddelforskriften") and the revised Blue Prescription regulations ("blåreseptforskriften").

Following a mandate from the Ministry of Health and Care Services (HOD), the Norwegian Medicines Agency has developed guidelines in cooperation with a multi-agency working group consisting of representatives from the Norwegian Institute of Public Health, the Norwegian Directorate of Health, the four regional health authorities and the Norwegian Hospital Procurement Trust, Division Pharmaceuticals (LIS).

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[1] https://legemiddelverket.no/offentlig-finansiering/dokumentasjon-for-metodevurdering/hvordan-sikre-tilgang-til-legemidler-for-serskilt-sma-pasientgrupper-med-svert-alvorlig-tilstand

[2] https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Dokumentasjon%20til%20metodevurdering/Retningsgivende%20notat%201.6.2019.pdf

[3] https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Dokumentasjon%20til%20metodevurdering/Rapport%20-%20Smittevern%20og%20resistens%20i%20metodevurderinger.pdf

The Norwegian Medicines Agency wishes to thank the working group and others who have taken part in the compilation of these guidelines, as well as all those who have contributed by way of discussion, suggestions and comments during the consultation process.

Norwegian Medicines Agency, 18 December 2017

Contents

Glossary of terms

Abbreviation	Definition
AFT	Accelerated failure time model
AIC	Akaike's Information Criteria
AS	Absolute shortfall
AUP	Pharmacy maximum sale price
BIC	Bayesian Information Criteria
CCTR	The Cochrane Controlled Trials Register
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curves
CrI	Credible intervals
CUA	Cost-utility analysis
DSU	Decision Support Unit
EQ-5D	EuroQol- 5 dimensions
EVPI	Expected value of perfect information
EVPPI	Expected value of partial perfect information
Funnel plots	A graphical figure which shows a study's precision in relation to the study size. The figure can be used to evaluate whether there is a link between the study size and the treatment effect.
Helfo	Health Economics Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value (also referred to as QALY weight)

Abbreviation	Definition
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICP	Infection control and prevention
IPD	Individual patient data
ISF	Activity based financing («Innsatsstyrt finansiering»)
ITC	Indirect treatment comparison
ITT	Intention to treat
KM	Kaplan-Meier
KOL	Key opinion leader
LIS	Norwegian Hospital Procurement Trust, Division Pharmaceuticals (Sykehusinnkjøp HF divisjon legemidler (LIS))
LYG	Life years gained
MAIC	Matching Adjusted Indirect Comparisons
MeSH	Medical Subject Headings
MTC	Mixed treatment comparison
n eff	Effective sample size, ESS
NICE	National Institute for Health and Care Excellence
NIPH	The Norwegian Institute of Public Health
NMA	Network meta-analysis
OS	Overall survival
outliers	Utliggere
PFS	Progression free survival
PH	Proportional hazards

Abbreviation	Definition
PICO	Patient population, intervention, comparator and outcome measures.
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analyses
QALYs	Quality Adjusted Life Years
RCT	Randomised controlled trial
RHF	Regional health authority
ROPE	Region of practical equivalence
RWD	Real World Data
SSB (KOSTRA)	Statistics Norway (Municipality-State-Reporting)
STC	Simulated Treatment Comparisons
TTE	Time-to-event
VoI	Value of information analysis

1. General information about submission of documentation

1.1 Template

A template has been developed for submission of documentation. This is available on the website of the Norwegian Medicines (https://legemiddelverket.no/English). Use the template to prepare and submit documentation. In the template, there are a number of tables and overviews which require the company making the submission to sum up information from different parts of the documentation. It is possible to send in appendices or additional information attached to the template.

1.2 Comparators

In the health economic analysis, which forms part of the STA, differences in efficacy (and benefit) and resource use between the intervention and the comparator(s) are to be shown. It is therefore important that the relevant comparison alternatives are used in the analysis. The principles for choice of comparator are discussed in Chapter 3.4. Contact the Norwegian Medicines Agency (NoMA) for guidance if there is any doubt about the choice of comparator.

1.3 Health economic model

The health economic model must be designed to show all the most likely scenarios. It is therefore important that the selection of time horizon, population (or sub-groups), parametric model for time to event data and other central variables used in the model can be modified by NoMA and are not fixed to one main analysis.

1.4 References

It is not necessary to include all references in the documentation. However, references for *all the most important efficacy studies* and references used as the *basis for input data* in the health economic analyses and in calculations of severity and budget impact must be included. References (in documents and models/spreadsheets) must be formatted so they are linked directly to the individual publication/file (enclosed as a PDF).

1.5 Responsibility

State who has the responsibility for preparation of the submitted documentation, and others who have taken part in the work

1.6 Language

Documentation for single technology assessment of pharmaceuticals must be written in Norwegian, Swedish, Danish or English.

1.7 Confidentiality

NoMA acts within the Public Administration Act and the Freedom of Information Act. There are guidelines for how NoMA deals with confidential information in connection with health technology assessments. These are published on the agency's webpages.

2. Scope

The scope will include a short description of which indications the STA includes, the patient population relevant to the STA, the pharmaceutical, the alternative(s) for comparison and the most important outcome measures in the analysis (PICO[4]).

Documentation will be submitted in accordance with the order from the Ordering Forum Bestillerforum/NoMA. Any variation from this must be agreed in advance with NoMA. Communication will go via NoMA both for pharmaceuticals financed by national insurance and for pharmaceuticals financed by the regional health authorities. (Companies will not contact the Ordering Forum or the regional health authorities directly).

Describe briefly which method of health economic analysis has been used (cost-utility analysis, cost-minimisation analyses etc., see chapter 9.1).

[4] PICO: Patient, Intervention, Comparator, Outcome

3. Description of the intervention and the therapeutic area

3.1 The disease and Norwegian clinical practice

Briefly describe the disease or condition to be assessed and how it is currently treated in Norway. Ideally refer to national guidelines and to current Norwegian clinical practice. Specify any clinicians or key opinion leaders who have been used to confirm clinical practice.

Describe the prevalence and incidence of the disease/condition in Norway, and developments during the last 5 years. For very small patient groups, also describe the prevalence on a global basis. Describe the size of the relevant patient population.

3.2 Description of the intervention

Describe the intervention in accordance with the template for submission of documentation, including, the pharmaceutical form, posology, method of administration, duration of treatment, whether the pharmaceutical is to be used with other pharmaceuticals or treatments, as well as any necessary monitoring.

3.3 The patient population and the intervention's position in Norwegian clinical practice

Describe the place the intervention is supposed to fill in the treatment algorithm for the defined population.
Describe and justify which pharmaceutical or other treatment will primarily be replaced by the introduction of the intervention (see chapter 3.4).

Describe as precisely as possible the patient population in Norway which is likely to use the intervention. Specify if the analysis only covers part of the pharmaceutical's indications/areas of use. Describe which age group is particularly affected the disease or condition and state the average age (if necessary median age) of the patient group in Norway which is relevant for treatment (not the age of the study population or populations). This age should be supported by clinical experts, registry data or other relevant sources.

If the company believes there are sub-groups of patients for whom the intervention may have a different efficacy and safety than for the whole population the STA is considering, reasons must be given. Refer to relevant data and specify whether these sub-groups were pre-defined in clinical studies. Describe briefly relevant diagnostic tests and methods which are used for the selection of patients.

3.4 Choice of comparator

Describe and explain the choice of comparator. The guidelines for choice of comparator are given below. Contact the Norwegian Medicines Agency for guidance if you are in any doubt about the choice of comparator.

3.4.1 Main rule

The comparator is the alternative or those alternatives which most probably will be completely or partially replaced if the intervention is taken into use.

This will often be current established practice (for example, according to national guidelines) or the treatment which is most commonly used (number of patients). The comparator may consist of a treatment other than pharmaceuticals (for example, surgery), and may take the form of prevention, curative treatment, palliative treatment or “wait and see” initiatives. Only in exceptional cases will comparison with no treatment be relevant.

In the STA it is also possible to compare different treatment sequences on condition that there is robust data to do this.

3.4.2 Several comparators

When there is no clear single alternative, but there are several commonly used alternatives, then more comparators should be included.

The comparators must be presented in their individual form, ie, not mergers of two or more alternatives using, for example, average effects, costs etc. A comparison using a combined alternative will not show whether the intervention is cost effective in relation to each of the individual comparators which have been combined.

Some randomised, controlled trials have an “investigator’s choice” control arm. In such cases, it is not always possible to individualise the alternatives, and even if it is possible, this can lead to reduced strength in the results. Whether the “investigator’s choice” or one of the individualised alternatives can be used in the STA, must be justified in each case.

3.4.3 The comparator has not been evaluated by the Norwegian Medicines Agency

If it has not been established whether the comparator is cost effective, an analysis against this comparator will not usually be adequate to show cost-effectiveness. The analysis should, then, as a rule be supported by an additional analysis. This could be an analysis against placebo, best supportive care, or an alternative which can reasonably be assumed to be cost effective.

If the comparator can be viewed as established practice over a long period of time and has a documentedefficacy for the population relevant to the STA, and the cost connected with this comparator is low, then it can be accepted as the only comparator in the analysis. It is recommended that such cases are cleared with NoMA in advance.

3.4.4 The comparator has previously been evaluated as not cost effective by the Norwegian Medicines Agency

If it has been established by an earlier STA that the comparator is not cost effective, but it has still been used in clinical practice, then the analysis needs to be supported by an additional analysis as in the point above.

4. Literature search and selection of relevant documentation

The aim of the literature search is to document how the central data sources used for the STA have been found. Use the literature search to identify relevant documentation for:
- Efficacy/safety data which is used for documentation of relativeefficacy
- Health state utility values (HSUV) (if the data from the literature is used in health economic analyses or calculations of severity)
- Any other, central data where the company considers that a literature search will help improve the quality of the documentation

Base the literature search on internationally validated methods, for example (5-8).

4.1 Literature search

Documentation of the literature search should, as a minimum, include the following:

- A written protocol which allows the search to be reproduced:
    - Precise formulation of the research question
    - Search strategy with the associated search strings
    - Description of the MeSH terms used
- An *a priori* definition of the inclusion and exclusion criteria and the reasoning for these.
- A list of the databases the search has been carried out in.
- Data extraction: Description of the selection of studies (including whether one or more reviewers have been involved, how disagreements were handled, eg, by an independent professional colleague). Log which studies were excluded and why.
- Justification of the chosen time period for the search (how far back in time). If the original literature search is more than a year old, it must be updated by repeating the search for the following period. Include a list of new, relevant studies.
- Flow chart that shows the study selection (eg, PRISMA).
- Funnel plots which give an indication of the publication bias where this is relevant.
- Discussion of the strengths and weaknesses of the literature search.

As a minimum, the following databases should be included:
- Efficacy and safety:
    - The Cochrane Controlled Trials Register (CCTR)
    - Other relevant electronic databases not covered by CCTR (eg, MEDLINE/PubMed, EMBASE, PsychInfo etc.).
- Quality of life:
    - MEDLINE/PubMed, EMBASE, and other more specific databases. For a detailed description of how a literature search for quality of life can be carried out, as well as which databases are relevant, you are referred to NICE DSU Technical Support Document 9 (8).

Manual search in other sources (eg, conference posters, conference abstracts, reference databases and other types of documentation not covered by electronic databases) as well as grey literature searches where this is relevant.

5. Documentation of clinical efficacy and safety

This chapter applies both to the intervention to be assessed and and to the chosen comparator (see chapter 3.4).

Unpublished data which the company has knowledge of and access to, must also be included if it is relevant.

According to the template for submission of documentation, studies of the relevant pharmaceuticals/interventions are to be presented with the following information: study design, intervention, comparator, sample size, patient population, endpoints (including definition of endpoint), and the extent to which these studies have been used in the health economic model.

Show the results for the primary and most important secondary endpoints in the table and follow-up time. Present other outcomes as well if they have been used in the health economic model. Document where these outcomes have come from, and why they are more relevant to the STA than the primary endpoints from the studies.

If there is important information which is not suitable for presentation in table form (aim of the study, inclusion criteria, exclusion criteria etc.), give a description of this.

Describe the most important patient characteristics which are relevant to the clinical response (effect modifiers).

5.1 Documentation of the clinical efficacy of the intervention

Give a description of the most important studies which form the basis of the marketing authorisation and other relevant studies which show the clinical efficacy of the intervention, regardless of whether they have been used in the model or not. The template for submission of documentation must be followed.

5.2 Documentation of the clinical efficacy of the comparator(s)

Give a description of the relevant studies which show the clinical efficacy of the comparator(s), regardless of whether they have been used in the model or not. The template for submission of documentation must be followed.

5.3 Description of adverse reactions which are relevant to the scope/STA

In accordance with the template for submission of documentation, an overview of adverse reactions will be included for the same studies as in point 5.1, both for the intervention and the comparator(s). Describe the adverse reactions which are relevant to the STA. These will most often be frequent, usual, and serious adverse reactions (eg, those described as “important identified” in the risk management plans).

Describe the management of adverse reactions in clinical practice (monitoring, follow-up, use of resources, costs etc). Justify why the relevant adverse reactions are or are not included in the health economic model, and how they have, if relevant, been modelled (eg. reduced quality of life, costs of monitoring, costs of treatment etc.).

5.4 Ongoing studies

Give an overview of studies which are ongoing on the pharmaceuticals which are relevant to the STA.

6. Documentation of relative efficacy

6.1 Methods for documentation of relative efficacy and safety

6.1.1 General information

The documentation of relative efficacy and safety will be based on systematic literature searches (see Chapter 4).

Efficacy and safety data from randomised controlled trials is preferred over data from studies of other designs.

If there is no efficacy data from direct comparison between the intervention and relevant comparators, then indirect comparisons can be made. This can include pairwise adjusted indirect comparisons, network meta-analyses (NMA) or other validated methods. For indirect comparisons the chosen studies/data sources must be evaluated both quantitatively and qualitatively. Use validated tools for this evaluation. Describe the risk of systematic bias in the studies/data sources.

Unadjusted indirect comparisons (naive comparisons) are generally not accepted.

For presentation and description of the studies, see the template for submission of documentation.

6.1.2 Direct comparisons

Efficacy and safety data is preferred from randomised controlled trials where the intervention is compared head-to-head with relevant comparators. If there are relevant systematic reviews, these can also be used as part of the documentation.

6.1.3 Pairwise indirect comparisons

Use appropriate, transparent, validated, statistical methods. Assumptions and conditions on which the method is based must be defined and discussed.

For more details, see Appendix 1–Documentation on the relative efficacy of indirect comparisons.

6.1.4 Indirect treatment comparisons (ITC)

Documentation of efficacy and safety data can be based on meta-analyses or network meta-analyses if there is relevant data which uses comparable endpoints. If there are both head-to-head and indirect studies, a mixed treatment comparison (MTC) can be carried out.

For more details, see Appendix 1Documentation on the relative efficacy of indirect comparisons.

6.1.5 Other statistical methods

In those cases where there is no coherent network of studies which link the two treatments together, the documentation of relative efficacy must be based on a comparison of the efficacy from single arm clinical studies or single arms from studies. However, statistical methods which give a better chance of evaluating relative efficacy rather than unadjusted indirect comparisons must be used. If individual patient data is available (IPD) for (at least) one study, then, for example, methods such as Matching Adjusted Indirect Comparisons (MAIC) or Simulated Treatment Comparisons (STC) can be used if the relevant conditions for these methods are fulfilled.

For more details, see Appendix 1–Documentation on the relative efficacy of indirect comparisons and, eventually, chapter 6.3.

6.2 Extrapolation of efficacy

Justify assumptions about differences in efficacy beyond the study period.

In health economic analyses a form of parametrisation is often used for extrapolation of the clinical time to event data beyond the actual study period. Examples are time to progression in cancer, i.e., progression free survival (PFS), and time to death, i.e. overall survival (OS). Time to a cardiovascular event is also time to event data.

Refer to Appendix 2 for the requirements and methods for parametrisation and extrapolation.

6.3 Use of Real World Data (RWD)

By Real World Data we mean, for example, data from cohort studies, phase IV studies and registry data. RWD in this context is nonrandomised studies and observational data from clinical practice.

Pivotal clinical studies are the preferred source of efficacy data in a cost-utility model.

However, RWD can be used to support evidence of, for example, epidemiology, treatment duration in clinical practice, resource use, survival, or adherence to treatment in the Norwegian clinical practice. If RWD are used as a source for modelling the comparator arm when relevant clinical data for comparator is lacking, a detailed discussion of RWD source quality, study design (including endpoint definition, inclusion criteria, timing of data collection), patient characteristics, statistical considerations (e.g. how missing data were managed) will be required. Similarities and differences between the pivotal clinical trial and RWD should be examined. A discussion on how representative RWD are of the population should also be provided. Any source of bias should be highlighted.

7. Documentation of health-related quality of life

Quality adjusted life years (QALY) will be used as the benefit measure for STAs at group level, and must, in general, be based on patient-reported measures, made with EQ-5D. Quality of life data which is used in STAs is to be reported in line with the template for submission of documentation.

Quality of life data can be taken directly from the clinical studies which form the basis for documentation of relative efficacy, or from external sources identified through a literature search. If measures of quality of life have been made using EQ-5D in the clinical studies which form the basis for relative efficacy, it must be justified if these have not been used in the health economic analysis. If quality of life data from the literature is used in the health economic model, this must be documented by a systematic literature search (see chapter 4) and the choice of sources/values justified and discussed.

Health state utility values (HSUV), both sourced and from the relevant clinical study, implemented in the model should ideally be adjusted to fit the Norwegian setting. The implemented utility values should be supplemented with relevant references to values used in previous appraisals by NoMA or NIPH, and values used in HTAs in other countries for the drug in question. References to other countries' values is of relevance only for countries which perform HTA/STA assessments comparable to those performed in Norway. NICE's assesments are of special interest. For the latter values, the company basecase utility values as well as values used in the final appraisal should be included. Table 1 and Table 2 show examples of how these may be presented.

Table 1 HSUV used in previous relevant assessments (HTA or STA) in Norway

	Patient population for which HSUV apply	Ultimate HSUV used in NoMA's or NIPH's basecase
HTA/STA 1		
HTA/STA 2		
Etc.		

NIPH The Norwegian Institute of Public Health

Table 2 HSUV used in STA/ HTA submissions and appraisals in other countries for the drug in question

	Basecase HSUV (include all utility values implemented in the health economic model)	**Ultimate HSUV in decision maker's appraisal (include all HSUV implemented in the health economic model)**
Reference: Country 1		
Reference: Country 2		
Etc.		

Uncertainty in HSUV must be examined in sensitivity/scenario analyses (see chapter 12).

7.1 Documentation and description of utility value calculations

NoMA requires documentation of and justification on how utility values are collected, calculated and used in the health economic model. This applies to utility values both sourced directly from the relevant clinical trials and identified through literature review. As a minimum, the following points should be addressed (see also appendix 1.4 and chapter 12):

- Overview of how many subjects responded to the PRO questionnaire (compliance rates by visit and by treatment) including reasons for missing questionnaires and differences, if any, between non-responders and responders.

- Choice of statistical model for HRQoL analyses (e.g regression model), including full model equation with a justification of variable selection and description and justification of the correlation structure.

- The statistical model assumptions for HRQoL analyses (e.g. homoscedasticity, normality of residuals, linearity of predictor-outcome association, independence if non-hierarchical model) should be explored and described.

- Handling of missing data, including description of patterns, assumptions and methods of imputation (9, 10).

Baseline adjustment of HSUV should be performed where relevant (11, 12). Methods accounting for repeated measures are generally preferred (13, 14). Sensitivity and/or scenario analyses addressing the above-mentioned points must be provided (see chapter 12). Where bias is unquantifiable, a qualitative discussion should be included. Utility values sourced from the literature must be documented and discussed to the extent of available information.

7.2 Instruments for measuring health-related quality of life

Health-related quality of life, as defined by Gold et al and Sanders et al (15, 16), must, as a rule, be based on generic preference-based measuring instruments. To make comparison between different STAs possible, EQ-5D must, as a rule, be used (17). If measurements of quality of life, which have been carried out with disease-specific instruments in the included studies, are available, these should be reported as supplementary information.

There are currently two versions of EQ-5D available. The original version (EQ-5D-3L) describes each dimension at three levels, while the new version (EQ-5D-5L) describes the same dimensions at five levels. Both versions may be used to capture health-related quality of life in patients over the age of 12. Until the new 5L version fully replaces the original 3L version in applied studies, we expect to see studies that have used one of the two versions. For consistency, the results from 3L and 5L should be converted to a comparable set of values. Data from 5L should therefore be converted to 3L using the method described by Hout et al (18). The use of EQ-5D-3L as the standard in STAs is based on recommendations from NICE (19). When measuring HRQoL in children aged 8 years and upwards, EQ-5D-Youth can be used (20, 21) Tariffs for EQ-5D-Y are currently being developed (22). The company must present the average age, age distribution and age range for the respondents, irrespective of data being sourced from own clinical study and literature (23).

Use of EQ-5D can be waived if there are no data from EQ-5D for the disease in question, or if EQ-5D has been judged not to be suitable for capturing relevant aspects of the patient population in

question. If EQ-5D is judged not to be an appropriate measure, this should be justified and supported by evidence that shows EQ-5D is not appropriate for the patient population in question[5]. For guidance in deciding whether or not EQ-5D is suitable for the patient population in question, you are referred to NICE DSU Technical Support Document 8 (24).

7.3 Tariffs for setting values of health-related quality of life

In STAs, as a rule, valuation of quality of life must be based on tariffs (value sets) from the preferences of the general population. This is done to ensure consistency across STAs, and to ensure internal consistency between measures of severity and health economic analyses in every STA. In principle there should be agreement between the tariffs used to calculate benefit in the health economic analyses and those that form the basis for calculating severity.
If, in a STA, there are particular reasons for using an experience-based tariff, this should be justified. There should be an explanation for how this tariff varies from a general population-based tariff.

The tariff used should be relevant to the adult population living in Norway. As yet there is no representative Norwegian tariff for EQ-5D. However, a representative Norwegian tariff has been estimated for the 15D instrument (25). For consistency, we recommend that the EQ-5D with the UK population-based EQ-5D-3L tariff (26) should be used for STAs in Norway until a more relevant and applicable tariff is available. The Norwegian 15D tariff can be applied in scenario analyses (25).

7.4 Mapping of quality of life data

Where there is a lack of patient-reported EQ-5D data, other generic preference-based instruments can be used (SF-6D, 15D, HUI, AQoL, QWB). The preference-based values from such alternative instruments must then be mapped to EQ-5D values, in accordance with validated methods. The results should, in such instances, be compared to published quality of life data for the relevant patient group.

If there is no data from generic instruments, but only from disease-specific instruments, these must be mapped to predict EQ-5D values.

The method used for mapping must be described and presented. For a more detailed description of the methods for mapping quality of life data to EQ-5D, refer to the NICE DSU Technical Support Document 10 (27).

The reason for carrying out this type of conversion is to achieve comparability across economic evaluations which are based on different methods.

7.5 Age adjustment of health state utility values (HSUV)

Increased morbidity and decreased function linked in general to increasing age, mean that health-related quality of life in the general population is reduced over time. Given this background, the development of HSUV should be adjusted for age in health economic models. It is the *development* of the HSUV used over time which should be adjusted, not the level of the HSUV used at the starting age in the models. If the HSUV are not adjusted for age, this must be justified[6].

[5] For example NICE has evaluated EQ-5D as being less suited to measurement of quality of life in connection with loss of hearing, restricted vision or schizophrenia.
[6] For example, when a health economic analysis has a short time perspective.

Adjusting for age will, in addition, ensure consistency with the severity calculations in STAs, where age-adjusted HSUV should be used in the calculations of expected remaining QALYs for the general population (see appendix 4.1.2).

In order to maintain consistency in the methodology for STAs, it is recommended that age-related adjustments are carried out based on the multiplicative method, as described in the NICE DSU Technical Support Document 12 (28). State the reason if another method is chosen.

Calculating HSUV over time, based on the multiplicative method, can be briefly described as the original value for the HSUV multiplied by an adjustment index[7], and gives an age-adjusted HSUV. An example of how to do this is shown in Appendix 3.

7.6 Treatment-specific HSUV for the same condition

If different treatment-specific HSUV are used for the same condition[8], this must be fully justified and documented. For different treatment-specific HSUV to be accepted, the differences in health-related quality of life should be shown in clinical studies. Different treatment-specific HSUV should have a clinical explanation.

7.7 Effect on the health-related quality of life of caregivers

If an intervention affects the health-related quality of life of a caregiver this can be accounted for by showing relevant documentation. Basically, the same requirements are made for documentation of changes in the quality of life of a caregiver as for a patient. The effects can be quantified in QALYs to be used in the cost-effectiveness ratio. The results of the analyses must then be presented with and without the inclusion of effect on the caregiver's quality of life. In cases where there is good reason to expect considerable changes in the health-related quality of life of caregiver, but where there is no good documentation available, this can be discussed but is then not included in the cost-effectiveness ratio.

The central effect that can be taken into account is how changes in the patient's health-related quality of life affects the health-related quality if life of the caregiver(s). If the intervention affects the *life expectancy* of the patient, the effects on the caregiver's quality of life of the increased life expectancy in itself should *not* be taken into account. There are both ethical and methodological reasons for this.

[7] Is set to 1 in the starting year in the health economic model, and decreases with increasing age.
[8] i.e. If different HSUV are used for the intervention and the comparator for the same condition in the health economic model. Example: HSUV X is used for the intervention and HSUV Y for the comparator for the health state progression-free survival in a HTA of a cancer medicine.

8. Efficacy, safety and quality of life data used in the model

8.1 Consistency between studies, Norwegian clinical practice and modelling

The health economic model must give a best possible description of the clinical course of the disease and must reflect Norwegian clinical practice. The data used in the model must originate in the clinical studies or in the indirect comparison/meta-analysis. As a rule, the effect estimate for the primary endpoint, or the hard endpoints, should be used in the model.

Explain the connection or any deviation between the data used in the model, clinical data and Norwegian clinical practice.
If the clinical studies used in the health economic analysis also include quality of life data, or data which can be translated into quality of life data, and these data are not used in the analysis, this must be justified.

8.2 Presentation

It must be shown clearly in table form, as described in the template for submission of documentation, which estimates (clinical efficacy, adverse reactions and quality of life) have been used in the health economics model and how these have been arrived at. The definition of the outcomes in the different sources must also be presented.

If the results from the studies and the estimates used in the health economic model are not the same, this must be described and justified.

9. Health economic analyses

For an overview of a reference case for health economic analyses see Appendix 5 Reference case – health economic analyses.

9.1 Analysis methods

9.1.1 Cost-utility analysis (CUA)

The recommended analysis method for health economic evaluations is CUA. When the intervention affects survival, the results must be presented separately as cost per QALY gained and cost per Life Years Gained (LYG).

9.1.2 Cost-minimisation analysis

Cost-minimisation analysis can be used in cases where, through documentation, it is shown to be likely that the efficacy and safety profiles for the intervention and the comparator approximate. In practice, the prerequisite for cost-minimisation analysis will be fulfilled if it has been shown that the intervention is not less effective than the comparator.

9.2 Analysis perspectives

Below there is a description of which benefits and costs must/must not be included according to the guidance from the Priority-setting White Paper. These are costs and benefits which either occur as a result of, or can be expected to change as a result of, the pharmaceutical being evaluated. In practice the guidance implies a form of *extended* health-service perspective.

The following benefits must be included (if relevant):
Effects on

- The patient's lifespan
- The patient's health-related quality of life
- The health-related quality of life of caregiver(s). The analyses must be presented both with and without inclusion of this effect

The following costs must be included (if relevant):

- Treatment or prevention costs, paid by the health service or by the patient/relatives
- Transport costs linked to travelling to and from treatment, whether paid by the health service, or by the patient/relative
- Patient's and relative's use of time in connection with treatment

In accordance with the Priority-setting White Paper the following must not be included:

- Productivity changes as a result of the intervention
- Consequences for patients' future use of public services and receipt of public benefits/pensions
- Unrelated health service costs and savings. For example, the health service costs related to future unrelated illness will not be taken into consideration.
- Tax expenses for public financing
- Public benefits, pension payments, value added tax and other transfer payments

Reference is made to the Norwegian Directorate of Health's guidance "Economic evaluation in the health sector" (updated version due 2018) for more in-depth information about the perspective of analyses and analysis methods for different types of interventions which affect health.

9.3 Resource use and costs

By resource use we primarily mean use of goods and services, use of time and use of capital. Market prices in the private sector should, as far as possible, be used as the basis for estimates of unit costs/calculation prices (29). Unit costs and resource use are to be presented and justified separately. As a rule, Norwegian unit costs must be used, and any deviation from this must be justified. Show any exchange rate used for converting calculations of costs in other currencies to Norwegian kroner.

Assumptions and justifications for costs included must be well documented. These must be reported in detail and the way the costs have been arrived at must be transparent, so the calculations can be assessed. This must be presented in accordance with the template for submission of documentation.

9.3.1 More about unit costs

For drug costs, analyses must be carried out using the maximum pharmacy retail price (PRP) available from NoMA without value added tax (VAT). A curve showing the relation between the ICER and percentage discount from the maximum price for the pharmaceutical being evaluated, must be presented. It must be possible to change the drug price in the model so that NoMA can carry out its own analyses using rebated prices, cf. Chapter 10 on the requirements for the model.

Transport costs linked to travel to and from treatment are to be included. If it is relevant and well-documented, necessary transport costs for caregivers can also be included.

If unit costs are not calculated directly as part of the STA, the unit costs can be taken from other cost studies/publications. The average cost can generally be used, and an alternative is to use "standard" calculations for average cost per resource type (eg, visits to doctors, hospital treatment, nursing home costs, laboratory services etc.). Some examples:

- **Hospital services:** The cost per hospital admission[9] or outpatient clinic attendance[10] can be calculated by multiplying the DRG-points by the relevant unit price. This gives an estimate of the total costs per admission/attendance for the hospitals[11]. The patient's co-payment for outpatient consultations can be ignored because the contribution is already accounted for through the DRG weighting. If there is no information in the data about the relevant DRG code, then a cost per day

[9] Applies to admissions to somatic departments.

[10] Applies to outpatient contacts/consultations in somatic departments, mental health services and multidisciplinary specialist addiction treatment.

[11] Activity based financing (ABF) (in Norwegian: "Innsatsstyrt finansiering – ISF") means that the hospital receives a refund for a share of the total cost of an activity/procedure (the ISF-share). The rest of the hospitals costs are covered by its basic funding allocation. Calculation of the ISF-refund is done using the following formula (taken from the Directorate of Health's annual document "Innsatsstyrt finansiering [YEAR]" which is available on the Directorate of Health's webpages):

$$\text{ISF-refund} = \sum \text{ISF-Point} \times \text{Unit price} \times \text{ISF-share}$$

In the formula it is clear that ISF-points multiplied by the unit price is an estimate of 100 % of the cost of an activity/procedure. The ISF-share defines how much of the cost of the activity/procedure is refunded. DRG-points will often be the same as ISF-points. In some cases, further adjustments are made to the DRG-points to calculate ISF-points. In these cases it will normally still be useful for our purposes to use DRG-points in the estimate of costs. This implies replacing ISF-points with DRG-points in the formula above, and uses an ISF-percentage of 100 % to estimate the costs of hospital services.

or per consultation can be taken from the Norwegian Directorate of Health's database (SAMDATA) for the specialised health services (covers somatic, mental health services and multi-disciplinary specialised addiction treatment). More information about activity-based financing, DRG weighting, unit prices and SAMDATA can be found on the Norwegian Directorate of Health's webpages.

- **General practitioner and specialist services:** As a rule, the cost per contact/consultation is calculated by multiplying the remuneration amount from "Normaltariffen" (30) (i.e. the tariff rate in Norwegian kroner) by two (x2). This is because the costs of general practitioner consultations and specialist services (for example, one consultation) is covered by both the remuneration (the total of the reimbursement amount and the patient's contribution) and the public subsidy (basic subsidy to general practitioners, operating subsidy to specialists). The calculation gives a rough estimate, but multiplying the remuneration amount by two is considered to give a better cost estimate than using the tariff rate directly. The Norwegian Medical Association publishes an overview of tariffs, patient contributions, and subsidies on its web pages.
- **Clinical laboratories and radiology services:** For these services a similar approach can be used as for general practitioner and specialist services. The unit costs is calculated as the total of the tariff per investigation /consultation and the patient's contribution, multiplied by two (x2). The Health Economics Administration (Helfo) publishes information on tariffs, patient contributions and subsidies on their webpages.
- **Nursing homes:** Statistics Norway publishes information (KOSTRA) on its website about the cost per day of nursing homes.

Estimates of average costs will, as a rule, reflect both fixed and variable costs. In some cases, one or more of the treatment alternatives included in the analysis may lead to further capital costs. This should be highlighted and included in the analysis. In other cases, it can be most relevant just to use the variable costs. This is for cases where the treatment alternatives are not expected to affect the fixed costs. Then the fixed costs should be taken out of the estimates mentioned above.

9.3.2 Use of patient's and caregiver's time– and unit costs

Use of time as an input for the intervention and comparator must be included

The intervention and the comparator can in some cases lead to different duration of treatment administration and/or travel time. In these cases, documented differences in use of time (for patient, and if relevant, for the caregiver) must be estimated and the results of the analysis must be presented with these costs.

For patients and caregivers

We recommend that the value of time be calculated at a common rate for all patients and relatives regardless of their employment situation, and that this rate is given at the value of leisure time.

The value of increased/decreased leisure time is given by: average salary in Norway after tax (31).

Changes in time for work and/or other daily activities/leisure time as a result of the pharmaceutical (productivity changes) must not be included[12].

[12]This is linked to the fact that treatment can allow the patient to experience more time in good health. If this time is used for paid work (return to work, or work more hours), this is called positive productivity changes ie, production gains. Such productivity changes must not be included in the analysis.

9.3.3 Projection of unit costs

Unit costs must normally be kept unchanged throughout the analysis period of the STA. This can be a reasonable approach because of uncertainty about technological developments or market developments in the future. If there are good reasons for using projections with changes to unit costs, this must be described and justified.

Several situations can lead to the price of drugs reducing considerably in the future. This includes the introduction of bioequivalent pharmaceuticals, generic pharmaceuticals and tenders. These could potentially affect the results of the analysis to a considerable degree. In cases where this situation is relatively imminent, then probable price paths must be included. The paths must be justified and the uncertainty must be discussed.

9.4 Present value and discounting

To compare benefits (measured in QALY, in line with the Priority-setting White Paper) and costs which occur in different years and which are used in the CUA, the annual benefits and costs must be converted to present value. In calculation of present value both benefits and costs are discounted by the applicable rate as given in the Priority-setting White Paper (Meld. St. 34 (2015-2016)). In the White Paper it is stated that the discount rate should be equal to the applicable rate at any time given by the Ministry of Finance [13]. As described in Rundskriv R-109-2014 the rate should be 4% per year for the first 40 years after the planned start of the intervention, i.e. in the years 0-39. In the years 40-74 a discount rate of 3% per is to be applied, while thereafter, from (and incuding) the year 75 and onwards 2% per year is to be used.

[13] https://www.regjeringen.no/globalassets/upload/fin/vedlegg/okstyring/rundskriv/faste/r_109_2014.pdf

10. Modelling

The choice of health economic model must be justified. The model should be as simple, straight-forward and transparent as possible, while still capturing all the relevant factors which could affect a decision. The model's construction, assumptions and how the different input data have been modelled must be documented and described fully.

There must be consistency between the clinical documentation (to document relative efficacy), Norwegian clinical practice and the model. Models should therefore, as far as possible, be validated. Internal and external validity should be described. Check carefully whether the calculations are precise and consistent (internal validity). The results from the model should be checked against independent sources (external validity). This can include comparing clinical events which are predicted by the model against data which have not been used in the model, for example, epidemiological studies.

International models can be used but they must be adapted to Norwegian conditions both in terms of clinical practice, costs and any relevant health effects. It should be clear how such models have been adapted for Norway. If they have not been adapted, this must be justified. Indicate the consequences any lack of adaptation may have for the results.

NoMA must be able to change all relevant variables and parameters in the model. This includes any parameterising functions. The model must be able to update the sensitivity analysis automatically.

The model must not be locked, time limited, password-protected unless the password is made available, or have any hidden elements that are not described or cannot easily be changed. The model should not be implemented (fully or partly) in proprietary or non-transparent programmes and/or programming language.[14]

10.1 Modelling of endpoints

If efficacy data are only available for intermediate endpoints (for example cholesterol levels or blood pressure), the analysis must report how changes to these affect the endpoints in the modelling (for example, heart attack or stroke). A documented causal relationship between the intermediate endpoints and the hard endpoints should be made available. See chapter 8.

10.2 Sequence modeling

In some cases, it can be relevant to model treatments as part of a sequence. A prerequisite for this type of approach is that there is enough good quality documentation of efficacy for the relative differences between different treatment courses and for the order of the different treatments within these.

10.3 Time horizon

The time horizon of the analysis must be long enough for all the important future differences in costs and health effects between alternatives to be captured. That is, the time horizon must be such that making it longer would not affect the results in any meaningful way. If the pharmaceutical has an effect on mortality, then the basis for the time horizon will be lifetime.

[14] Normally it will be useful if the model is designed using Excel, but other alternatives can also be acceptable such as, TreeAge and R.

In some cases, it may be relevant to consider a shorter time horizon. There can be several reasons for this, for example if:

- Biologically it is not realistic to use a longer time horizon.
- There is no documentation /it is not likely that the relative efficacy will be maintained over a longer time horizon.
- For other reasons, it is reasonable to use a shorter time horizon.

11. Calculation of severity

Severity must be quantified using absolute shortfall (AS) in health technology assessments. Absolute shortfall is the number of future healthy life years an average patient in the patient group will lose because of his/her disease, compared to the average in the population of the same age. Absolute shortfall is the same as the reduction in expected future healthy life years without the treatment under consideration (ie, with the current standard treatment). The term 'healthy life years' contains two dimensions – lifetime and life quality – and these are expressed using quality-adjusted life years (QALYs), see Chapter 7. Absolute shortfall is thus stated in QALYs lost.

In the following, we specify the principles for calculating absolute shortfall. There is a differentiation between treatment interventions and preventive measures. Comorbidity is discussed separately.

11.1 Types of economic analysis

Absolute shortfall must, in general, be calculated when cost-utility analyses are used.

If the analysis submitted is in the form of a cost-minimisation analysis, it is not necessary to calculate the absolute shortfall.

11.2 Treatment interventions

The calculation of absolute shortfall is done in stages

1. Define the mean age at start of treatment for the relevant Norwegian patient group which is being considered for the new treatment. We refer to the age as A.
2. Estimate the number of remaining healthy life years for an average person from the general population with the age A. We refer to this as $QALYs_A$.
3. Calculate the prognosis for the relevant Norwegian patient group. The prognosis is the average number of remaining healthy life years for the patient group with the current standard treatment. We refer to this as P_A.
4. The absolute shortfall is the difference between the estimate in point 2 and the projection in point 3:
   $AS = QALYs_A - P_A$

In calculations, the undiscounted values for $QALYs_A$ and P_A must be used.

A detailed description of this approach, with examples, can be found in Appendix 4 – Calculation of severity.

11.3 Interventions which treat several diseases/conditions

The principle for quantifying severity, when an intervention has a treatment effect on several diseases in the patient group, corresponds to the principle for calculations when a pharmaceutical has a preventive effect on several diseases. This is described in Chapter 11.5.2 below.

11.4 Calibrating two data sources

In calculations, data for the prognosis for the patient group and data for the expected number of remaining QALYs for the average population will usually come from different sources.

HSUV (QALY weights) in the prognosis calculation will come from clinical studies of the pharmaceutical being evaluated, or from other studies where the quality of life for the

disease/condition has been measured. The HSUV for the average population will, as a rule, have come from other sources, see appendix 4, section 4.1.2. This means that HSUV can come from different populations and may have been measured using different instruments and tariffs.

In some cases, the HSUV for symptom-free conditions in the health economic analyses, (which form the basis for the prognosis calculations), are higher than the HSUV for the average populaton (used in calculating the expected number of remaining QALYs). If so, this should usually be corrected for by calibration.

An example of calibration is shown in appendix 4 section 3.

11.5 Preventive measures

Calculating the severity must be linked to the disease that is being prevented, for the subgroup who would have developed the disease in the absence of the new intervention, measured from the time the disease would be expected to occur in the average patient. Examples of calculating the degree of severity for preventive measures are shown in appendix 4, section 4.4.

11.5.1 Case 1 – Only one disease/condition is prevented

To calculate the absolute shortfall for conditions, the following must be taken into account:

- Not all the individuals in the group will actually be affected by the disease/event
- There is a time difference between when the prevention starts and when the disease/event may occur

Procedure:

1. First consider which of the individuals/patients in the group must be included in the calculations. Severity is only calculated for that part of the group which is expected to be affected by the disease the preventive measure is aimed at in the current situation. The current situation includes any preventive measures already being carried out (the current standard prevention), but does not include the new preventive measure which is to be evaluated.
2. Then calculate the average prognosis and absolute shortfall for the subgroup expected to get the disease with the current standard prevention and expected standard treatment of the disease from the time the disease occurs.

11.5.2 Case 2. Several diseases/conditions are prevented

Calculation and weighting of severity can be done in several stages:

1. Calculate the absolute shortfall for each of the diseases/conditions for the relevant population with current preventive practice (the comparator in the health economic analysis). This is explained in “Case 1 – Only one disease/condition is prevented”.

2. After this, calculate a weighted absolute shortfall for the diseases/conditions. Example: for prevention of two diseases/conditions, the disease that is most important for the estimated benefit (gained QALYs) of the new preventive measure must be weighted heaviest in the calculation of the weighted absolute shortfall. Absolute shortfall for disease A must be weighted at 90 % in the weighted absolute shortfall if 90 % of the benefit, measured in QALYs, can be attributed to prevention of disease A.

The justification for this type of weighting is given in appendix 4, section 4.5.

11.6 Comorbidity and adverse reactions

For pharmaceuticals directed towards one main condition, it is the overall degree of severity of the main condition and the issues which result from the main condition which are to be assessed and calculated.

For pharmaceuticals aimed at symptoms which are a *result* of the main condition (and do not affect the main condition), it is the degree of severity for the resultant symptoms alone – and not of the main condition – which must be evaluated and calculated. For example: If a disease causes pain, the pain medication should be assigned a degree of severity which corresponds with the absolute shortfall for the pain alone, independently of the main condition.

For interventions aimed at treating adverse reactions which *result from* the treatment of the main condition, this is about adverse reactions – not comorbidity. It is the degree of severity of the adverse reaction – and not of the main condition – which must be evaluated and calculated. For example: If the treatment for a disease leads to nausea, then the medicine for nausea should be assigned a degree of severity which corresponds to the absolute shortfall for nausea alone, so the degree of severity is the same regardless of who is affected.

For interventions aimed at symptoms which *are not related to* the main condition, it is the degree of severity of the symptoms – and not the main condition – which must be evaluated and calculated.

12. Uncertainty

Uncertainty in health economic analyses must be explored and discussed. In this section, we describe different sources of uncertainty in health economic analyses and ways of dealing with different types of uncertainty.

12.1 Terminology about uncertainty

It is useful to differentiate the following in relation to uncertainty in health economic models (32, 33).

- **Stochastic uncertainty**: This means that patients with the same risk may experience different outcomes of the disease or intervention due to random variability.
- **Parameter uncertainty**: This relates to uncertainty about the "true value" of a parameter. This applies to variables which are estimated from sample data or are based on other data/sources. This will typically be costs, HSUV, treatment effects and the probability of events. Uncertainty can be caused by sampling data, contradictory studies, lack of internal or external validity, limited generalisability or lack of data.
- **Model uncertainty or structural uncertainty**: This relates to uncertainty over assumptions and choices made in the construction of the model. Examples are the relationships between variables in the model, the chosen functional form for modelling the time to event data, extrapolation of treatment effect, and the choice of which health states are included in the model.
- **Heterogeneity**: The effect of patient heterogeneity (variation in patient characteristics) on the model's results is not related to uncertainty, and is best analysed by sub-group analysis.
- **Methodological uncertainty**[15]: This will typically be about areas within health economics where there is methodological disagreement. An example is the choice of instrument to measure health-related quality of life.

12.2 Dealing with uncertainty in the analyses

Uncertainty in the health economic analysis must be explored and presented through sensitivity analyses. This should be done using both deterministic and probabilistic sensitivity analyses, described in more detail below. Not all uncertainty can be reflected this way. It can, for example, be very difficult to analyse structural uncertainty and generalisibilty fully in sensitivity analyses.

The impact of uncertainty on the outcomes of the analysis must be discussed in order to highlight what drives the uncertainty, whether the uncertainty can be reduced, whether additional data can be expected, whether any bias is present, and how the results of the analysis are affected by changes in the parameters or assumptions.

12.2.1 Deterministic sensitivity analysis

In deterministic sensitivity analyses selected variables are changed to explore how sensitive the model outcomes are to these changes. This type of analysis is carried out in the form of one-way, two-way or multiway sensitivity analyses and in scenario analyses.

We recommend that methodological and structural uncertainty is analysed, as well as uncertainty linked to generalisibility, by using deterministic sensitivity analyses as far as possible.

[15] Methodological uncertainty is reduced by the recommendaton of a preferred method/approach, for example our recommendation to use of one quality of life instrument (EQ-5D) and a set discounting rate (4 %).

Deterministic sensitivity analyses alone will not be able to show all the uncertainty, and should be supplemented by probabilistic analyses and discussion. One-way sensitivity analyses cannot capture correlation between variables and the impact of joint parameter uncertainty on the model outcomes. For two-way and multiway sensitivity analyses, the number of possible parameter combinations can easily become insurmountable, and the decision maker cannot see how likely different outcomes are. Deterministic sensitivity analyses alone are therefore not sufficient to reflect the impact of parameter uncertainty.

One-way sensitivity analyses
In a one-way sensitivity analysis, the values are varied one and one variable at a time. For example, parameter values can be varied within their corresponding 95% confidence interval or relevant credibility interval.

All parameters are investigated in a one-way sensitivity analysis. This should be summed up in a table in the model. The most important parameters in one-way sensitivity analyses are to be presented in both tables and in a tornado diagram. Time horizon, the drug prices for the intervention and the comparator(s), HSUV, parametric functions for time to event data as well as effect parameters must always be included.

Two-way and multiway sensitivity analyses
In two-way and multiway sensitivity analyses the values of two or more parameters respectively are varied at the same time.

Scenario analyses
A scenario analysis is used to evaluate the impact of alternative values for selected sets of parameters on the model outcomes. Selection is often made so that it represents, for example, a base case, a “worst case” and a “best case” analysis, or alternative plausible scenarioes.

12.2.2 Probabilistic sensitivity analyses (PSA)

In a PSA a range of chosen variables are defined as stochastic variables, with an associated probability distribution. Justify the choice of variables included in the PSA and their probability distribution. The probability distribution of the variable and its most important moments (usually the expected value and standard error), will by preference be based on empirical data. If there is a lack of empirical data, a plausible probability distribution must be chosen for the variable. Each type of variable will usually only have a few types of probability distributions that are relevant for use in PSAs (see for example Drummond 2015 (32)).

PSAs should be used to capture the impact of joint parameter uncertainty. In principle, model uncertainty can also be explored in the PSA, for example by assigning probability weights and distributions are assigned to alternative assumptions.This is recommended if it is possible and appropriate.

The results of the PSA must be presented as a scatter plot of the simulated ICERs and as cost-effectiveness acceptability curves (CEACs).

12.2.3 "Value of Information" analyses

Value of Information analysis (VoI) can be carried out on the basis of results from the probabilistic sensitivity analysis. Such an analysis can include estimation of the Expected Value of Perfect Information (EVPI), which combines the probability of making a wrong decision with the consequential losses of that decision. The EVPI should be calculated when a PSA has been done and there is decision uncertainty (when the probability that the new treatment is cost effective is less than 100 %, but higher than 0 %, for a range of common willingness to pay thresholds). The EVPI should be presented in a graph for a range of willingness to pay thresholds.

Further analyses can be requested to investigate whether the decision to introduce the pharmaceutical should be postponed, either to obtain, or in anticipation of, further evidence. This can include estimation of the Expected Value of Partial Perfect Information (EVPPI) to identify key parameters. S See the relevant literature for more information about the method and presentation of VoI analyses (33-35).

13. Budget impact

In STAs budget impact must be estimated. The analyses must be delivered in a spreadsheet that allows NoMA to do its own calculations with different assumptions. The assumptions for the budget analyses must be documented.

13.1 Single technology assessments for pre-approved reimbursement of pharmaceuticals

In STAs for pre-approved reimbursement the budget impact must be split into impact on the drug budget of the National Insurance Scheme ("folketrygdens legemiddelbudsjett") 13.1.1 and impact on the health and care services overall budget ("helse- og omsorgstjenesten samlet") 13.1.2.

13.1.1 Budget impact on the drug budget of the National Insurance Scheme ("folketrygdens legemiddelbudsjett")

The expenditure to the National Insurance Scheme is to be calculated using two different scenarios – one as if the new pharmaceutical has been granted pre-approved reimbursement, and the other as if the new pharmaceutical has not been granted pre-approved reimbursement. The budget impact is the difference between the two scenarios in each of the first five years.

Expenditure for national insurance is calculated on the basis of the following factors:

- The expenditure to the National Insurance Scheme for the pharmaceutical being assessed and for competing pharmaceuticals. Only the drug costs are to be included, and only the expenditure to the National Insurance Scheme is to be included.
- Calculations must be made using the drug's maximum pharmacy retail price (PRP). The prices must include value added tax (VAT). It must be possible for NoMA to change the prices of the drugs in the budget calculation model in order to carry out their own analyses with discounted prices.
- Expenditure must be calculated without discounting.
- The estimated market share of the pharmaceutical among those patients who fulfil the reimbursement conditions for each of the first five years after the date of the reimbursement decision.
- Expenditure for each of the first five years with pre-approved reimbursement. Year 1 is the first full calendar year after the documentation is submitted. Expenditure must not be calculated cumulatively for the first five years.
- Expenditure on individual reimbursement. [16] is usually usually estimated as follows:
    - When evaluating *new* pharmaceuticals and/or new indications the expenditures to the National Insurance Scheme by granting reimbursement of the pharmaceutical are to be compared to a scenario of *not granting* reimbursement of the pharmaceutical:
        - In the first scenario the expenditures on the new pharamceutical are included.
        - In the second scenario the expenditures on the new pharmaceutical are not included.

[16] Ministry of Health and Care's consulation paper on suggestions for changes to the Norwegian Act on Medicinal Products and the Blue Prescription regulations etc

- When evaluating *established* pharmaceuticals/indications, which previously have been covered by individual reimbursment, the expenditures to the National Insurance Scheme by granting reimbursement of the pharmaceutical are to be compared to a scenario of *not granting* reimbursement for *new users*:
  - In the first scenario the expenditures on the assessed pharmaceutical are included
  - In the second scenario realistic forecasts for individual reimbursment for existing users are to be estimated
- For comparators/competing pharmaceuticals (both for assessment of new and established pharmaceuticals):
  - Regardless of whether these pharmaceuticals are financed by pre-approved reimbursement or by individual reimbursement for the indication in question, the reimbursement expenditures are included in each of the scenarios using realistic forecasts.

- Patients' co-payment must not be included.

The tables below show how the calculation of budget impact for the drug budget of the National Insurance Scheme should be presented

Number of patients
The number of patients expected to be treated with the intervention, together with the number of patients expected to be treated with competing pharmaceuticals in the first five years, should be presented in Table 3 . This applies for the scenario where the intervention being assessed is granted pre-approved reimbursement. If the pharmaceutical to be evaluated is not granted pre-approved reimbursement, the number of patients is estimated in Table 4.

Table 3 Number of patients expected to be treated over the next five-year period – if the pharmaceutical is granted pre-approved reimbursement

	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmaceutical to be assessed					
Competing pharmaceutical 1					
Competing pharmaceutical 2 (etc.)					

Table 4 Number of patients who are expected to be treated during the next five-year period – if the pharmaceutical is NOT granted pre-approved reimbursement

	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmaceutical to be assessed					
Competing pharmaceutical 1					
Competing pharmaceutical 2 (osv.)					

Expenditure per patient
Calculate the expenditure per patient per year for the different treatments. The estimates should be consistent with the corresponding calculations in the CUA. If the company chooses to use the health economic model to calculate expenditure per year in the budget calculations, these calculations of expenses must be made inclusive of VAT, without discounting and with the relevant costs, as set out in the various sections in this chapter.

Budget impact
Multiply the expenditure per patient per year by the number of patients per year for the pharmaceutical in question and the other affected pharmaceuticals. Total these costs for each year and enter this figure into Table 5 below. In the bottom row of the table, present the estimated budget impact of introducing the pharmaceutical.

Table 5 Expected budget impact of pre-approved reimbursement for the pharmaceutical for the relevant indication.

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is granted pre-approved reimbursement	X1	X2	X3	X4	X5
Minus: The pharmaceutical under consideration is not grantedpre-approved reimbursement	Y1	Y2	Y3	Y4	Y5
= budget impact of the recommendation/decision	X1 - Y1	X2 – Y2	X3 -Y3	X4 – Y4	X5 –Y5

13.1.2 Budget impact for the health and care services overall

For calculating the overall budget impact for the health and care services, the budget impact for the drug budgetof the National Insurance Scheme is included as described in Chapter 13.1.1. In addition, the budget impact on other related cost components in the health and care services are to be estimated as follows:

- Two scenarios are constructed – one with pre-approved reimbursement and one without pre-approved reimbursement for the pharmaceutical under consideration
- For each scenario the costs for each of the first five years are calculated
- The costs are calculated with VAT, but without discounting
- Costs relevant to the health and care services are included, such as drug costs which are not financed by the national insurance scheme. Other expenses can be linked to treatment monitoring and consultations, laboratory tests, admissions, personell requirements etc. Only the expense types which are expected to be different in the two scenarios are included in the calculations. Estimates should be consistent with the corresponding calculations in the cost-utility analysis.
- The budget impact is the difference between the two scenarios in each of the first five years.

The company can choose not to include these costs in its budget calculations but must then explain why it is plausible that the budget impact on these costs are negligible or negative (ie, that the effect of these costs in themselves will lead to budget savings).

13.2 STAs for hospital pharmaceuticals (in Nye metoder)

The budget impact is split into three:

1. The drug costs for the specialist health services
2. Other related costs for the specialist health services
3. Other related costs in the health and care services (outside of the specialist health services)

The costs are calculated using two scenarios – one if the new pharmaceutical is introduced to the specialist health services, and another if the new pharmaceutical is not introduced. The budget impact is the difference between the two scenarios in each of the first five years.

The drug costs for the specialist health services (number one in the list above) are calculated in a way that corresponds to how the drug costs for the National Insurance Scheme is calculated in STAs for pre-approved reimbursement, see Chapter 13.1.1. However, the guidance on individual reimbursement in Chapter 13.1.1 is not relevant here, as individual reimbursement in the National Insurance Scheme is not included in the calculations of drug costs for the specialist health services.

The last two points in the list above (other costs for the specialist health services and for the health and care services respectively) are calculated in a way that corresponds to that shown in Chapter 13.1.2. The guidance on individual reimbursement in Chapter 13.1.1 is relevant for the calculation of "Other related costs in the health and care services (outside of the specialist health services)", where drug costs to the National Insurance Scheme are included.

The company can choose not to include the two final points in the list above (other costs for the specialist health care services and health and care services respectively) in their budget calculations, but must then explain why it is plausible that the budget impact on these costs are negligible or negative (ie, that the effect of these costs in themselves will lead to budget savings).

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Appendix 1. Documentation of relative efficacy in indirect comparisons

1.1 General

Justify why it is necessary to use an indirect comparison.

The research question /scope must be clearly formulated.

Before an indirect comparison is carried out the known effect modifiers and prognostic factors must be described as fully as possible from previous knowledge.

1.2 Literature search

Carry out a full systematic literature search. Describe the literature search in detail, both for the relevant intervention and for the chosen comparator(s). For literature searches intended to support the documentation of relative efficacy, PICO[17] must be taken into account.

All relevant data from the literature search must be described according to the template for submission of documentation.

1.3 Assumptions

Describe which assumptions form the basis for the indirect comparison and evaluate whether the assumptions have been satisfied. Describe how differences, heterogeneity and (lack of) consistency have been dealt with.

1.4 Statistical methods

Justify the choice of the statistical method. Use appropriate statistical methods and describe these in detail. Present all relevant aspects of the statistical analyses in a transparent way. This applies, among other things, to how the adjusted indirect comparisons are carried out, how multi-armed studies are dealt with, use of random effects or fixed effect models, technical details, programming codes, how outliers and particularly influential studies/datasets are dealt with, and sensitivity analyses.

The choice of a fixed effect or random effects model must be based on the extent to which the studies have been carried out with sufficient similarity. Meta-analyses include studies which are clinically and methodologically diverse, and heterogeneity in the study effects is to be expected.. For this reason, the random effects model is usually preferable.

If Bayesian statistics is used, then the following must also be described as a minimum (36):

[17] PICO: Patient, Intervention, Comparator, Outcome

Choice of priors: If informative priors are used, a sensitivity analysis with non-informative priors should be presented as well. If informative priors are used, there must be documentation showing which assumptions and which data these informative priors are based on.

Calculation of credible intervals (CrI): Describe the methods for calculating and defining credible intervals (CrI).

Definition and discussion of region of practical equivalence (ROPE): Describe the criteria and the information sources the ROPE is based on.

Enclose a graphical presentation of the relevant posterior distributions with the chosen prior for the most relevant outcome measures.

If MAIC or STC is used, the following must be done as a minimum:

Describe in detail the population the STA is relevant to and describe the extent to which the adjusted population (MAIC or STC) deviates from this.

Describe and discuss on the basis of clincial evidence, whether the studies being compared overlap sufficiently in terms of study design, inclusion criteria, patient characteristics, definition of outcome measures and reporting of data.

Account for those effect modifiers (for MAIC and STC) and prognostic (for MAIC) factors which are not balanced in the studies being compared, and assess the extent to which there is enough information in the studies to correct completely for all these factors. Account for covariates which cannot be taken into account in the analysis. Discuss the risk of unmeasured confounding factors which could affect the analysis.

In a MAIC, patients from the study with individual patient data (IPD) are assigned weights[18], so that the weighted average patient characteristics equal to what is reported from the studies without IPD (published, aggregated data). Effective sample size (*n eff*) should be reported for the "balanced" population, ie, how much of the information from the index population contributes to the adjusted outcome measures in the indirect comparison.

Based on clinical evidence, describe and justify the possible consequences of a variable being excluded from the weighting.

For a more detailed description of how to carry out an MAIC or STC we recommend Jansen et al and Signorovitch et al (37, 38) as well as DSU from NICE (6, 39-44).

[18] Patients in a treatment arm (study with IPD) are weighted with inverse odds in order to be in the relevant treatment group versus the other treatment group (study with only published aggregated data).

Appendix 2. Use of time to event data in health economic analyses

2.1 Introduction

Examples of time to event data (also known as survival or event history) are time to progression in cancer, ie, progression-free survival (PFS), time to death, ie, overall survival (OS), or time to a cardiovascular event or treatment discontinuation. The randomisation time point is usually the starting point in time to event analyses.

In health economic analyses it is normal to use a form of parametrisation with extrapolation of the clinical time to event data beyond the actual study period. Below we specify how parametrisation and extrapolation of survival data must be carried out for health economic analyses sent to NoMA for evaluation. This applies regardless of whether the relative efficacy has been obtained by direct or indirect comparisons. For choice of time horizon, see Chapter 10.3 Time horizon.

2.2 Parametrisation of data from clinical studies

Data extrapolation beyond the study follow-up period is common in health economic analyses. In such analyses a type of a parametric function is often used. Parametric functions are based on an assumption that the underlying risk of the event (baseline risk) follows a given distribution, in contrast to non-parametric (eg, Kaplan-Meier) or semi-parametric (eg, Cox model) functions. Different parametric functions can give very different estimates.

The choice of a parametric function is based on statistical analyses of best mathematical fit, in combination with biological criteria related to knowledge of how the risk of event is expected to develop for the current condition/disease and endpoint. For example, some conditions will have a high risk of an event initially, but will then decrease (biphasically), while for others the risk of event will increase or decrease in monotonously.

Parametrisation must be based on the actual data from the clinical studies, thus highlighting the direct effect of the treatment under consideration.

Statistical tests and graphic evaluations must be carried out systematically to allow the choice of the most accurate parametric function (45-52).

For a given function to fit satisfactorily, the following two criteria must be fulfilled:

1. The function must fit well with the observed efficacy data from the study or studies
2. The extrapolated part is clinically and biologically plausible

Justify in detail the choice of a function in light of the two criteria above. Functions which do not fulfill both these criteria are probably not suitable.

2.2.1 Curve fitting to observed study data

By curve fitting, we mean how well suited a parametric function is to the clinical data from the study or studies (usually Kaplan-Meier data). For optimal evaluation of the curve fit an extensive description and analysis of any assumptions and properties regarding the parametric functions and relevant clinical data should be submitted. In order to document the adjustment(s) to the observed study data all of the points in the list below must be included as a minimum:

- The following parametric functions should, as a minimum, be included in the health economic model: exponential, Weibull, Gompertz, gamma, log-logistic, log-normal and Generalised gamma distributions.

- Statistical tests and graphical presentation for testing of proportional hazard (PH), accelerated failure time modell (AFT) and for assessing the fit of standard parametric functions (53):
    - log-kumulativ hazardplot for PH: $\log(-\log(S(t)))$ vs. $\log(\mathrm{t})$ with linear trendlines for the intervention and comparator
    - plot based on Schoenfeld residuals
    - Quantile-Quantile-plot for AFT $t_0(p)$ vs $t_1(p)$ with a linear trendline, using the percentiles of the inverse survival functions for the intervention and comparator:
    $$t_0(p) = S_0^{-1}\left(\frac{100-p}{100}\right),\ t_1(p) = S_1^{-1}\left(\frac{100-p}{100}\right)$$
    - $\log(S(t)/(1-S(t)))$ vs. $\log(\mathrm{t})$ with linear trendlines for the intervention and comparator
    - inverse.normal$(1-S(t))$ vs. $\log(\mathrm{t})$ with linear trendlines for the intervention and comparator

- If neither PH nor AFT appears suitable, standard parametric models fitted to each treatment arm independently should be considered before other, more flexible functions are considered, such as a piecewise function, Royston-Palmer models, spline models.

- smoothed and unsmoothed hazard plots for the observed data from the clinical study per treatment arm (54, 55)

- smoothed hazard plots for the observed data from the clinical study with the hazard function of all the standard parametric functions plotted in the same figure, per treatment arm (54, 55)

- Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC) and/or other suitable tests for those functions which are relevant on the basis of the criteria described above, per treatment arm.

- Graphical presentation of time to event data curves, where both Kaplan-Meier (KM) data and the parametric distribution is shown in the same figure. Similar graphical presentation should also be included in the health economic model (in the spreadsheet).

- In some cases, curves with KM data for the first part of the study period can be appropriate, and then a parametric tail which shows the extrapolation beyond this point (transition point). Transition point must be evaluated in the individual case. As a minimum requirement an analysis must be presented where the tail is set at the time point where 50 % of the included population in each treatment arm is still "at risk".

- Parametrization of survival data should be conducted in a transparent way that allows the analysis to be reproduced.

2.2.2 Plausibility of the extrapolated part of the curve

The plausibility of the extrapolated part of the survival curve must be documented and justified biologically and clinically for the patient group in question. External data can be used to evaluate the assumptions made in the extrapolation. External data can include data from another study of a similar patient group or data from a national/international registry with long-term follow-up of a relevant patient group. The patient population must be relevant in terms of patient characteristics, pre-treatment and treatment.

External data can only be seen as indicative. Use of external data requires a balanced discussion of how far any differences in long-term survival between the projected survival curve and the external data source is due to:

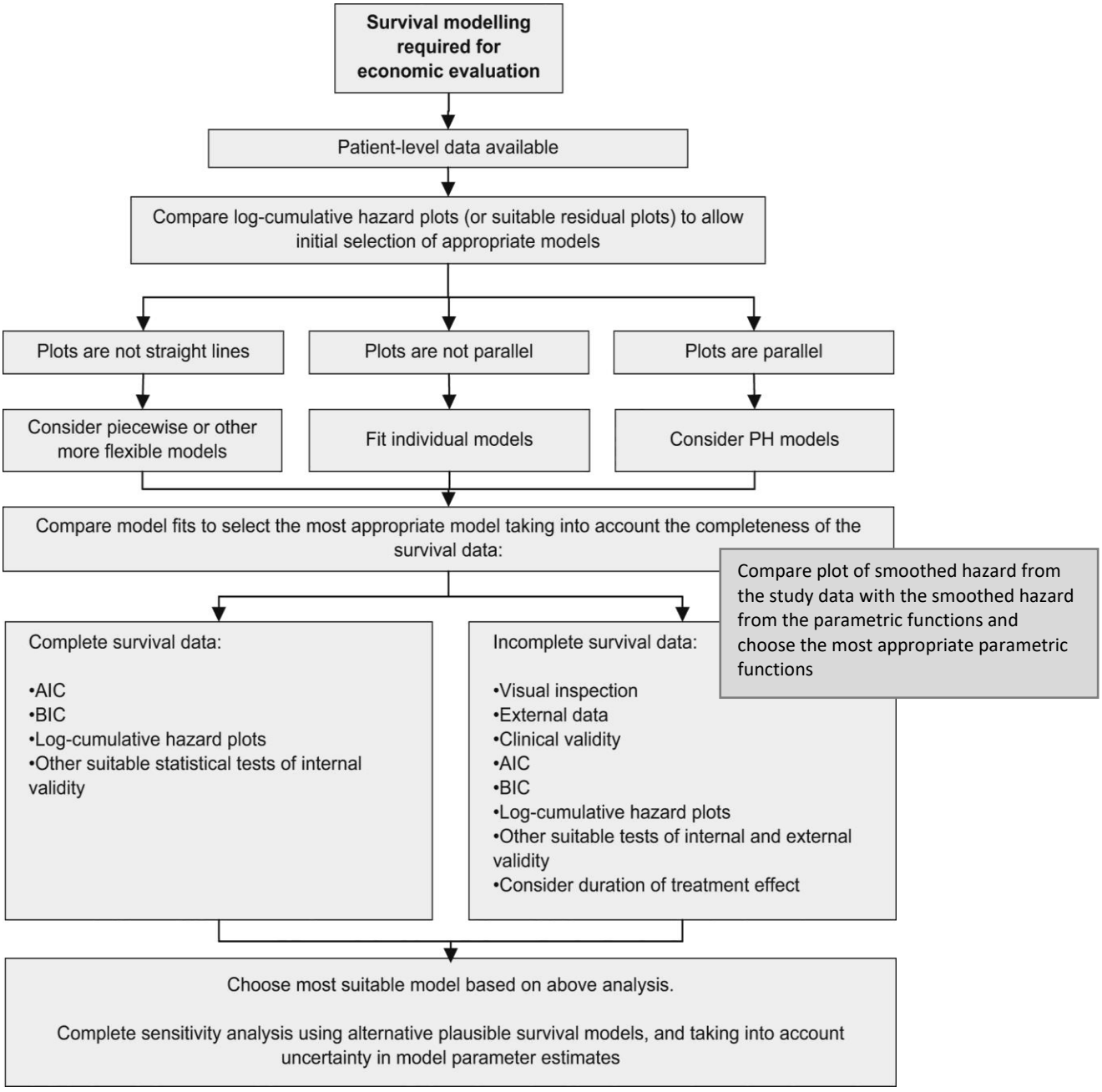
- Weaknesses in the chosen parametric function and/or
- Limitations in the external data source

External data will most likely, only be available for the comparator arm, and will therefore be most useful for evaluating the plausibility of projecting the comparator arm. Therefore the clinically valid assumptions on the duration of treatment effect will be necessary for extrapolating the effect of the intervention. The assumptions can be sourced from clinical expert statements, evaluation of the mechanism of action and biological plausibility. Different assumptions must be tested in the scenario analyses. The significance of each of these factors in assessing plausibility will depend on the current issue and will vary from case to case.

2.2.3 Algorithm and implementation in the health economic model

The figure below shows the algorithm for selection of a parametric model in time to event data analysis.

Figure 1: Algorithm for selection of a parametric model. Modified from Latimer 2013 (49)



2.3 Studies where patients can switch to active (new) intervention

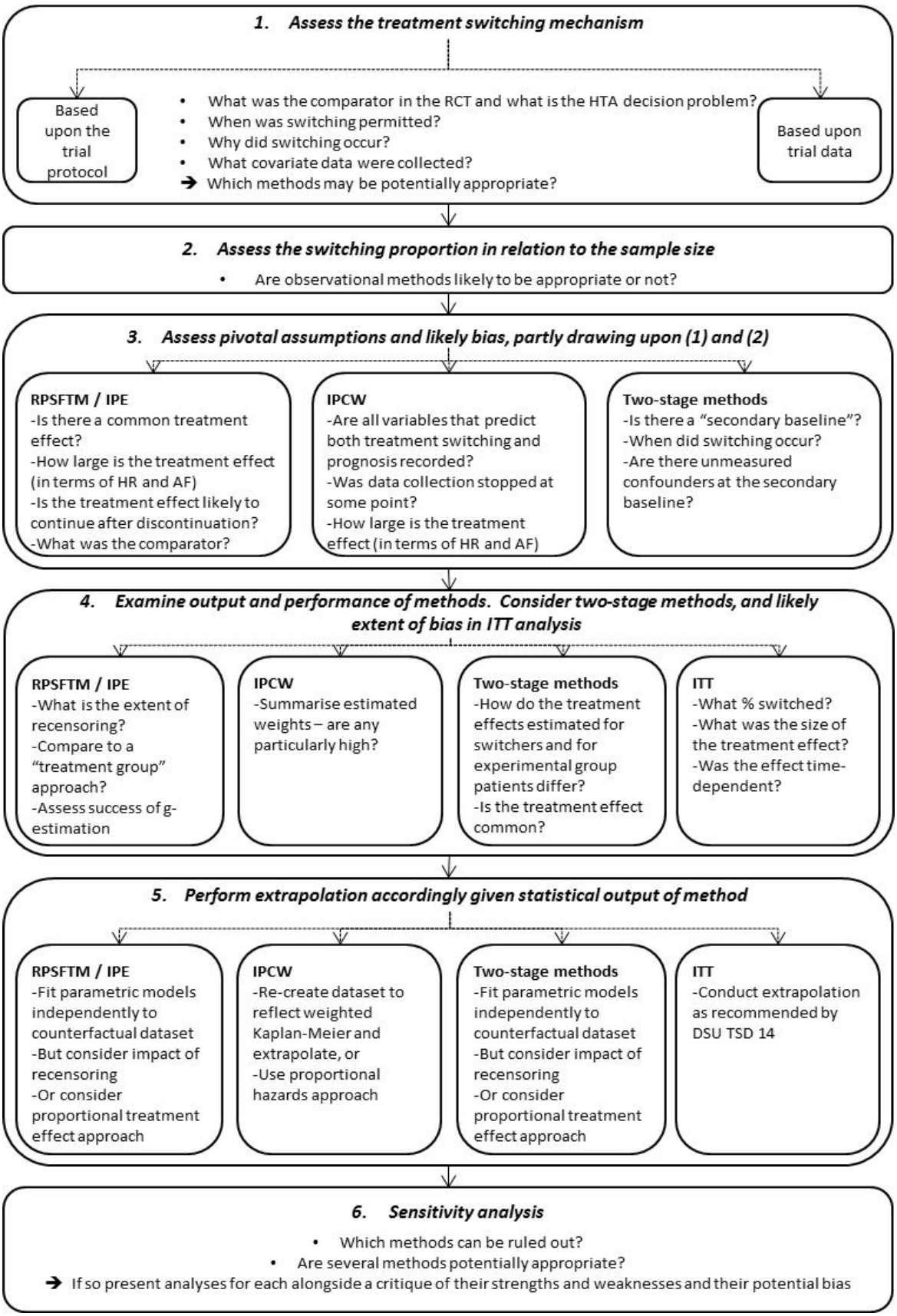
For ethical reasons, many controlled clinical studies allow patients in the control arm to switch over to the intervention arm or another active treatment at a given time point, often at progression of disease (treatment switching, crossover). In the submitted documentation it must be explained why this has been done and when the patient changed treatment.

For ethical reasons, treatment switching is relatively common in cancer studies. In such cases the effect estimate for overall survival will be affected by the treatment switching. There are several correction methods which can be used to give an estimate of survival, as if the switch had not taken place. Which method is most suitable, depends on the data in question, and must be evaluated in the individual case. Often a certain method is specified in the study's statistical analysis plan. An intention to treat (ITT) analysis (or the relevant primary analysis if there is no ITT) with an estimate without adjustment for the treatment switch must always be submitted.

Analyses which have been corrected for treatment switch can be submitted. In such a case, justify why the particular correction method has been used and other correction methods have not been used, with a related discussion of the strengths, weaknesses and assumptions of the different methods (56).

Figure 2 shows the procedure both for the choice of correction method and for which considerations form the basis for parametrisation and projection depending on the adjustment method. The intention to treat analysis (ITT) or another primary analysis parameterised and extrapolated as described in appendix 2.2 above.

Figure 2: Flow diagram for analyses with treatment switching. From Latimer 2014 (56)



Appendix 3. Quality of life data

3.1 Example of age adjustment of future expected HSUV using the multiplicative method

Suppose that when modelling a chronic disease, we have a HSUV of 0.780 for the "best" health state that can be expected for the patients. The mean patient age is 50 years, and the health economic model is using a lifetime perspective. Without age adjustment, this HSUV will be constant for the proportion of patients who reach the "best" health status for the rest of their lifetime. Age-specific HSUV based on the study by Stavem et al (57), indicate a HSUV of 0.846 at age 50 years in the general population. Similarly, the HSUV at age 81 is 0.730 in the general population (see appendix 4.6). Without age adjustment one would then be using a higher health-related quality of life for a patient population over 81 years than that assumed for the general population, as shown in Figure 3. This can be unrealistic/unreasonable, and is the justification for recommendations about age adjustment in expected future health states.

Age-adjusted HSUV for patients in this example will be a result of a HSUV of 0.780 multiplied by an adjustment index which is set at 1 at the start of the model. In this example, the index is reduced over time on the basis of age-specific HSUV based on Stavem et al (57), as shown in Table 6 (refer also to appendix. 4.6). This is illustrated in Figure 3, where HSUV for the general population based on data from Stavem et al (57) are represented by the blue line. The yellow and the grey line show HSUV for patients with and without age adjustment respectively.

Figure 3: : Development of HSUV over time

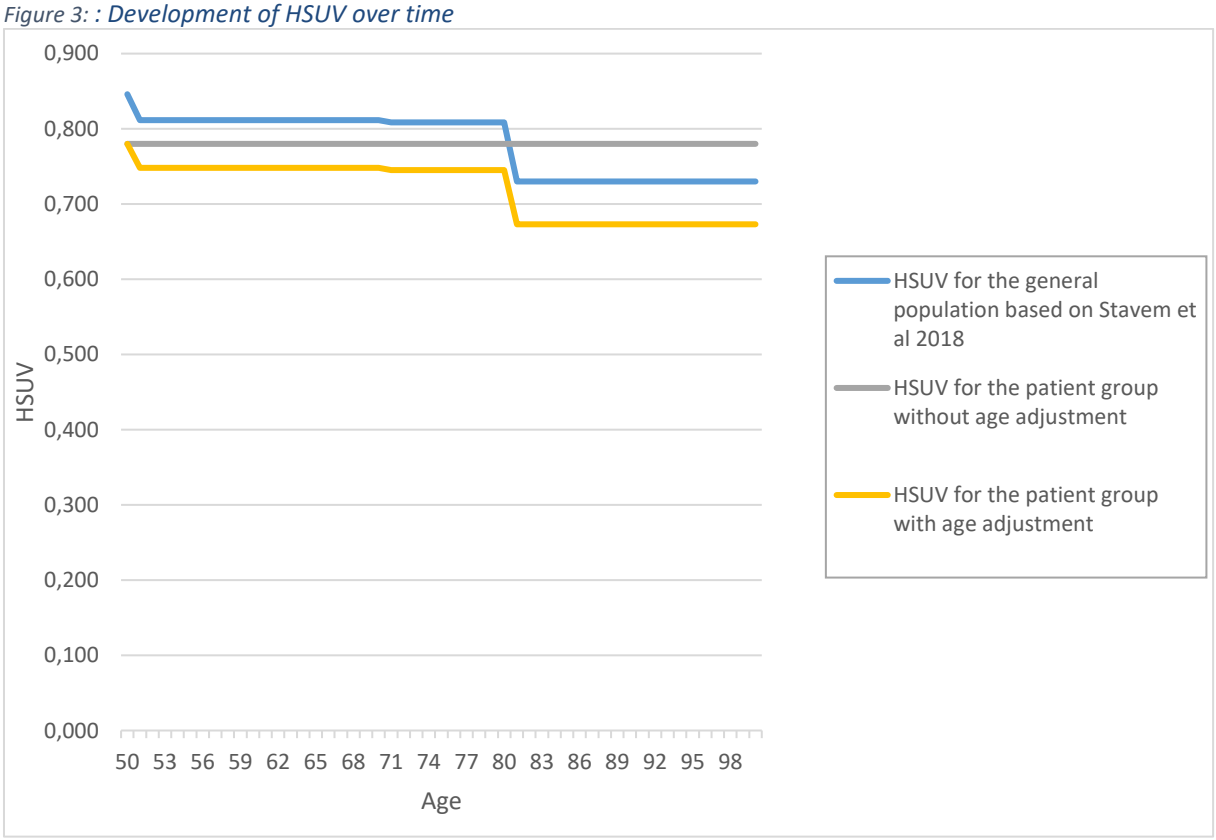


Table 6 Calculating age-adjusted HSUV

Baseline HSUV for the patient group	Age	HSUV for the general population based on Stavem et al 2018	Adjustment index	HSUV for the patient group with age adjustment	HSUV for the patient group without age adjustment
0.78	50	0.846	1.000	0.780	0.780
	51	0.811	0.959	0.748	0.780
	52	0.811	0.959	0.748	0.780
	53	0.811	0.959	0.748	0.780
	54	0.811	0.959	0.748	0.780
	55	0.811	0.959	0.748	0.780
	56	0.811	0.959	0.748	0.780
	57	0.811	0.959	0.748	0.780
	58	0.811	0.959	0.748	0.780
	59	0.811	0.959	0.748	0.780
	60	0.811	0.959	0.748	0.780
	61	0.811	0.959	0.748	0.780
	62	0.811	0.959	0.748	0.780
	63	0.811	0.959	0.748	0.780
	64	0.811	0.959	0.748	0.780
	65	0.811	0.959	0.748	0.780
	66	0.811	0.959	0.748	0.780
	67	0.811	0.959	0.748	0.780
	68	0.811	0.959	0.748	0.780
	69	0.811	0.959	0.748	0.780
	70	0.811	0.959	0.748	0.780
	71	0.808	0.955	0.745	0.780
	72	0.808	0.955	0.745	0.780
	73	0.808	0.955	0.745	0.780
	74	0.808	0.955	0.745	0.780
	75	0.808	0.955	0.745	0.780
	76	0.808	0.955	0.745	0.780
	77	0.808	0.955	0.745	0.780
	78	0.808	0.955	0.745	0.780
	79	0.808	0.955	0.745	0.780
	80	0.808	0.955	0.745	0.780
	81	0.730	0.863	0.673	0.780
	82	0.730	0.863	0.673	0.780
	83	0.730	0.863	0.673	0.780
	84	0.730	0.863	0.673	0.780
	85	0.730	0.863	0.673	0.780
	86	0.730	0.863	0.673	0.780
	87	0.730	0.863	0.673	0.780
	88	0.730	0.863	0.673	0.780
	89	0.730	0.863	0.673	0.780
	90	0.730	0.863	0.673	0.780
	91	0.730	0.863	0.673	0.780
	92	0.730	0.863	0.673	0.780
	93	0.730	0.863	0.673	0.780
	94	0.730	0.863	0.673	0.780
	95	0.730	0.863	0.673	0.780
	96	0.730	0.863	0.673	0.780
	97	0.730	0.863	0.673	0.780
	98	0.730	0.863	0.673	0.780
	99	0.730	0.863	0.673	0.780
	100	0.730	0.863	0.673	0.780

Appendix 4. Calculating severity

4.1 Detailed procedure for calculating absolute shortfall (AS) for treatment interventions

4.1.1 Age

Define the mean age at start of treatment for the relevant Norwegian patient group under consideration for the new treatment. If the age spread in the patient group is very uneven, the median age can be considered. There must be consistency between the age used in the severity calculations, the age in clinical practice and the age in the health economic model. Where there is considerable uncertainty or divergent estimates of age from different sources, it can be useful to use an age interval. Account for where in the interval the mean or median is most likely to lie.

Sources for mean age estimation can be registry data, study data and/or information from clinical experts. Use the source which best reflects the relevant population in Norway.

4.1.2 Expected remaining QALYs for the general population

Estimate the number of remaining QALY for an average person from the general population with the age found in point 4.1.1. This can be called the quality adjusted expected remaining lifetime from the relevant age. We use the term $QALYs_A$ – short for remaining QALYs at age A. It is the remaining QALYs of both men and women, seen as one, which is used in the calculations, not the gender-specific expected QALYs.

In order for the calculations to be as comparable as possible, the following main sources are recommended for use in calculating $QALYs_A$: Use mortality data for the Norwegian population from Statistics Norway in calculating expected remaining lifetime at different ages(58). This is combined with age-specific quality of life data to calculate quality adjusted remaining lifetime for different ages. We recommend using Table 7 in appendix 4.6. The table shows the expected remaining quality adjusted life years according to age in the average population..

4.1.3 Prognosis

Calculate the prognosis for the relevant patient population at the start of treatment. The prognosis is the average number of remaining healthy life years for the patient group with the current standard treatment P_A. The prognosis is therefore calculated for the treatment the patient group would have received if the new pharmaceutical were not used, ie, the current standard treatment (comparator). If there is currently no active treatment, the choice of patient population for calculating the prognosis must be in accordance with the guidelines for choice of comparator in health economic analyses, for example, best supportive care or no treatment, see choice of comparator, Chapter 3.4. The prognosis is calculated for the rest of the patient group's lifetime and is based on the mean value. The prognosis is measured in QALYs. Calculate the prognosis from the number of QALYs the patients can expect with the comparator treatment (usually the current standard treatment) in the health economic analysis. When the health economic calculations are based on a lifecycle model (eg,

Markov), it is normally useful to have a model-based estimate to ensure consistency between the different priority-setting criteria. In the following, we use P_A to denote prognosis at age A.

Sources for prognosis calculation: Prognosis, measured in undiscounted QALYs, for the patient group being treated with the comparator in the health economic model, will usually be useful as a source for the severity calculation. Alternative sources are relevant clinical studies, registry data or data from systematic literature searches.

4.1.4 Absolute shortfall

$AS = QALYs_A - P_A$

In the calculations, undiscounted numbers for $QALYs_A$ and P_A are used.

Uncertainty in calculating AS must be discussed. This applies for example to uncertainty in the estimates of age or prognosis.

4.2 Examples – calculation of degree of severity for treatment interventions

4.2.1 Example of calculation of absolute shortfall for disease A.

Based on a health economic model with a lifetime perspective.

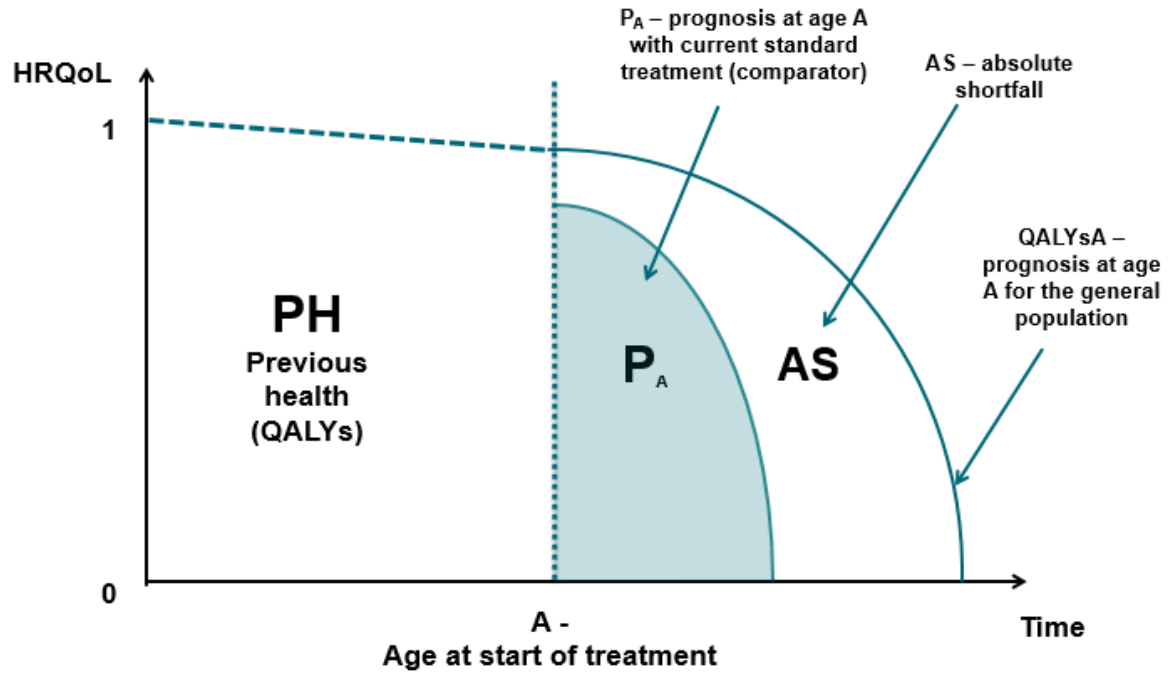
1. Age. The mean age at treatment start in the patient group relevant for treatment is estimated by clinical experts to be 57 years. This is supplemented by data from national registries.
2. For a 57 year old the expected remaining healthy life years ($QALYs_{57}$) is calculated as 22.0 QALYs. See appendix. 4.6.
3. Prognosis. Patients have an expected remaining life time of 2.5 years, corresponding to 1.5 QALYs (undiscounted) with the current standard treatment (the comparator). This is based on simulations with the health economic model included in the company's documentation, after the Norwegian Medicines Agency has evaluated the documentation.
4. The absolute shortfall (AS) will then be 22.0 QALYs – 1.5 QALYs = 20.5 QALYs.

Figure 4 below illustrates the AS calculation for the treatment intervention. The figure applies on a patient group level. The Y-axis shows health-related quality of life, (HRQoL) on a scale from 0 (dead) to 1 (full health). The X-axis shows time. The new treatment is considered at age A. Without the disease, the future health would be given by the area under the solid blue line from timepoint A. This is given as $QALYs_A$, cf. the example above. The disease leads to a shortening of lifetime and a reduction in the quality of life (with the current standard treatment). The prognosis with the disease and current treatment is shown in the shaded area P_A. The absolute shortfall (AS) is shown as the difference between $QALYs_A$ and P_A.

The figure does not include any potential health loss linked to the disease before the start of treatment. This is because the Priority-setting White Paper only recommends future health loss for quantifying severity.

Note that theefficacy of the new treatment/pharmaceutical which is being evaluated, is *not* included in the calculation of severity. Theefficacy is included in evaluation of the other priority-setting criteria: namely, benefit. In the calculation of severity (absolute shortfall) the efficacy (prognosis) with the current standard treatment is included.

Figure 4: How to quantify severity



4.2.2 Example of calculating absolute shortfall for disease B.

Based on a health economic model with shorter time perspective than lifetime, eg, with a one-year perspective. This could be a chronic, non-fatal condition.

1. Age. The mean age for treatment start in the relevant patient group is estimated at 50 years.
2. For a 50 year old the expected remaining healthy life years ($QALYs_{50}$) is calculated as 27.3 QALYs. See appendix 4.6
3. Prognosis. The prognosis (undiscounted) in the health economic model analysis is 0.750 QALYs. But this is the prognosis on a 1-year timescale, not for the rest of life. The prognosis for the rest of life must be calculated. The calculation will depend on the disease and the disease progression with the current standard treatment. A stylized way to calculate lifetime prognosis can be as follows: assume that from another source, eg, Stavem et al (57), the HSUV for a 50 year old is 0.846. Assume also that the relative QALY loss caused by the disease is constant for the rest of life: Then the prognosis can be simply estimated in this way: Prognosis= (0.750/0.846) * 27.3 QALYs = 24.2 QALYs. In the calculation 27.3 QALYs is the expected remaining QALYs for a 50 year old.
4. AS will then be 27.3 QALYs – 24.2 QALYs = 3.1 QALYs.

4.3 Example of calibrating two data sources – level adjustment

In some cases, the HSUV for symptom-free states in the health economic analyses which form the basis for prognosis calculation are higher than the HSUV for the average population used in the calculation of remaining QALYs. This should, as a rule, be corrected for by calibration.

Example:
A single technology assessment of a new pharmaceutical where the mean age at treatment start is 70 years. The prognosis estimate for established treatment is taken from the health economic model. The prognosis is 3 QALYs. From the quality-adjusted lifeyears tables (see appendix 4.6) the remaining QALYs for a 70 year old will be 12.9 QALYs. The AS is 12.9 QALYs – 3 QALYs = 9.9 QALYs.

The HSUV in the prognosis calculation will come from clinical studies of the pharmaceutical being evaluated or from other studies where the quality of life for the disease/condition have been measured, while the HSUV included in the quality-adjusted lifeyears table come from another source. This must be taken account of in the way shown in our example:

In the health economic analysis the condition has a "symptom-free" HSUV of 0.850. This weight is used in the prognosis calculation. In the calculation of remaining $QALYs_{70}$ however, the HSUV for an average 70 year old is lower at 0.811 and is based on Stavem et al (57).

This should be adjusted for by multiplying the prognosis estimate by the factor 0.811/0.850.

Thus the adjusted prognosis will be 3 QALYs* 0.811/0.850 = 2.9 QALYs. The adjusted absolute shortfall will then be 12.9 QALYs – 2.9 QALYs = 10.0 QALYs.

In this example, the adjustment did not lead to major changes in the calculated absolute shortfall. In other cases, it can make more difference. In general terms, when adjustment has been used, companies should consider whether the adjustment is reasonable.

4.4 Examples – calculation of degree of severity for preventive measures

4.4.1 New measure which prevents one type of disease.

1. Age. The new preventive measure is given to the relevant population from a mean age of 40 years. For the population, the disease occurs on average from age 60 with the current preventive practice (the comparator in the health economic analysis). The age that must be used in the calculation of absolute shortfall is 60 years.
2. For a 60 year old the expected number of remaining healthy lifeyears ($QALYs_{60}$) is calculated as 19.8 QALYs. (See appendix 4.6).
3. Prognosis. For this disease and the relevant population, the prognosis is 7.3 QALYs with the current standard treatment. The prognosis reflects the fact that some individuals who get the disease will die of it, while the majority will survive, albeit with somewhat reduced quality of life. Heart attack is an example of a disease/event of this type. The average prognosis will thus be a weighted average of the prognosis for those who die of the disease/event and those who survive.
4. AS is estimated as 19.8 QALYs – 7.3 QALYs = 12.5 QALYs.

Calculation of absolute shortfall for prevention can also be shown by the figure above, but then the absolute shortfall is calculated

- From the timepoint that the disease manifests (timepoint A), not from the timepoint that the preventive measure is carried out or started.
- for a patient who gets the disease the prevention is aimed at, not for a person who gets the preventive measure. The figure will thus refer to the sub-group who get the disease at a later timepoint (timepoint A).
- with prognosis based on the current standard *treatment* of the disease.

4.4.2 New measure that prevents two types of disease, A and B – Calculation of weighted absolute shortfall

Procedure for calculating weighted absolute shortfall (weighted AS):

1. Calculated AS for disease A: 10 QALYs
   Calculated AS for disease B: 6 QALYs

2. In the health economic analysis the benefit is estimated as 2.0 QALYs. This is the average incremental effect per person who receives the measure. 1.8 QALYs, ie, 90 %, of the benefit is linked to prevention of disease A. 0.2 QALYs, ie, 10 % of the benefit is linked to prevention of disease B.

The weighted AS for disease A and B in this case will then be: 90% * 10 QALYs + 10 % * 6 QALYs = 9.6 QALYs.

4.5 Justification of the suggested principle for weighted AS for measures which prevent and/or treat several types of disease

1. Severity must be taken into account along with the other two priority-setting criteria, benefit and use of resources, in prioritising between measures/pharmaceuticals. Benefit and use of resources are included directly in a cost-effectiveness analysis for calculating the cost per QALY-ratio of the measure. Severity is included in the form of severity weights where, after the cost-effectiveness analysis, it is decided what is the highest acceptable cost per QALY- ratio. A higher AS gives a higher severity weight, and therefore a higher acceptable cost per QALY ratio.

2. All relevant benefits and costs must be included in the analysis to give the best possible basis for decision-making with regard to the *effectiveness* of the measure. Severity is a consideration of *distribution or fairness* which is considered in addition to effectiveness. If a measure is to be given a high overall severity weighting in prioritisation, it should appear as a good measure for the treatment or prevention of severe diseases. Then the benefit from the measure should be linked to the treatment or prevention of severe diseases. If the measure is aimed a several diseases, then the disease which is most important when estimating the benefit of the new measure, should be given the greatest weight when the measure is accorded a severity weighting.

3. All the benefit components which are included in the benefit evaluation of the measure, will individually contribute towards making the measure more cost effective. If a company chooses to include benefit for prevention or treatment of *several* diseases in its analysis, in order to

achieve a better cost-benefit ratio, then the company must expect that the overall severity weight (weighted AS) across the diseases will be calculated using a weight based on the different diseases' share of the benefit.

4. This means that weights according to the diseases' share of benefit in the cost-effectiveness analysis are logical and consistent for use in the severity evaluation based on the weighted AS (given the use of weighted AS in the prioritising between interventions/pharmaceuticals, cf. point 1 above). Such a weighting can be used whether it is the same patient group which has/will get several diseases or different groups which each have/will get one of the diseases.

4.6 Expected remaining QALYs in the general population

NoMA has updated the population norms for EQ-5D[19] (HSUV) with the recently published population norms by Stavem et al (57). The population samples included are representative of the Norwegian general population, and the collected data are more recent than the Swedish population norms used in our previous versions (59, 60), though the number of respondents is lower. We have not changed tariff for scoring the EQ-5D index and use the population based UK tariff (61). Table 7 shows the expected remaining QALYs and (health-related) HSUV respectively, by age for the general population. Expected remaining QALYs are based on mortality data for the Norwegian population from Statistics Norway (58) and the age-specific HSUV in the right hand column.

Stavem *et al* (57) covers the age group from 19 to 97. HSUV (values in parentheses) for the age groups 19-50 years in 10-year brackets are directly incorporated from Stavem *et al* (57): 19-30 (0.906), 31-40 (0.870), 41-50 (0.846). Using the raw data[20] from Stavem *et al* (57), we have calculated a simplified weighted average[21] for the age groups 51-70[22] (0.811) and 71-80 (0.808). The raw data is also used for the HSUV for the age group above 80 (0.730). This sharper decrease in HSUV after age 80 compared with the decrease between ages 50 and 80 is supported by findings in the Tromsø Study (T7, unpublished) and in European health status surveys (62-64). Furthermore, NoMA assumes that HSUV are somewhat higher in the younger age group (0-19) and uses the same increment as before (0.02) yielding a HSUV of 0.926

[19] NoMA uses the same strategy in calculating and extrapolating the Norwegian HSUV as we did with the previous Swedish based figures.
[20] Stavem – Personal communication
[21] The raw data were available for the groups 71-75 and 76-80; the average is weighted by the fraction of responders in each of the two age groups.
[22] Stavem *et al* reported lower utility values in the age bracket 51-60 compared with 61-70 years. Such fluctuations are not reported in other comparable studies, and NoMA chose to smooth the HSUV by weighting an average for the pooled 51-70 group.

Table 7: Expected remaining QALYs and HSUV in the general population

Age	Expected remaining QALYs	HSUV	Age	Expected remaining QALYs	HSUV	Age	Expected remaining QALYs	HSUV
0	70.9	0.926	36	38.8	0.870	72	11.6	0.808
1	70.2	0.926	37	37.9	0.870	73	11.0	0.808
2	69.2	0.926	38	37.1	0.870	74	10.4	0.808
3	68.3	0.926	39	36.2	0.870	75	9.8	0.808
4	67.4	0.926	40	35.4	0.870	76	9.2	0.808
5	66.5	0.926	41	34.6	0.846	77	8.7	0.808
6	65.6	0.926	42	33.7	0.846	78	8.1	0.808
7	64.6	0.926	43	32.9	0.846	79	7.5	0.808
8	63.7	0.926	44	32.1	0.846	80	7.0	0.808
9	62.8	0.926	45	31.3	0.846	81	6.5	0.730
10	61.9	0.926	46	30.5	0.846	82	6.0	0.730
11	61.0	0.926	47	29.7	0.846	83	5.6	0.730
12	60.0	0.926	48	28.9	0.846	84	5.2	0.730
13	59.1	0.926	49	28.1	0.846	85	4.9	0.730
14	58.2	0.926	50	27.3	0.846	86	4.5	0.730
15	57.3	0.926	51	26.5	0.811	87	4.1	0.730
16	56.4	0.926	52	25.7	0.811	88	3.8	0.730
17	55.4	0.926	53	25.0	0.811	89	3.5	0.730
18	54.5	0.926	54	24.2	0.811	90	3.2	0.730
19	53.6	0.906	55	23.5	0.811	91	3.0	0.730
20	52.7	0.906	56	22.7	0.811	92	2.8	0.730
21	51.9	0.906	57	22.0	0.811	93	2.6	0.730
22	51.0	0.906	58	21.2	0.811	94	2.4	0.730
23	50.1	0.906	59	20.5	0.811	95	2.2	0.730
24	49.2	0.906	60	19.8	0.811	96	2.0	0.730
25	48.3	0.906	61	19.1	0.811	97	1.8	0.730
26	47.4	0.906	62	18.3	0.811	98	1.8	0.730
27	46.6	0.906	63	17.7	0.811	99	1.6	0.730
28	45.7	0.906	64	17.0	0.811	100	1.5	0.730
29	44.8	0.906	65	16.3	0.811	101	1.5	0.730
30	43.9	0.906	66	15.6	0.811	102	1.4	0.730
31	43.0	0.870	67	14.9	0.811	103	1.3	0.730
32	42.2	0.870	68	14.2	0.811	104	1.0	0.730
33	41.3	0.870	69	13.6	0.811	105	0.8	0.730
34	40.5	0.870	70	12.9	0.811			
35	39.6	0.870	71	12.3	0.808			

Appendix 5. Reference case - health economics

The table below sums up by key words *some* of the requirements for health economic analyses in these guidelines.

Table 8 Reference case

Element in the analysis	***Standard analysis***	***Chapter in the guidelines***
Comparator	The treatment alternative(s) the new pharmaceutical is likely to replace	3.4
Analysis perspective	A form of extended health service perspective	9.2
Time horizon	Long enough that all the important future differences in costs and benefits between the interventions are captured	10.3
Analysis method	Cost-utility analysis (CUA)	9.1
Measure of benefit	QALY	7
Method for measuring benefit	Generic preference-based instruments (mainly EQ-5D-3L)	7.2
Method for valuing benefit	Population-based tariffs (mainly UK tariffs)	7.3
Value added tax (VAT)	Should not be included	9.2
Productivity changes as a result of the new pharmaceutical	Should not be included	9.2 og 9.3
Unrelated, future health service costs and savings	Should not be included	9.2
Marginal costs of public funds	Should not be included	9.2
Discounting	4 % per year for costs, benefit and life years.	9.4
Methods for dealing with uncertainty	One-way sensitivity analyses (shown in tornado diagram), multiway sensitivity analyses (mainly scenario analyses) and PSA	12.2
Degree of severity	Absolute shortfall	11