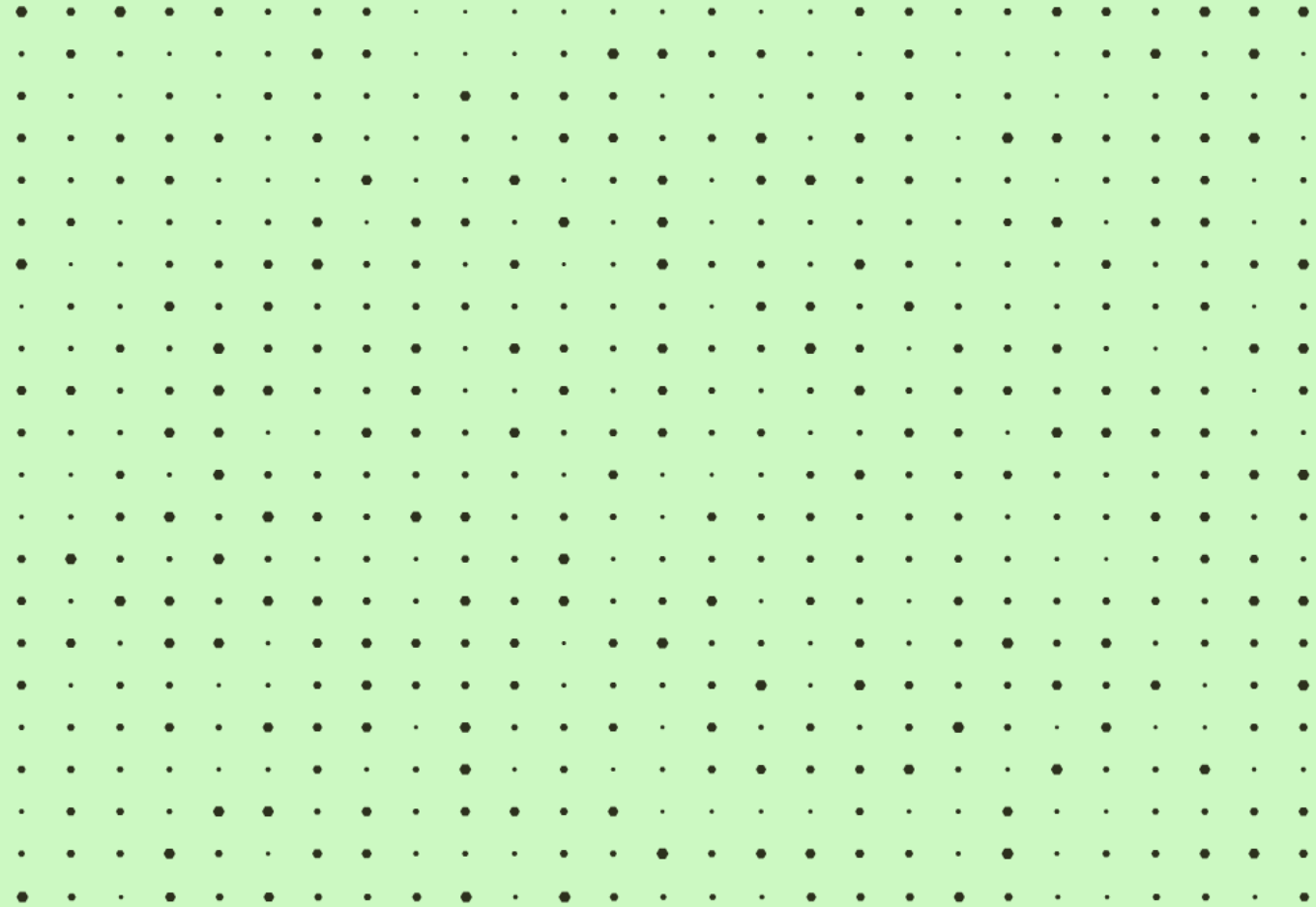
Norwegian Medical
Products Agency

# Submission guidelines

## For Single Technology Assessment of Medicinal Products

**Valid from: 01.01.2018**
**Updated: 02.07.2025**



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# Foreword

The Norwegian Medical Products Agency (NOMA) is the sole HTA body for single technology assessments (STA) of medicinal products in Norway and conducts both assessments for new interventions and new indications of existing medicinal products.

NOMA is an agency under the Ministry of Health and Care Services. This document and its content reflect the principles described in White Paper 34 (2015-2016) [1], White paper 38 (2020-2021) [3], White Paper 21 (2024-2025) [4]. White Paper 21 is hereafter referred to as the priority-setting White Paper (*Prioriteringsmeldingen*). The purpose of conducting STAs in Norway is to address the three prioritisation criteria outlined here; benefit, resource use and severity, as well as uncertainty and budgetary consequences. Depending on the scope of the submission the prioritisation criteria are assessed in a quantitative (CUA, CMA) or qualitative manner.

This guideline details principles and methodological requirements for submission of documentation for technology assessments of medicinal products, promoting the production of assessments that are timely, reliable, consistent, and relevant to the needs of decision-makers and key stakeholders. The guidelines do not detail how assessment are conducted by NOMA.

The guidelines are intended to inform Health Technology Developers preparing documentation for economic evaluations. The guidelines are not applicable for clinical decision-making on an individual patient level. They should be used in the preparation of documentation for STA of medicinal products both for Health Technology Developers requesting public financing under the National Insurance Scheme (“Folketrygden”) or in the specialist health services.

This document, Submission Guidelines for Single Technology Assessments of Medicinal Products, includes guidance on the type of documentation and methods required in cost-effectiveness and budget impact analysis. Whereas the submission template specifies the requirements of the different sections in the STA, the intention of these guidelines is to function as a reference document, accompanying the specific sections in the submission template as needed. The guidelines will be reviewed and revised as necessary.

The last major revision of these guidelines (October 2023) was done primarily to harmonise with the HTA-regulation coming into action within the EU in 2025 in which Norway is committed to take part.

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# Glossary of terms

| Abbreviation | Definition |
|---|---|
| AFT | Accelerated failure time model |
| AIC | Akaike's Information Criteria |
| BIC | Bayesian Information Criteria |
| CCTR | The Cochrane Controlled Trials Register |
| CUA | Cost-utility analysis |
| DSU | Decision Support Unit |
| EQ-5D | EuroQol- 5 dimensions |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| HSUV | Health state utility value (also referred to as QALY weight) |
| HTA | Health technology assessment |
| ICER | Incremental cost-effectiveness ratio |
| IPD | Individual patient data |
| ITC | Indirect treatment comparison |
| ITT | Intention to treat |
| KM | Kaplan-Meier |
| LYG | Life years gained |
| MAIC | Matching Adjusted Indirect Comparisons |
| MeSH | Medical Subject Headings |
| NICE | National Institute for Health and Care Excellence |
| ML-NMR | Multi-level network meta regression |
| NMA | Network meta-analysis |
| OS | Overall survival |
| PFS | Progression free survival |
| PH | Proportional hazard |
| PICO | Patient population, intervention, comparator and outcome measures. |
| QALYs | Quality Adjusted Life Years |
| RCT | Randomised controlled trial |
| RWD | Real World Data |

| | |
|---|---|
| SSB (KOSTRA) | Statistics Norway (Municipality-State-Reporting) |
| STA | Single Technology Assessment |
| STC | Simulated Treatment Comparisons |
| VBA | Visual Basic for Applications |

# 1. General submission requirements and information

## 1.1 Pre-submission meetings

Pre-submission meetings with NOMA are not mandatory but may be arranged upon request and are in some instances highly recommended. Guidelines for pre-submission meetings are available on the NOMA website.

## 1.2 Notification of planned submission

Health Technology Developers should notify NOMA by email at least three months in advance of their preferred submission week/date. NOMA will collaborate with the Health Technology Developer to agree on a specific week/date for submission, taking into account guidance, pre-meetings, recruited medical experts, and other ongoing assessments.

If the Health Technology Developer cannot meet the agreed deadline, they should inform NOMA as early as possible, and no later than two weeks before the agreed submission date. They should outline the specific challenges, propose a new submission date, and provide a timeline for progress. Extensions may be granted in cases of illness or other unforeseen circumstances.

Failure to meet agreed deadlines disrupts NOMA's resource planning and may result in limited capacity to process all submissions. In such cases, NOMA will need to prioritize which submissions to address first.

## 1.3 Application and relevance of this guideline

The scope of the submission with accompanying documentation must adhere to the order from Bestillerforum RHF (for description refer to chapter 2) or Norwegian Medical Products Agency (NOMA).

This guideline should be read as a reference manual, and requirements pertaining to specific types of evidence or analyses are only applicable if they align with the scope of the submission.

Chapters 8, 9, 11, 12 and 13 are typically relevant only if a health economic analysis is submitted. Chapter 7 is only relevant if an evidence synthesis forms the basis for establishing relative efficacy.

## 1.4 Templates

A submission template is available on the NOMA website. The template should be used for preparing and submitting documentation. Appendices or additional information may be submitted along with the template. All tables must be formatted as tables, i.e. not inserted as pictures. The completed submission dossier must be submitted as Word and PDF files. Appendices or accompanying files containing embedded documents are submitted in Word format.

When the order from Bestillerforum RHF or NOMA requests an STA without a health-economic analysis, the submission should still adhere to the submission template and must contain a budget impact analysis, but sections only relevant for assessing relative efficacy and health economic modelling can be omitted. To clarify what is considered relevant content in each specific case, it is recommended to contact NOMA for guidance.

The budget impact model should be based on NOMAs BIA template available on the NOMA website, and must be submitted as an Excel file.

Input in the health economic model (if submitted) and/or budget impact analysis must be consistent with the description in the submission dossier.

## 1.5 References

It is not necessary to include complete text documents for all references in the submitted documentation. However, complete text documents for *all the most relevant 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. Files must follow a naming convention. E.g., Author, Year. Include compressed EndNote library (.enlx including enl-file and data folder) if available.

## 1.6 Language

Documentation for STAs of medicinal products must be submitted in either Norwegian, Swedish, Danish, or English.

## 1.7 Responsibility

The entity responsible for preparing the submitted documentation, in addition to others who have been involved, must be stated.

## 1.8 Confidentiality

NOMA acts within the Public Administration Act and the Freedom of Information Act. Guidelines on handling confidentiality in relation to health technology assessments are available on the NOMA website.

## 1.9 Small patient groups

When preparing STA submissions for medicinal products intended for *very small patient groups with extremely severe conditions*, the guidelines outlined in the "Arrangements for single technology assessment of pharmaceuticals for very small patient groups with extremely severe conditions" should be consulted as a supplement to these guidelines.

## 1.10 Vaccines, infectious diseases control and prevention, and antimicrobial resistance

When preparing STA submissions for vaccines, the guidelines outlined in the document "Retningsgivende notat om dokumentasjonsgrunnlag for hurtig metodevurdering av vaksiner" should be consulted as a supplement to these guidelines.

Similarly, for guidance on addressing infection control and prevention or antimicrobial resistance in STAs, refer to the guidance document "Smittevern og resistens i metodevurderinger", which supplements these guidelines.

# 2. Health technology

In this context, health technologies include any pharmaceutical intervention that may be used to promote health, prevent, or treat a disease.

The Norwegian health care service consists of the primary health care and the specialist health care. NOMA performs STAs of medicinal products that might be suitable for public funding either by the regional health authorities (RHF; specialist health care) or through the National Insurance Scheme (*Folketrygden*; primary health care).

For health technologies that may be eligible for public funding through the regional health authorities, NOMA only conducts assessments following an assignment from Bestillerforum RHF. This is an ordering forum consisting of the four medical directors from each regional health authority and two delegates from the Norwegian Directorate of Health.

For NOMA to initiate an assessment of a health technology that may be eligible for public funding through the National Insurance Scheme, the submitted documentation must comply with the requirements outlined in § 14-4 of legemiddelforskriften, and the health technology must be assumed to comply with § 1b of blåreseptforskriften (the regulation for the National Insurance Scheme). § 1b states that reimbursement according to § 2 (general reimbursement) or § 3 (individual reimbursement) may only be provided for medicinal products intended for the treatment of serious diseases or risk factors likely to cause or exacerbate such illnesses, and where there is a need for, or risk of, repeated treatment over an extended period of time.

# 3. Comparator(s)

A health economic analysis in an STA, aims to quantify differences in efficacy/benefit and resource utilisation between the intervention and the relevant comparator(s).

## 3.1 Choice of comparator

The comparator should represent the alternative intervention most likely to be exclusively or partially replaced by the intervention under assessment. The comparator must be as specified through the ordering process, if applicable.

In most cases, the comparator will reflect current standard of care (for example, according to national guidelines), or the treatment that is most extensively used in terms of number of patients treated. The comparator may be best supportive care, medicinal treatments, or current treatments that are not medicinal products. In rare cases a relevant comparator could be no treatment, or a treatment sequence, provided robust data exist.

## 3.2 Multiple comparators

If there are several commonly used comparator treatments, then all relevant comparators should be included in the assessment. The comparators must be included as is, meaning not as a combination of two or more alternatives using, for example, average effects, costs etc. Such a combination will not reveal the cost effectiveness of the intervention in comparison to each comparator.

Some randomised controlled trials (RCTs) may have an “investigator’s choice” control arm. In such cases, it may not be possible or advisable to individualise the alternatives, as this could impair the reliability of the study results. In such cases, include justification for an “investigator’s choice” comparator in the health economic analysis, whether the comparator includes all choices or only one of the alternatives.

## 3.3 Comparator(s) not previously assessed

If NOMA has not previously established the cost-effectiveness of a chosen comparator, an analysis against that comparator alone will, in most cases, not be sufficient to demonstrate cost-effectiveness of the intervention. An additional analysis should then always be provided against placebo, best supportive care, or an alternative that can reasonably be assumed cost-effective.

If the comparator has been considered as established practice for an extended time, has documented efficacy for the population relevant to the STA, and has low associated costs, it may be accepted as the only comparator in the analysis.

## 3.4 Comparator(s) previously evaluated not cost-effective

If NOMA has previously concluded that the comparator is not cost-effective, but is still in use in clinical practice, an additional analysis as described above should always be included.

# 4. Documentation of Population, Intervention, Comparator, and Outcomes (PICO)

Documentation of Population, Intervention, Comparator, and Outcomes (PICO) from studies forming the basis for clinical evidence must be included and represented as follows, using subheadings for clinical documentation, health economic model input, and Norwegian clinical practice:

- The patient population must be described with relevance to Norwegian clinical practice. Relevant effect modifiers and prognostic factors must be elaborated. The extent to which these parameters have been included in the health economic model must be clearly stated.

- The intervention must be described as specified in the SmPC. Any deviation from the SmPC in the relevant clinical trial, expected in Norwegian clinical practice, and/or health economic model input must be detailed. This includes, but is not limited to, mode of administration, frequency, dosing, relative dose intensity, and duration of treatment (TTD). Pre-treatment and subsequent treatment included in the health economic model should be described.

- The comparator(s) must be described as specified in the SmPC. Any deviation from the SmPC in the relevant clinical trial, expected in Norwegian clinical practice, and/or health economic model input must be detailed. This includes, but is not limited to, mode of administration, frequency, dosing, relative dose intensity, and duration of treatment (TTD). Pre-treatment and subsequent treatment included in the health economic model should be listed.

- Definitions and results of primary and key secondary outcomes including efficacy, safety and health related quality of life should be presented with relevant tables and figures. Other outcomes relevant for the health economic model should also be included.

Requirements regarding parametrisation and extrapolation of time-to-event outcomes are outlined in Chapter 8. If treatment switching was allowed in the study protocol, refer to Chapter 9 for requirements.

## 4.1 Efficacy outcomes

Outcomes applied in the health economic model should be clearly described, and any assumptions with respect to relative efficacy and duration of efficacy, and how this is modelled must be justified. In case of lack of conformity between clinical documentation, health economic model input, and Norwegian clinical practice, this must be highlighted, and choices made for model input must be justified.

The effect estimate based on the primary outcome or the “hard” outcomes in the studies should be applied in the model. A hard outcome is an endpoint that is patient important, well defined, and can be measured directly and unambiguously. Any reasons for not adhering to this must be justified in detail. Composite endpoints may be more relevant modelled separately.

**Surrogate outcomes**

Intermediate outcomes[1], surrogate outcomes[2] or biomarkers, are used to predict clinical benefit in market authorisation and HTA/reimbursement processes in situations where direct measurement of clinically meaningful (final) outcomes are unavailable. A surrogate outcome may be a biomarker, or it may be an intermediate outcome.

Establishing that a surrogate lies on a causal pathway and is correlated with a clinical outcome is important but not sufficient to validate a surrogate outcome. In addition, it should be demonstrated that modification of a surrogate without and with therapeutic intervention reliably modifies the clinical outcome [5]. Surrogate outcomes should be validated using multivariate meta-analytic methods if possible.

If intermediate outcomes, surrogate outcomes or biomarkers are used in the health technology assessment, the level of evidence should be established and accompanied with appropriate literature (Table 1). A surrogate outcome originating from a RCT (hierarchy level 1) is always the preferred source of evidence with the level of uncertainty increasing downwards in the hierarchy, from hierarchy level 1 to 3.

Table 1. Hierarchy of evidence for surrogate end point validity [6].

| Hierarchy level | Requirement | Source of evidence |
|---|---|---|
| 1 | Treatment effect on surrogate corresponds to treatment effect on final outcome | Randomised controlled trials showing that changes in the surrogate are associated with commensurate changes in the final outcome |
| 2 | Consistent association between surrogate and final outcome | Epidemiological/observational studies |
| 3 | Biological plausibility of relation between surrogate and final outcome | Pathophysiological studies and understanding of the disease process |

Literature to support/document the level of evidence should be acquired through systematic literature review. Documentation of the literature searches and the relevant publications should be included in the dossier.

The uncertainties associated with the evidence should be described and if possible, quantified.
When a health economic model is submitted, the uncertainty associated with the relationship between the surrogate outcome and health-related quality of life and/or survival should be explored and quantified. Whether a surrogate endpoint is accepted as part of the STA will be assessed by NOMA on a case-by-case basis.

[1] An intermediate outcome is a surrogate outcome such as a measure of a function or of a symptom (disease-free survival, angina frequency, exercise tolerance) but is not the final outcome of the disease, such as survival or the rate of irreversible morbid events (stroke, myocardial infarction) (EUnetHTA-21-D4.4-practical-guideline-on-Endpoints-v1.0.pdf, Version 1.0, 25/01/2023). Intermediate outcomes should be clinically meaningful for the patient.

[2] A surrogate endpoint is an endpoint that is intended to replace a clinical endpoint of interest that cannot be observed in a study - it is a variable that provides an indirect measurement of effect in situations where direct measurement of clinical effect is not feasible or practical. (REF ICH Guideline E9, Statistical Principles for Clinical Trials, 1998).

## 4.2 Safety outcomes

An adverse event is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”[7]. Adverse events relevant for the health economic analysis must be tabulated. Frequent, and serious adverse event should all be included as relevant.

An adverse drug reaction regarding marketed medicinal products is defined as “a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function”[7]. Management of adverse drug reactions in clinical practice (monitoring, follow-up) and how they have been included in the model (resource use and disutility) must be described.

## 4.3 Quality of life outcomes

See chapter 11.

# 5. Information retrieval and selection of relevant documentation

The aim of an information retrieval process is to identify all studies relevant for the STA in question. Systematic literature searches should be submitted. In order to achieve comprehensive information retrieval, systematic literature searches in several databases and further information sources and search techniques are required.

## 5.1 Systematic literature search

The systematic literature search should be exhaustive and aim to identify all relevant documentation on efficacy and safety data, health related quality of life (HRQoL), health state utility values (HSUV), and any other data sources relevant for the submission. The search should be performed according to internationally validated methods and follow the PRISMA statements for reporting [8]. Include the following at a minimum:

- A written protocol allowing for 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 with justification.
- The search date of the systematic literature review should be no older than six months prior to the date of submission, otherwise the search should be repeated, and a list of new, relevant studies included.
- A list of all databases where the search was carried out.
- Study selection: Detail the selection process of chosen studies.
- List studies that were excluded and why.
- Justification of the time period for the search.
- A flow chart showing study selection (e.g., PRISMA).
- Funnel plots indicating publication bias where applicable.
- A discussion of the strengths and weaknesses of the literature search.

The following bibliographic databases should be included in the search at a minimum:

- Efficacy and safety:
  - The Cochrane Controlled Trials Register (CCTR)
  - Other relevant electronic databases not covered by CCTR (e.g., MEDLINE/PubMed, EMBASE, PsychInfo etc.).
- HRQoL and HSUV:
  - MEDLINE/PubMed, EMBASE, and other more specific databases. For details refer to NICE DSU Technical Support Document 9 [9].

Manual searches in conferences, reference databases, or other not included in electronic databases and grey literature searches can be used where relevant.

## 5.2 Studies performed or sponsored by the Health Technology Developer

Published and unpublished pivotal marketing authorisation studies for the population in question must be submitted. Other documentation relevant for the STA, i.e., studies, data, analyses, other evidence and documents, for which the Health Technology Developer was sponsor, must be included in the submission. This also include relevant documentation submitted in relation to a regulatory approval (i.e., a market authorisation application) in cases where the regulatory document European Public Assessment Report (EPAR) is not yet publicly available. Information on ongoing or discontinued studies in the relevant population must be made available.

## 5.3 Risk of bias assessment

Risk of bias assessment should be performed using validated instruments, for instance ROB2 and ROBINS-I [10, 11]. Inclusion of such an assessment is encouraged.

# 6. Documentation of relative efficacy by direct comparative studies

## 6.1 General considerations

This chapter describes requirements in cases where relative efficacy is established through direct comparative studies. A systematic literature search (information retrieval see Chapter 5 for details and requirements) should always form the basis for clinical evidence. When evidence synthesis is necessary, refer to Chapter 7 for guidance.

For establishment of relative efficacy and safety profile of a new intervention, the gold standard evidence is a RCT with low risk of bias. Basket and umbrella trials are built on master protocol designs that can be encompassed by any of the experimental study design setups in Figure 1.

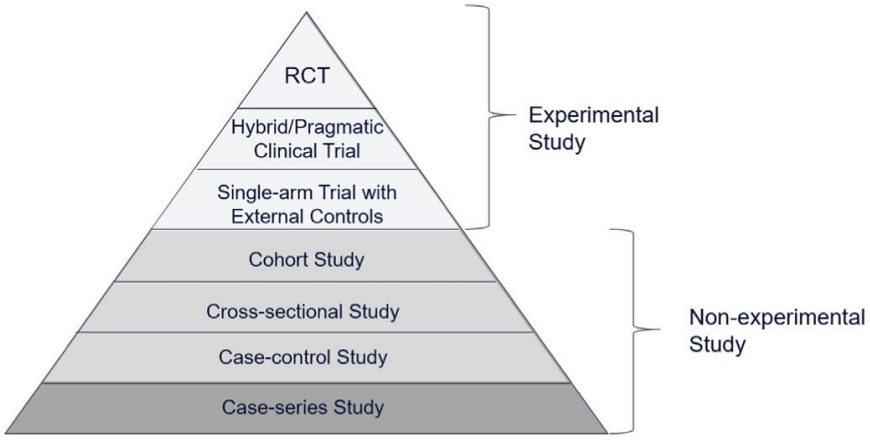


Figure 1. Pyramid level of evidence. There are other levels of evidence; for example, systematic review or meta-analysis could be on the top of RCTs [2].

## 6.2 Reporting of pivotal studies and direct evidence

Detailed description of the pivotal study/studies (inclusion and exclusion criteria, sample size etc.) forming the basis for the marketing authorisation and other relevant studies for establishing direct relative efficacy, must be presented irrespective of design.

Study follow up time and dates for subsequent data-cuts must always be included in the submission. Always include data from the last available data-cut. Supportive and relevant ongoing studies should also be tabulated.

# 7. Documentation of relative efficacy through evidence synthesis

In cases where evidence synthesis is the basis for relative efficacy, PICO should still be described as outlined in chapter 4.

## 7.1 Definitions

The following paragraphs describe terms used in this chapter [12, 13].

Exchangeability refers to the fundamental assumption for evidence syntheses, which implies that if patients from one treatment group were substituted into another, the same treatment effect is expected. The term encompasses similarity, homogeneity, and consistency.

Indirect comparison refers to any evidence synthesis in which treatment groups from different studies are compared.

Network meta-analysis (NMA) is a generalisation of meta-analysis to include more complex evidence networks and can include both direct evidence and indirect evidence. The term NMA incorporates other terms used in the literature to describe the synthesis of both direct and indirect evidence, such as mixed treatment comparisons and indirect treatment comparisons.

Population-adjusted method for indirect comparisons refers to methods for indirect comparisons where individual patient data (IPD) from one or more studies are used to adjust for relevant population characteristics that differ between studies with the aim to estimate relative treatment effect.

## 7.2 General considerations

This section outlines the requirements for evidence synthesis methods used to combine multiple sources of evidence to estimate comparative effectiveness and/or safety (e.g., a pairwise meta-analysis [direct comparison], indirect comparison or network meta-analysis) between the intervention and comparator.

Efficacy and safety data from RCT are preferred over data from studies of other designs. All evidence included in the evidence synthesis must be selected following a systematic review, conducted, and reported in accordance with PRISMA guidelines [8]. The analysis, reporting, and interpretation of the results from evidence synthesis analyses should adhere to good practice principles.

A full systematic literature search must be carried out and the search described in detail as outlined in chapter 5. For literature searches intended to support the documentation of relative efficacy, PICO must be described. The studies included in the evidence synthesis should reflect the established PICO.

A table outlining the following must be submitted along with an evidence synthesis and the differences between studies discussed:

- Overview of study design (phase, randomisation, blinding, condition)
- Definition of endpoints

- Statistical analysis (including estimand[3] [14], and how intercurrent events and missing data were addressed)
- Dates of the study recruitment period
- Duration of follow-up
- Reasons for and proportion of censored observations
- Countries covered by the studies
- The posology of the intervention and comparator
- Types and distributions of a subsequent treatment received in the studies

Furthermore, any other factors that might differ between the studies and that can affect the treatment effect must be tabulated.

Risk of bias assessment using validated tools (e.g., ROB2, ROBINS-I) must be included irrespective of the statistical approach for the evidence synthesis [10, 11].

## 7.3 Assumption of exchangeability

Exchangeability (similarity, homogeneity, consistency) is the fundamental assumption required for evidence synthesis based on meta-analysis and network meta-analysis [15-17].

The assumption of similarity requires studies to be comparable with regards to possible effect modifiers across all treatments included in the evidence synthesis. The following must be evaluated for identification of potential effect modifiers:

- A priori list of potential effect modifiers related to study and patient characteristics, intervention and comparator characteristics, outcome characteristics, and observed values of relevant outcomes at baseline, especially in the comparator arms.
- Description of the methodology applied for identification of effect modifiers, which should include a comprehensive review of the literature and consultation of healthcare professionals in the disease area.
- Description of the magnitude and direction of the interaction effect of the identified effect modifiers.
- Description of likely missing effect modifiers in one or more of the included studies and their potential effect.
- Conclusion with reasoning whether the assumption of similarity is expected to hold.

The assumption of homogeneity requires that there is no meaningful heterogeneity in the effect estimates from the studies included in each direct comparison, requiring at least two direct comparisons and at least five for reliable assessment [18, 19]. It is important to note that heterogeneity can be caused by effect modifiers which are unknown, and factors initially considered similar or not initially considered as effect modifiers. The following must be included for assessment of homogeneity:

- Forest plots of the comparisons.
- Statistical tests for heterogeneity.
- Conclusion with reasoning of whether the assumption of homogeneity is expected to hold, and the studies can be pooled.

Decision on the choice of model for inference, i.e., random vs. fixed, should be guided by the sampling frame and not solely rely upon statistical tests. Both random and fixed effects models should be submitted.

The consistency assumption can only be tested in networks of evidence where both direct and indirect evidence exists for a particular contrast (i.e., a loop structure), and it is thus assessment of the

[3] An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective

between-study variation of different treatment contrasts [15, 20, 21]. The following must be included for assessment of consistency:

- Identification of loops in the network where consistency can be evaluated.
- Method used to test for inconsistency with justification and criteria used for conclusion on whether the consistency assumption can be considered violated.
- Results of the tests and models used with interpretation and uncertainty in the results.
- Description of effect modifiers that are possible sources if inconsistency is detected, preferably including direction and magnitude of effect modification.
- Conclusion with reasoning on whether the assumption of consistency is expected to hold.

If any of the assumptions concerning exchangeability is violated, description of how the violation is handled including complete results of all analyses, must be submitted [21-25].

## 7.4 Statistical methods for evidence synthesis

Requirements for the statistical methods applied in evidence synthesis are described in the following paragraphs. A description of the software used should be submitted, along with codes and scripts.

### 7.4.1 Direct comparisons

Direct comparison also means one single comparison within a single study (see chapter 6). Direct comparisons of treatments described in this section include two or more studies comparing the same intervention against the same comparator in a pair-wise meta-analysis. For the last described situation, the following must be included:

- Description with justification of the chosen statistical model (frequentist or Bayesian) and method for the meta-analysis and heterogeneity parameter.
- Tabular presentation of individual study results, including the number of patients per study.
- Forest plots with point estimates and confidence and prediction intervals.
- In case of Bayesian analysis, information on the nature of the prior distribution for all relevant parameters and evaluation of the impact of the prior distribution on the results of the analyses.

Selected methodological references [12, 13, 26-39]

### 7.4.2 Indirect comparisons

Methods for indirect comparisons include the Bucher method, Bayesian or frequentist network meta-analysis, and anchored population-adjusted methods. Anchored population-adjusted methods are described in chapter 7.4.4, while unanchored and disconnected evidence networks are described in 7.4.4 and 7.4.5.

Provided that the assessment of exchangeability is deemed to be fulfilled (chapter 7.3), the following must be included:

- Full statistical description of the chosen model.
- Appropriateness of the chosen method according to the evidence base.
- Graphical and tabular presentation of the evidence network with number of studies per contrast.
- Tabular presentation of number of patients and individual study results for the endpoints included in the evidence base.
- Forest plots and tabular presentation of the relative effect estimates with measure of uncertainty for the intervention versus all comparators included.
- Presentation and assessment of the results from both direct and indirect evidence if present in the network.
- In case of Bayesian analysis, the number of iterations for burn-in and estimation, the number and convergence of Markov chains, and information and justification for choice of prior distributions for all relevant parameters.

- In case of inconsistency models within the Bayesian framework, plots of posterior mean deviance for both the model and the inconsistency model.

Selected methodological references [12, 13, 15, 40-47].

### 7.4.3 Indirect comparisons of time-to-event data

When the indirect comparisons are based on time-to-event data and the assumption of proportional hazard is violated, the hazard ratio can vary over the follow-up time and differently across the included studies (time-varying effects). In these cases, meta-analysis and network meta-analysis of hazard ratios produce implausible results. Whenever endpoints analysed are time-to-event data, the following must be included:

- Assessment of the proportional hazard assumption with standard methods (log-cumulative hazard plots, Schoenfeld residual plot, statistical tests, any external evidence/clinical expert opinion on the plausibility of the proportional hazard assumption).
- Description of the method applied (restricted mean survival time, flexible survival time models or piecewise exponential models).
- For restricted mean survival time model: rationale for the selected base case follow-up time for the analysis should be prespecified, with a range of follow-up times presented as sensitivity analyses.
- For flexible survival time models with fractional polynomials: justification and assessment of model fit of the chosen model for the hazard rates (i.e., powers of the time variable), and other hazard rate models as sensitivity analyses.
- For piecewise exponential models: reason for that the proportional hazard assumption holds within each piece by statistical assessment and/or clinical expert opinion.
- Table and/or plots with comparisons of observed and modelled hazard ratios at different time points.
- Graphical comparison of the modelled survival time distributions with Kaplan-Meier data.

Selected methodological references [48-54].

### 7.4.4 Population-adjusted methods

The most common population-adjusted methods are matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) [55]. Multi-level network meta regression (ML-NMR) is currently restricted to data that are not time-to-event [56]. Population-adjusted methods can be used when the similarity assumption is considered violated.

In cases of anchored comparisons (connected evidence), it should be justified that bias in the analyses will be reduced by use of population-adjustment method. The following must be included:

- Complete description of the method and model for population adjustment and treatment effect estimation.
- Evidence that one or more of the observed patient characteristics are effect modifiers, and that distribution of effect modifiers is imbalanced enough to result in bias in the relative treatment effect.
- Method for identification and selection of effect-modifying covariates which are adjusted for, and the potential for un-measured effect modifiers.
- Potential for residual bias in the results and indicate size and direction.
- Specification and interpretation of a shifted null hypothesis, if applied.

Regression-based methods (STC, ML-NMR) fit an outcome regression model to the available individual patient data. The following must be included:

- Model fit and appropriateness of the chosen model.
- Description of degree of covariate overlap between the studies included.

- For STC: the method used to estimate outcome and the treatment effect that is targeted by the chosen approach.
- For ML-NMR: whether the data are sufficient to handle treatment-covariate interactions, if the shared effect modifier assumption is required, and whether any other assumptions have been made for model estimation.

In MAIC, the patient population for the intervention is weighted to the aggregated data for the comparator (target) population. The following must be included:

- Distribution of effect modifiers before and after weighting in the intervention population versus the comparator population and impact of any residual imbalance.
- Distribution of weights and effective sample size after matching.
- Method for confidence interval estimation; the robust or bootstrapping methods are preferred.

Unanchored MAIC and STC can be applied in cases with disconnected networks. These analyses compare absolute values of outcome, and to obtain an unbiased estimate all factors affecting the outcome must be adjusted for. The points described above apply also for unanchored analyses and, in addition, the following must be submitted:

- Method for identification of all relevant prognostic variables.
- Description of whether the unanchored indirect comparison is appropriate with regards to which data are available for adjustment, outcome definition, and comparability of study characteristics.
- The extent of missing prognostic variables and the direction and size of bias from the lack of adjustment for prognostic factors.

In unanchored analyses where a prognostic factor for the intervention is of unknown distribution in the comparator study and hence unadjusted for, the results are encumbered with bias of unknown size and direction [12, 13, 55, 57]. Such analyses results might be rejected as source for quantification of relative efficacy in the STA.

Selected methodological references [13, 55-59].

### 7.4.5 Non-randomised evidence

Comparisons based upon non-randomised evidence include single-arm studies, cohort studies, case-control studies, other observational studies, and historical controls from different types of registries. In non-randomised evidence, there is high risk of confounding bias which can violate the underlying assumption of exchangeability. The following must be submitted for all the included evidence:

- Comparison of the inclusion and exclusion criteria.
- Comparison of baseline patient characteristics.
- Method for identification of prognostic and effect modifying factors and method to adjust for confounding.
- Size and direction of bias which arise from missing prognostic and effect modifying variables.
- Risk-of-bias assessment using an appropriate tool.

Propensity score methods can be applied to adjust for confounding in comparisons based on non-randomised data. These analyses, however, require complete access to individual patient data, and whenever used, the following assumptions must be addressed:

- The positivity assumption by assessing patient eligibility/contraindications and propensity score distribution.
- The overlap assumption using histograms or density plots in the whole, matched, and/or weighted populations.
- The balance assumption before and after matching, weighting, or stratification by the absolute standardised difference.

Results should be presented for crude and propensity score analyses with appropriate sensitivity analyses for evaluation of robustness.

Selected methodological references [10, 12, 13, 55, 60-67].

# 8. Extrapolation of relative efficacy

## 8.1 Extrapolation of time-to-event data

Time-to-event data, also known as survival or event history, encompasses instances such as time to progression in cancer, (i.e., progression-free survival or PFS), time to death (i.e., overall survival or OS), or time to a cardiovascular event or treatment discontinuation.

Health economic analyses commonly involve parametrisation and extrapolation of clinical time-to-event data beyond the study period. This section outlines the requirements for parametrisation and extrapolation of survival data for health economic analyses, applicable to both direct and indirect comparisons of relative efficacy. See chapter 12.6 for guidance on selecting time horizon.

### 8.1.1 Parametrisation of data from clinical studies

Extrapolating data beyond the study follow-up period usually involves utilising a parametric function. These functions assume that the underlying event risk (baseline risk) adheres to a specific distribution, as opposed to non-parametric (e.g., Kaplan-Meier) or semi-parametric (e.g., Cox model) functions.

The selection of a parametric function relies on statistical analyses of best mathematical fit and biological criteria, which pertain to the expected development of risk for the current condition/disease and endpoint.

Parametrisation must be based on the actual data from clinical studies to emphasise the direct effect of the treatment under evaluation.

Systematic statistical tests and graphic evaluations must be carried out to allow the choice of the most accurate parametric function [68-75].

To achieve satisfactory fitting, a given function must fulfil the following criteria:
1. The function must align well with the observed efficacy data from the study or studies.
2. The extrapolated segment must be clinically and biologically plausible.

Provide a detailed justification for the chosen function, considering the two criteria above. Functions that do not meet both criteria are likely unsuitable.

When fitting a parametric survival model one may include explanatory variables, typically treatment, but also other variables. When choosing from a large number of potential explanatory variables, the variable selection process should be described. Automated stepwise approaches are prone to overfitting and can lead to a poor fit in out-of-sample data and in extrapolated data. The theoretic arguments or expert opinion should therefore always be considered.

### 8.1.2 Curve fitting to observed study 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 must 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 model (AFT) and for assessing the fit of standard parametric functions[76, 77]:
    - Log-cumulative hazard plot for PH: $\log(-\log(S(t)))$ vs. $\log(t)$ with linear trendlines for the intervention and comparator
    - Plot based on Schoenfeld residuals for assessment of PH
    - Quantile-Quantile-plot for AFT of the times of survival percentile $t_0(p)$ vs $t_1(p)$ with a linear trendline, using the percentiles (p) 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. $\log(t)$ with linear trendlines for the intervention and comparator (graphical test for the suitability of log-logistic, and joint AFT modelling)
    - inverse.normal $(1-S(t))$ vs. $\log(t)$ with linear trendlines for the intervention and comparator (graphical test for the suitability of log-normal, and joint AFT modelling)

- If neither PH nor AFT appear 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, and spline models [78].

- Smoothed and unsmoothed hazard plots for the observed data from the clinical study per treatment arm [79, 80].

- 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 [79, 81]

- Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC) and/or other suitable tests for those functions which are relevant based on 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, followed by a parametric tail which shows the extrapolation beyond this point (transition point). The transition point must be evaluated in each 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".

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

### 8.1.3 Plausibility of the extrapolated part of the curve

The plausibility of the extrapolated part of the survival curve must be documented and justified both biologically and clinically for the patient group in question. External data (e.g., survival curves, hazard functions) can be employed to evaluate the assumptions made in the extrapolation. Systematic and reproducible identification of evidence is essential.

External data may include data of the same medicinal product(s) used in the same indication (e.g., phase 1/2 study data for the invention and/or randomised controlled trials, observation studies, or registry data for the comparators), more mature data from the same medicinal product(s), used in a later line of treatment for the same disease, data of the same medicinal product(s) used in a similar

indication or evidence from a medicinal product with a similar mechanism of action used in the same indication [82].

Consider external sources as indicative only. Use of external data necessitates a balanced assessment of the degree to which discrepancies between long-term survival projections and external data sources can be attributed to:

- Shortcomings/weaknesses in the chosen parametric function, and/or
- Limitations in the external data source

Typically, external data is available solely for the comparator arm, rendering it most suitable for assessing the plausibility of projecting the comparator arm. Therefore, the clinically valid assumptions about 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. Various assumptions must be tested in the scenario analyses. It is recommended to include three alternative scenarios [83] for the long-term effect of a treatment that so far has been shown effective in studies with limited follow-up time:

- pessimistic scenario where the effect is null beyond study follow-up time,
- optimistic scenario where the effect beyond study follow-up time is assumed constant and the same as in short-term, and
- compromise scenario where the effect beyond study follow-up time is diminishing.

### 8.1.4 Algorithm and implementation in the health economic model

Figure 2 below depicts the algorithm for selection of a parametric model in time to event data analysis for health economic analyses.

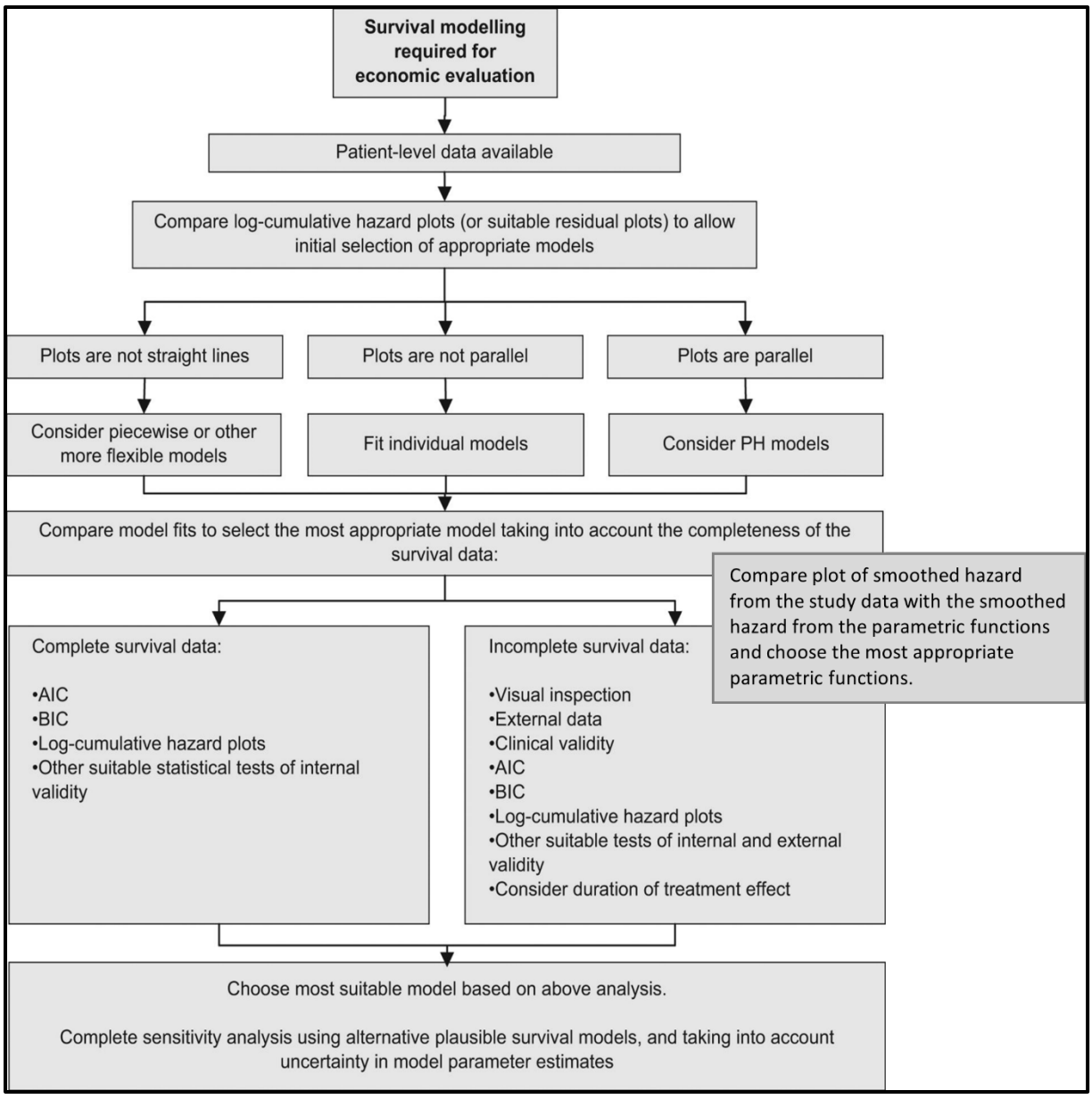


Figure 2 Algorithm for selection of a parametric model. Modified from Latimer 2013 [84]

## 8.2 Extrapolation of other endpoints

For extrapolation of other endpoints than time-to-event data, justify the assumptions made and sources used to model long-term efficacy beyond the study period and the transitions between health states in the model.

# 9. Treatment switching

For ethical reasons, RCTs may allow patients in the control arm to switch to the intervention treatment or another active treatment at a given time point, often at time of progression of the disease, here referred to as treatment switching.

Treatment switching is relatively common in cancer studies. In such cases the effect estimate for overall survival can be affected. There are several adjustment methods that can be applied to provide an estimate of survival, as if the switch had not occurred. The most suitable method depends on the specific data and must be evaluated for the individual case. A particular method may be specified in the study's statistical analysis plan.

Analyses that have been corrected for treatment switch can be submitted. In such a case, the following must be provided:

- A description of the switching mechanism, i.e., timepoint when the patients switched treatment.
- The number and proportion of patients who switched treatments.
- Baseline patient characteristics for both patients who switched and patients who did not switch treatment.
- Response status of patients before switching (response/no response/partial response etc)
- 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.
- A detailed description of the applied adjustment method with justification of why the underlying method-specific assumptions are fulfilled or not.
- An explanation for why other adjustment methods was not applied.
- A discussion of the assumptions, strengths, and weaknesses of the various methods [84].

Figure 3 illustrates the algorithm for selecting an adjustment method.

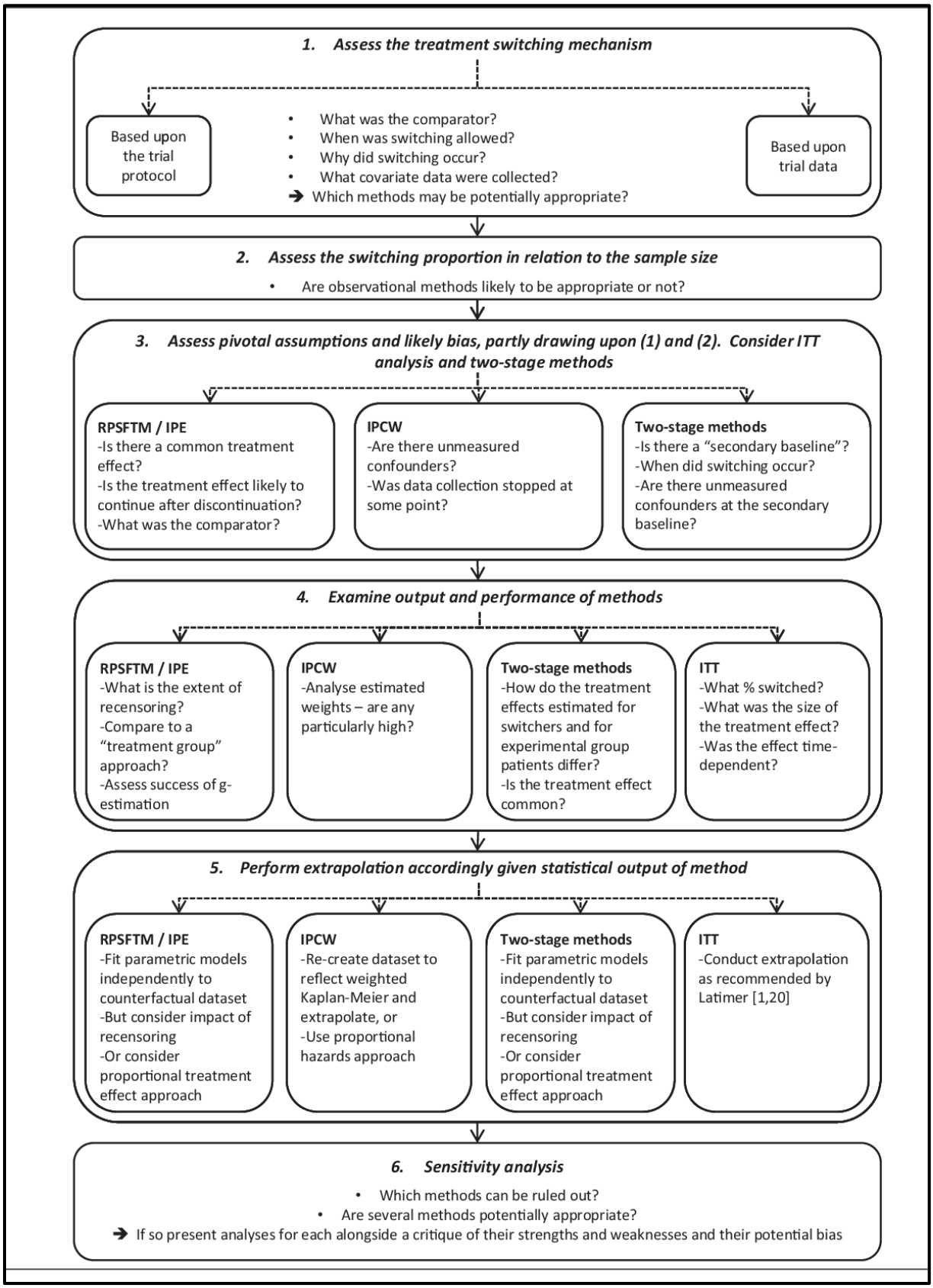


Figure 3. Flow diagram for selection of treatment switching methods. From Latimer 2014 [84].

# 10. Use of Real-World Data (RWD)

Real-world data (RWD) is a comprehensive term that refers to various types of data generated within the context of routine healthcare (e.g., electronic health records, administrative healthcare databases, clinical and disease registries, patient-generated data, and data produced from other various sources) that can inform on health status [85]. RWD may be derived from sources such as cohort studies, registries, and phase IV studies.

Real-world evidence (RWE) refers to the clinical evidence of a health technology or medical condition derived from the analysis of RWD for a specific research question [85].
RWD can be employed to generate RWE for various purposes within health technology assessment such as epidemiology, demographics, treatment duration, usage of a health technology in real-world setting, and assessing the effectiveness and/or safety of health technologies (e.g., for new indications of already-used technologies or for documenting long-term follow-up).

In cases where RWD are the source for quantifying relative efficacy, data should be identified, analysed, and evidence developed through transparent and reproducible approaches as described for evidence synthesis based on non-randomised evidence (see Chapter 7). Potential bias and uncertainties in the data source should be characterised and relevance for clinical practice in Norway should be described.

# 11. Documentation of health-related quality of life (HRQoL)

The health benefit in STAs is quantified using quality-adjusted life years (QALYs) and should ideally be based on patient-reported EQ-5D-5L measurements which are used to estimate health state utility values (HSUV) in the health economic model.

Whenever EQ-5D-5L measurements of health-related quality-of-life (HRQoL) are collected in the pivotal clinical studies for the intervention in question, these must be submitted and included as an option in the model. Use of HRQoL data from the literature must be supported by a systematic literature search (Chapter 5), and the choice of sources must be justified and discussed.

## 11.1 Instruments

HRQoL data for use in health economic analyses must be measured using generic preference-based measuring instruments, preferably EQ-5D-5L to enable comparison between therapeutic areas and STAs [86-88]. Any disease-specific instruments used should be reported as supplementary information.

The EQ-5D-5L should be used to measure HRQoL in patients 12 years or older [86].

For measurement of HRQoL in children 8 years or older, both EQ-5D-Youth-3L and ED-5D-Y-5L [89-91] can be used, for which tariffs are currently being developed [92]. Average age, age distribution, and age range of the respondents, must be submitted [93].

Where EQ-5D or other generic preference-based measuring instruments are deemed inappropriate for capturing certain aspects of a disease or the patients' health-related quality of life, for example when coping/adaptation ("mestring") is affected, this must be supported by empirical data as well as by a qualitive discussion. For guidance consult NICE DSU Technical Support Document 8 [94].

Figure 4 below depicts the hierarchy of preferred sources for health-related quality of life data [95].

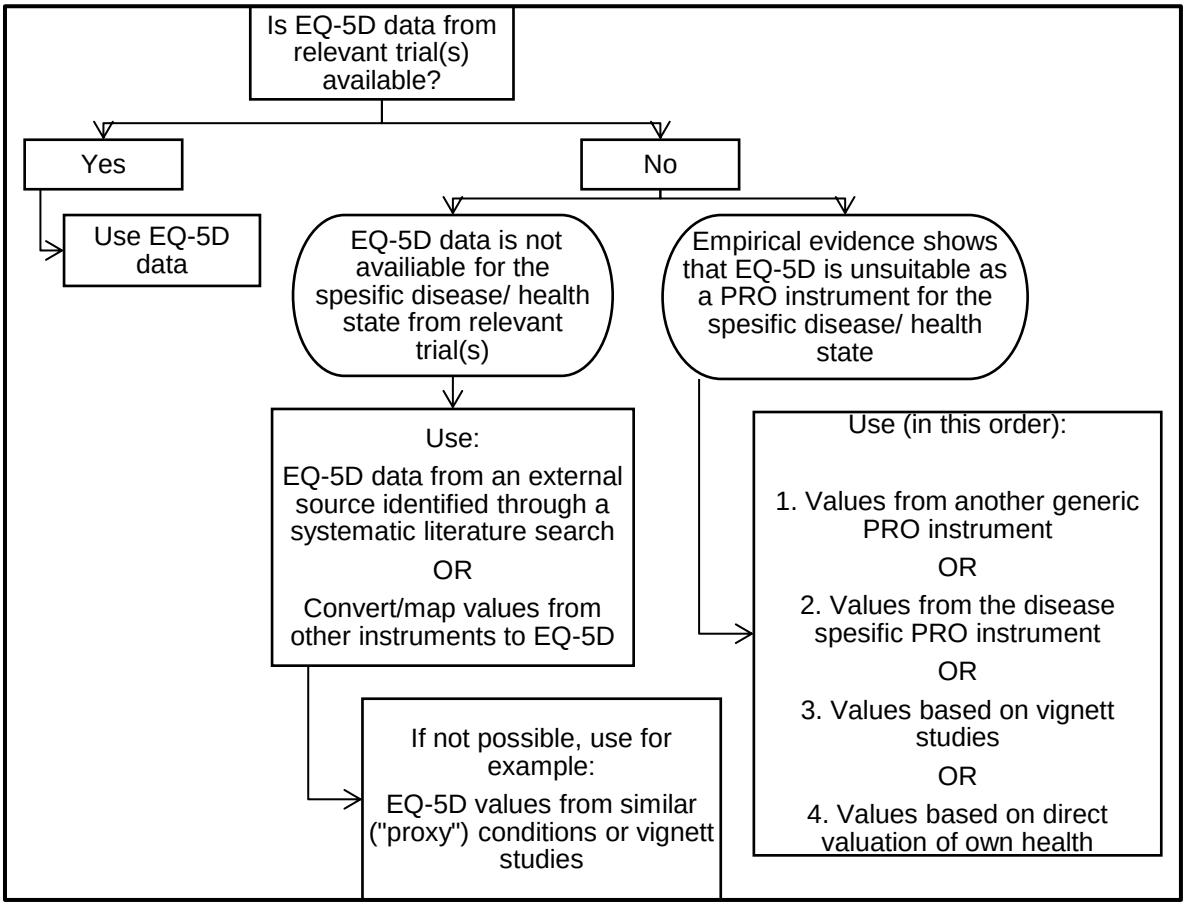

Figure 4. Hierarchy of preferred sources for health-related quality of life data (modified from [95])

## 11.2 Calculations

Any utility value calculations must be described transparently, and the following must be included:

- Description of how many subjects responded to the patient-reported outcomes questionnaire (compliance rates by visit and treatment), reasons for missing questionnaires, and differences, if any, between non-respondents and respondents.

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

- Exploration and description of the statistical model assumptions for HRQoL analyses (e.g., homoscedasticity, normality of residuals, linearity of predictor-outcome association, independence if non-hierarchical model).

- Handling of missing data, including description of patterns and assumptions supported, where possible, with graphical approaches or formal tests for association and methods of imputation [96, 97].

Methods that assume data are MCAR should be avoided unless the MAR mechanism has been ruled out analytically, or the proportion of missing data is low (i.e., <5%). Methods assuming MCAR include complete case analysis or single imputation (e.g., mean, or last observation carried forward). Methods

accounting for repeated measures that assume MAR such as likelihood-based mixed models, are generally preferred as they make the most of the observed data [98-100]. Lastly, methods based on MNAR, an assumption that cannot be validated, should be restricted to sensitivity analyses. These include control-based multiple imputation or pattern mixture models.

Statistical model results should be presented as per the statistical software output, along with the interpretation of the coefficients and their relation to the utilities used in the economic model. When arm-specific utilities are used for the base case, the results of a statistical model without a treatment covariate must be presented in addition.

Utility values sourced from the literature must be documented and discussed to the extent of available information. The chosen source of utilities must be justified and identified through an exhaustive literature search (Chapter 5).

## 11.3 Valuing

To ensure consistency across STAs and between measures of severity and health economic analyses in an STA, HRQoL are valued using tariffs derived from the general population and relevant to the Norwegian adult population. The Norwegian population-based EQ-5D-5L tariff [101] must be applied when HRQoL is measured using the EQ-5D-5L instrument.

Use of an experienced-based tariff should be justified providing explanation of the differences between this tariff and a general population-based tariff.

If HRQoL values have been collected using the 3L version of EQ-5D questionnaire, use the EQ-5D-3L tariff from the UK general population from Dolan based on 3L for valuation [102], and use the Norwegian 3L population norms from Stavem et al. [103] for severity calculation, available on NoMAs website (see Appendix A.6. for link to the excel sheet).

## 11.4 Mapping

Other generic preference-based instruments such as SF-6D, 15D, HUI, AQoL, and QWB can be used in instances were patient-reported EQ-5D data are lacking. The values from alternative HRQoL-instruments must be mapped to EQ-5D values using validated methods, and the results should be compared to published quality-of-life data for the relevant patient group.

If only disease-specific instruments are available, mapping must be used to predict EQ-5D values accompanied by a transparent description of the method. For details, refer to NICE DSU Technical Support Document 10 [104].

## 11.5 Age adjustment

In general, increased morbidity and decreased function related to increasing age means that health-related quality of life in the general population decreases over time. To account for changes in morbidity and mortality in the general population with increasing age, development of HSUV over time must be age adjusted using the multiplicative method, refer to NICE DSU Technical Support Document 12 for details [105]. An example is provided in the Appendix, together with a link to an Excel spreadsheet that can be used to calculate age adjustment.

EQ-5D-5L norm data from the Norwegian general population [106] as published on NoMA's website have to be used for estimating age-adjusted HSUV (see Appendix A.6. for link to the excel sheet).

Age-adjusted HSUV are used in the calculations of expected remaining QALYs for the general population (Chapter 13), hence such adjustments ensure consistency with calculation of severity.

Lack of age adjustments must be justified.

## 11.6 Level adjustment

When the best health state exceeds the utility weight of the general population (see online Excel spreadsheet), utility values should be adjusted using a multiplicative method. This approach preserves the relative differences between stages while preventing utility values from exceeding those of the general population. The method corresponds to the adjustment DMP applies to utility values for age over time in models.

Without adjustment:

Health state A from study: 0.91
Health state B from study: 0.73
General population: 0.87 (age 50)

With adjustment:

Health state A from study: 0.91 * (0.87 / 0.91) = 0.87
Health state B from study: 0.73 * (0.87 / 0.91) = 0.69
General population: 0.87 (age 50)

The adjustment is applied only to utility values derived from the same source. If external sources are used for subsequent or worse health states, these are not adjusted using the same value. If the external sources also report utility values exceeding those of the general population, they should be adjusted in a similar manner but using their own baseline value.

The adjustment, the inclusion of external utility values, and the associated uncertainty (internal/external validity) should be discussed.

If there are very small differences (≤0.01) between utility values for health states from the study and the general population, one may consider not making adjustments.

The calibration of absolute shortfall (AS), as previously practiced when utility values exceeded normative values, is obsolete.

## 11.7 Treatment specific HSUV

If treatment specific HSUV are used, this must be comprehensively justified and documented. Treatment specific HSUV can only be considered when differences in HRQoL are documented in clinical studies and have a clinical rationale.

## 11.8 HRQoL for caregivers

If an intervention impacts HRQoL for caregivers, the effects for the caregiver may be included in health economic analyses quantified as QALYs. Inclusion of HRQoL for caregivers require the same level of evidence as that required for HRQoL for patients. Include the following:

- Description of the condition in question.
- Description of the condition's specific effect on caregiver HRQoL.
- Description of the intervention and the comparator's effects on caregiver HRQoL.
- Analysis with and without effect on HRQoL for the caregiver.

For ethical and methodological reasons, effects of increased life expectancy for patients on caregivers' HRQoL should not be included.

# 12. Health economic analyses

The health economic model must be designed such that all relevant scenarios can be elucidated. Selection of time horizon, population (or sub-groups), parametric model for time-to-event data, and all other variables used in the model must be modifiable and not restricted to a single analysis.

## 12.1 General aspects

The choice of health economic model must be well-justified, and should aim to be as simple, straightforward, and transparent as possible, while comprehensive enough to capture all the relevant factors that could impact a decision. The model should provide an adequate picture of the condition being modelled and the course of the condition. The model's construction, assumptions, potential restrictions, and how input data were modelled must be fully documented and described. For increasing model complexity, stronger requirements for model transparency are requested.

The model should ideally be consistent with both the clinical documentation that establishes relative efficacy, and Norwegian clinical practice.

If globally developed models are used, they must be adapted to reflect Norwegian clinical practice, costs, and other potentially relevant aspects. It must be clearly stated how the model has been adjusted to fit a Norwegian setting. Any lack of adaptation must be justified with a description of its potential impact on the results of the analysis.

## 12.2 Specific requirements

- Microsoft Excel is the preferred software for HTA submission. Contact NOMA prior to submission if alternative software is used.
- A description of function and purpose of each sheet in the spreadsheet must be provided.
- If the model uses macros, provide a description of the macros used. Visual Basic for Applications (VBA) code should include brief description for all procedures. Make sure all macros run successfully before submitting.
- Spreadsheets must be transparent and fully user modifiable.
- Spreadsheets must not contain password protected sheets or cells, contain no hidden cells, or utilise proprietary or non-transparent programmes and/or programming language.
- All sheets should include visible headers by default. Do not hide rows, columns, or sheets that are not used. If sheets (or parts of sheets) are not used but cannot be easily deleted (due to offset functions, macros, etc.), this should be clearly stated/highlighted.
- Provide Markov-traces and /or other plots that can aid reviewers critically appraise the modelling assumptions.
- When survival analysis techniques are applied, present KM-curves and all extrapolations within the same graph, within the health economic model. Include all-cause mortality for the general population.
- Attach the model technical report both with and without local country adaptation.

# 12.3 Analysis methods

## 12.3.1 Cost-utility analysis (CUA)

The recommended method for health economic evaluations is CUA. The result of such an analysis is an incremental cost-effectiveness ratio (ICER). When the intervention affects survival, cost-per-QALY gained and cost-per-Life Years Gained (LYG) must be separately accounted for in the analysis.

## 12.3.2 Cost-minimisation analysis

Cost-minimisation analysis is appropriate when there is documentation to support that the efficacy and safety profiles for the intervention and the comparator are, or can be assumed to be, equal or non-inferior.

# 12.4 Treatment sequence modelling

Sometimes it may be appropriate to model treatments as part of a sequence. High-quality documentation on the relative differences in efficacy between different treatment sequences is necessary.

# 12.5 Analysis perspective

Benefits and costs that must/must not be included in the analysis, in accordance with the Priority-setting White Paper guidance, is outlined below. Benefits and costs related to the medicinal product under evaluation can either result from, or be expected to change, due to the intervention. The following guidance implies an extended health-service perspective.

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

- The patient's lifespan.
- The patient's health-related quality of life.

The following benefits may be included (if applicable):
Effects on:

- The caregiver's health-related quality of life. Results of the analyses must be presented both with and without inclusion of this effect.

The following costs must be included (if applicable):

- Treatment or prevention costs, paid by the health service or by the patient/caregiver.
- Transport costs related to travelling to and from treatment, whether paid by the health service or by the patient/caregiver.
- Patients and their caregivers use of time during patient treatment.

In accordance with the Priority-setting White Paper, the following is <u>not</u> to be included:

- Productivity changes resulting from the intervention.
- Consequences of patients' future use of public services and receipt of public benefits/pensions.
- Unrelated health service costs and savings.
- Tax expenses for public financing.
- Public benefits, pension payments, value-added tax, and other transfer payments.

## 12.6 Time horizon

The time horizon must be sufficiently long to capture all important future differences in costs and health effects between two or more alternatives. If the medicinal product influences mortality, the time horizon should be based on the patient's expected lifetime. If there is no documentation for, or it is unlikely, that the relative efficacy will be sustained, a shorter time horizon may be more appropriate.

## 12.7 Resource use and costs

Resource utilisations refers to the consumption of goods, services, time, and potential capital cost. Whenever possible, market prices in the private sector should serve as the basis when estimating unit costs or calculation prices [107]. Unit costs and resource use are to be presented and justified separately. Norwegian unit costs must be used. If calculations are performed in currencies other than Norwegian kroner, the exchange rate used must be clearly stated.

All assumptions and justifications for included costs must be thoroughly documented and reported in detail to ensure transparency and facilitate assessment.

When calculating medicine costs, the maximum pharmacy retail price (PRP) available from NOMA website without value added tax (VAT) must be used. It must be possible to change the price of the medicinal product to perform analyses using discounted prices. It is preferable to model all medicinal costs per package, e.g., the complete package collected from the pharmacy. If wastage and/or vial sharing is included in the health economic model, the calculations must be transparent and editable.

Transportation costs associated with travel to and from treatment site must be included in the analysis if relevant, while necessary transportation costs for the caregiver can also be considered if relevant and well-documented.

NOMA unit cost database includes relevant sources for unit costs and is intended to ensure a consistent approach for inclusion of unit costs in STAs and health economic models.

If unit costs are not calculated directly as part of the STA, they can be sourced from other cost studies/publications. Average costs can generally be used, and "standard" calculations for average cost per resource type (e.g., visits to doctors, hospital treatment, nursing home costs, laboratory services etc.), for instance:

- **Hospital services:** The cost per hospital admission or outpatient clinic attendance can be calculated by multiplying the DRG-points by the corresponding unit price providing an estimate of the total costs per admission/attendance. Co-payments made by patients for outpatient consultations can be disregarded as it is already accounted for through the DRG weighting. If no information on the relevant DRG code is available, cost per day or per consultation can be obtained 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 on activity-based financing, DRG-weighting, unit prices, and SAMDATA can be found on the Norwegian Directorate of Health's website. Apply values from «Kostnadsvekt», not «DRGBasispoeng». The cost weights and the value of a cost weight are updated annually in relation to changes in medical practice and changes in operating conditions.
- **Nursing home, general practitioner, specialist services, imaging diagnostics, and laboratory tests:** The Norwegian Medical Association provides an overview of relevant tariffs, patient contributions, and subsidies on its website. A database published on the NOMA website contains most of the relevant costs incurring at nursing homes, in the general

practitioner's office, specialist health care, imaging diagnostics and laboratory tests. The database should be used as the main source of unit costs.

- **Other costs:** If unit costs are included and they are not collected from the NOMA cost database, the source and a justification must be included in the submission. If the costs are meant to reflect costs incurring in the general practitioner's office or a specialist, the cost per contact/consultation/unit is calculated by multiplying the remuneration by a factor of two. This is a pragmatic approach to account for both remuneration and public subsidy, as well as other overhead costs. The calculation gives a rough estimate, however multiplying the remuneration amount by two is considered to give a better cost estimate than using the tariff rate directly.

Average costs estimates will encompass both fixed and variable costs. However, in certain instances, one or more treatment options under consideration may result in additional capital costs. Such costs should be explicitly highlighted and included into the analysis. Alternatively, when treatment options are not anticipated to impact fixed costs, it may be more relevant to solely consider the variable costs.

### 12.7.1 Time- and unit costs for patient and caregiver

If the intervention and comparator have different duration of treatment administration and/or travel time, differences must be accounted for in the health economic analysis.

Value of time for patients and caregivers is recommended to be calculated as a common rate, regardless of employment situation, and assigned the value of leisure time. The value of increased/decreased leisure time is determined by the net real wages in Norway [108]

Any changes in time for work and/or other daily activities/leisure time owing to the medicinal product (productivity gains) must not be included.

### 12.7.2 Projection of unit costs

Unit costs are generally kept unchanged throughout the modelled time horizon, due to uncertainty surrounding future technological and market developments. However, if there are good/compelling reasons to project changes in unit costs, a description and justification must be provided.

Introduction of bioequivalent or generic medicinal products and tenders could substantially decrease the cost of medicinal products in the future and thus have a considerable impact on the health economic analysis. When such situations are imminent, likely price paths can be included in addition to the base case analysis.

## 12.8 Present value and discounting

Comparisons of benefits and costs that occur over different time periods in a CUA must be converted to present value by discounting both the annual benefits and costs by the applicable rate provided in the Priority-setting White Paper [1], which states that the discount rate should be equivalent to the rate set by the Ministry of Finance. As per *Rundskriv R-109* [108], the discount rate should be 4% annually for the first 40 years of the time horizon (years 0-39), 3% annually for the next 35 years (years 40-74), and thereafter 2% annually (year 75 and onwards).

# 13. Severity

## 13.1 General aspects

In health technology assessments, severity must be quantified using absolute shortfall [109]. Absolute shortfall is the reduction in expected future healthy life years without the treatment under consideration (i.e., with the current standard treatment), expressed in terms of QALYs lost compared to the general population of the same age. Absolute shortfall is required in cost-utility analyses, while cost-minimisation analyses do not require calculation of shortfall.

The quantification of absolute shortfall is performed in stages and described in detail below. Absolute shortfall differs between treatment interventions and preventive measures. Comorbidity is discussed separately below.

When presenting results, any uncertainties in the estimation of absolute shortfall, such as age or prognosis uncertainties, should be addressed.

An Excel spreadsheet ("*Tools for severity calculation and age adjustment*") is available on NOMA' website.

## 13.2 Quantification of absolute shortfall

**Step 1 - Age**

Define the mean age at start of treatment for the relevant Norwegian patient group considered for the new treatment. If the group has a substantial age disparity, consider including the median age in addition. Ensure consistency between the age used in the severity calculations, clinical practice, and the health economic model. If there is considerable uncertainty or conflicting age estimates from different sources, consider using an age range/interval, noting the likely position of the mean or median within the interval.

Sources for mean age estimation can be registry data, study data and/or clinical expert information. Utilise the source that best represents the relevant population in Norway.

**Step 2 - Expected remaining QALYs for the general population**

Estimate the remaining undiscounted QALYs for an average person from the general population with the age identified in step 1, by the combined remaining QALYs. This is referred to as quality adjusted expected remaining lifetime from the relevant age ($QALYs_A$).

Mortality data for the Norwegian population from Statistics Norway is recommended for calculation of expected remaining lifetime at different ages [80, 81]. This is combined with age-specific quality of life data to calculate quality adjusted remaining lifetime for different ages. Refer to the Excel spreadsheet, which displays the expected remaining quality-adjusted life years according to age in the average population.

**Step 3 - Prognosis**

Calculate the prognosis for the relevant patient population at treatment initiation. The prognosis refers to the average number of remaining healthy life years for the patient group with the current standard treatment ($P_A$ = prognosis at age A). Hence, prognosis is calculated for the current standard treatment (comparator) and is measured in QALYs. It is calculated for the remaining lifetime for the patients, taking into account the expected number of undiscounted QALYs patients can anticipate with the

comparator treatment. If there is no active treatment, select a patient population for prognosis calculation according to the guidelines for comparator choice in health economic analyses, such as best supportive care or no treatment (Chapter 3). When health economic calculations are based on a lifecycle model, a model-based estimate is preferred to ensure consistency.
Alternative sources may include relevant clinical studies, registry data, or data from systematic literature searches.

**Step 4 - Absolute shortfall**

Utilise undiscounted values for $QALYs_A$ and $P_A$ to quantify absolute shortfall = $QALYs_A – P_A$

# 13.3 Preventive measures

Preventive measures target both diseases and conditions, but in the following text for simplicity the term ‘diseases’ is exclusively applied.

Take into consideration that all individuals in the group will not contract the disease, and that there is a time lag between prevention and disease onset.
Quantification of severity for preventive measures must

- be applicable for the disease that is prevented,
- be applicable for the patient group contracting the disease in absence of the preventive measure,
- be measured from average disease onset.

Description of quantification of severity for preventive measures is provided below, with examples provided in the appendix.

## 13.3.1 Prevention of a single disease

Consider which individuals/patients from the relevant population to include in the calculation. Severity is calculated from the average prognosis and absolute shortfall for those expected to be affected by the disease, targeted by the preventive measure under the current standard prevention.

## 13.3.2 Prevention of multiple diseases

Calculate the absolute shortfall for each of the diseases for the relevant population with current preventive practice (the comparator in the health economic analysis), as described in 13.3.1 above.

Calculate weighted absolute shortfall for the diseases assigning largest weights to conditions with highest health benefit (gained QALYs).

If 90% of the benefit, measured in QALYs, can be attributed to the prevention of disease A, then the absolute shortfall for disease A should be weighted at 90% in the weighted absolute shortfall.

# 13.4 Interventions which treat multiple diseases

When an intervention impacts multiple conditions, the principle for quantifying severity equals the procedure for medicinal products which have preventive effects on multiple conditions as described in Chapter 13.3.2.

# 13.5 Sequelae and adverse reactions

For medicinal products targeting a primary condition, the assessment and calculation should focus on the overall severity of the primary condition and symptoms directly related to the primary condition.

For medicinal products aimed at symptoms resulting from the primary condition, sequelae, the severity of the sequelae itself must be evaluated and quantified, and not the primary condition. For interventions targeting adverse reactions, it is the severity of the adverse reaction, not the primary condition, that must be evaluated and calculated.

In certain instances, quantifications of severity for sequelae can also include the severity of the primary condition if [110]:

- Sequela(e) and primary condition are strongly related clinically
- Wording in the indication of the medicinal product links it to the primary condition.
- Sequela(e) are specific for the primary condition in question.
- Mechanism of action for the treatment of sequela(e) is specific for patients with the condition in question.

For interventions targeting symptoms that are not related to the primary condition, the severity of the symptoms, not the primary condition, must be evaluated and calculated.

# 14. Uncertainty

Uncertainty in health economic analyses must be explored and discussed [111, 112].

## 14.1 Addressing uncertainty in the analyses

Uncertainty in health economic analyses must be examined and presented through sensitivity analyses. The impact of uncertainty on the analysis outcomes must be discussed, highlighting the following:

- factors that are drivers of uncertainty
- whether uncertainty can be reduced
- if and when additional data can be expected
- presence of any bias
- how changes in parameters or assumptions affect the results

## 14.2 Deterministic sensitivity analysis

Methodological and structural uncertainty, as well as uncertainty related to generalisability, must be analysed using deterministic sensitivity analyses (if a health economic model is submitted).

In deterministic sensitivity analyses, selected variables are adjusted to examine the sensitivity of the model outcomes to these changes. This type of analysis is conducted in the form of one-way, two-way, or multiway sensitivity analyses and scenario analyses.

Scenario analyses must be performed in addition to assess the impact of alternative values for specific sets of parameters on the model outcomes (if a health economic model is submitted). These analyses represent a base case, “worst case”, and “best case”, or other alternative plausible scenarios. See example in chapter 8.1.3.

## 14.3 Probabilistic sensitivity analyses

Probabilistic sensitivity analyses may be employed to address the impact of joint parameter uncertainty. Justify the choice of the included variables and their probability distribution. Ideally, the probability distribution of each variable and its key moments (usually the expected value and standard error) should be based on empirical data. When empirical data is lacking, a plausible probability distribution must be selected for the variable. For each type of variable, there are usually only a few relevant probability distributions for use in probabilistic sensitivity analyses [112].

If probabilistic sensitivity analyses are submitted, the results must be presented as a scatter plot of the simulated incremental cost-effectiveness ratios (ICERs).

# 15. Budget impact analysis

The requirements for budget impact analyses varies depending on whether the medicinal product under review is intended for coverage through the National Insurance Scheme (*Folketrygden*, typically products prescribed by general practitioners) or by the Regional Health Authorities (typically hospital-initiated treatments). Specific requirements are described in the following paragraphs.

Use the provided budget impact template for budget impact analyses, which includes the requirements for products covered by both the National Insurance Scheme and the Regional Health Authorities. The assumptions regarding inputs in the budget analyses must be documented and justified.

The budget impact analyses must include:

- Expected number of patients treated with the intervention for each of the initial five years.
- Expected number of patients treated with the comparator(s) for each of the initial five years.
- Maximum pharmacy retail price including values added tax (VAT) and excluding discounting.
- A scenario where the intervention under review is approved for reimbursement.
- A scenario where the intervention is not approved for reimbursement.
- The difference between the two scenarios for each of the initial five years.
- All relevant costs affected by reimbursement of an intervention.
- Costs considered negligible and omitted must be discussed and justified.

## 15.1 Budget impact analysis for medicinal products covered by the Regional Health Authorities

The budget impact analysis must clearly present the expected budgetary consequences for the Regional Health Authorities.

The budget impact is split into three parts:

- Consequences for the Regional Health Authorities medicinal budget.
- Budgetary consequences for the Regional Health Authorities overall.
- Budgetary consequences for the health care sector overall.

If costs not related to the medicinal products are considered negligible, they may be omitted from the analysis.

## 15.2 Budget impact analysis for medicinal products covered by the National Insurance Scheme

The budget impact analysis must clearly present the expected budgetary consequences related to medicinal products covered by the National Insurance Scheme separately from the overall budget impact on the health care sector.

The budget impact is split into two parts:

- Consequences for the National Insurance Scheme medicinal budget.
- Budgetary consequences for the health care sector overall.

If costs not related to the medicinal products are considered negligible, they may be omitted from the analysis.

Regardless of whether the medicinal products are financed by pre-approved reimbursement or by individual reimbursement for the indication in question, the reimbursement expenditures should be included in each of the scenarios using realistic forecasts.

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# Appendix

## Examples

### A.1. Age adjustment of future expected HSUV using relative utility decrements

Consider a chronic disease modelled with a HSUV of 0.820 for the patients' "best" expected health state. The mean age of the patients is 50 years, and the health economic model utilises a lifetime perspective. Without age adjustment, the HSUV remains constant for the proportion of patients reaching the "best" health status throughout their lifetime.

The utility values for the general population are generally not fixed across all ages. Without age adjustment, the health-related quality of life for a patient population over 81 years in the example above would be higher (0.820) than that assumed for the general population (0.811).

Age adjusted HSUV results from the initial HSUV of 0.820 multiplied by an adjustment index. This index is set at 1 at the start of the model and changes over time based on the age specific HSUV. An example of how this can be done is demonstrated in "*Tools for severity calculation and age adjustment*".

### A.2. Quantification of severity/absolute shortfall in a model with lifetime perspective

Mean age at treatment initiation in the relevant patient group is 57 years, based on clinical experts' opinion supplemented by data from national registries.

Expected remaining healthy life years for a mean age of 57 years is estimated to 24 QALYs (see *"Tools for severity calculation and age adjustment"*).

Based on the health economic model, the prognosis for the relevant patient group is an expected remaining lifetime of 2.5 undiscounted years or 1.5 undiscounted QALYs with the current standard treatment (comparator).

Absolute shortfall is:

24 QALYs – 1.5 QALYs = 22.5 undiscounted QALYs.

Figure 5 illustrates graphically quantification of absolute shortfall for an intervention on group level. New treatment is considered at age A. In the absence of the disease, future health is represented by the area under the solid blue line ($QALYs_A$) from timepoint A. The disease shortens lifespan and reduces quality of life with the current standard treatment, as-shown by the shaded area ($P_A$). Absolute shortfall is the difference between $QALYs_A$ and $P_A$.

The figure does not take into account potential health loss related to the disease before treatment start, as the Priority-setting White Paper recommends considering only future health loss when quantifying severity.

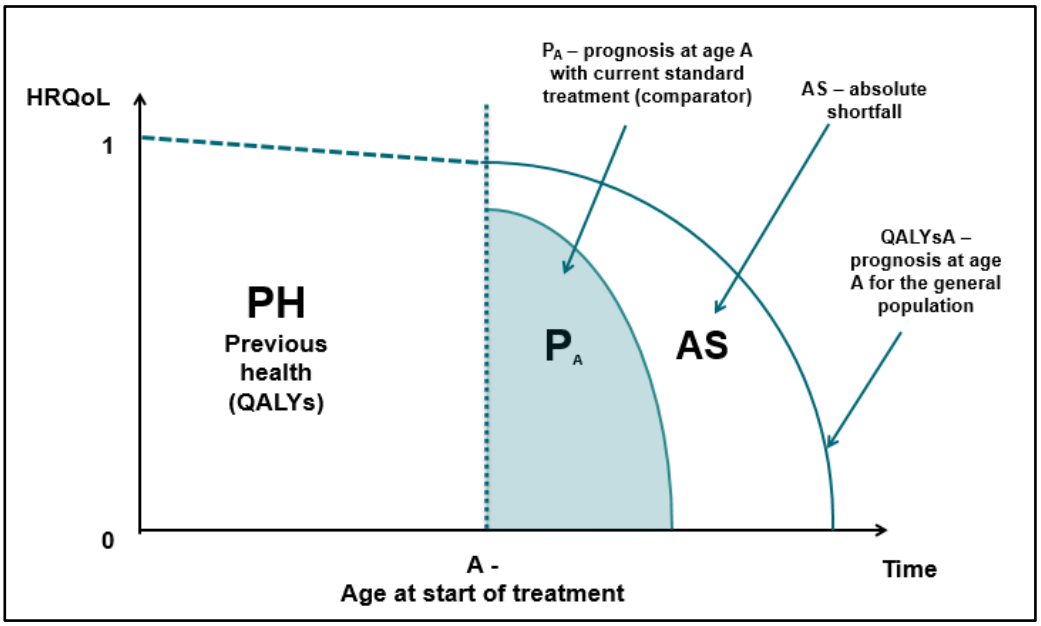


Figure 5. Graphical illustration of severity quantification, where health-related quality of life (HRQoL) on a scale from 0 (dead) to 1 (full health) is presented on the vertical axis, time is presented on the horizontal axis.

### A.3. Quantification of severity/absolute shortfall in a model without lifetime perspective

A chronic, non-fatal condition could be modelled with a perspective shorter than lifetime.

Mean age for treatment initiation in the relevant patient group is estimated to be 50 years.

For a 50-year-old, the expected remaining healthy life years ($QALYs_{50}$) is estimated to 29.6 QALYs.

The prognosis (undiscounted) from the health economic analysis is 0.750 undiscounted QALYs, applicable to a one-year time horizon. To calculate the lifetime prognosis, consider the disease and its progression given current standard treatment. Assuming relative QALY loss caused by the disease is constant over time, the prognosis is estimated as:

(0.750/0.870) * 27.0 QALYs = 23.3 undiscounted QALYs,

where 27.0 QALYs is expected remaining QALYs, and 0.870 is HSUV for a 50-year-old [103].

Absolute shortfall is:

27.0 QALYs – 23.3 QALYs = 3.7 QALYs.

### A.4. Quantification of severity/absolute shortfall when preventing one disease

The new preventive measure is administered to the relevant population starting at a mean age of 40 years. With the current preventive practice (the comparator in the health economic analysis), the disease generally manifests at a mean age of 60 years. Thus, 60 years is used as input age in the calculation of absolute shortfall.

For a 60-year-old the expected number of remaining healthy life years ($QALYs_{60}$) is calculated as 21.6 QALYs.

For this disease in the relevant population, the prognosis with the current standard treatment is 7.3 QALYs. The prognosis takes into consideration that some individuals affected by the disease will die, but the majority will survive although with diminished quality of life to a certain extent (for instance myocardial infarction). The average prognosis is calculated as a weighted average of the prognosis for those who die and those who survive.

Absolute shortfall is:

21.6 QALYs – 7.3 QALYs = 14.3 QALYs.

Calculation of absolute shortfall for preventive measures can also be shown as in Figure 5, the absolute shortfall is then calculated as:

- From timepoint A when the disease manifests (not the timepoint when the preventive measure is initiated).
- For a patient who develops the targeted condition, the subgroup who develops the disease at timepoint A (not for those who receives the preventive measure).
- With prognosis based on the current standard treatment of the condition.

### A.6. Quantification of weighted severity/absolute shortfall when preventing two diseases

Calculated absolute shortfall for disease A: 10 QALYs. Calculated absolutes shortfall for disease B: 6 QALYs.

In the health economic analysis, the benefit is estimated as 2.0 QALYs, representing the average incremental effect per person who receives the preventive measure. Of this, 1.8 QALYs (90%) are linked to prevention of disease A, and 0.2 QALYs (10%) to prevention of disease B.

The weighted absolute shortfall for disease A and B in this case is calculated as follows:

90% * 10 QALYs + 10 % * 6 QALYs = 9.6 QALYs.

### A.6. Quantification of expected remaining QALYs in the general population

Expected remaining QALYs and (health related) HSUV by age for the general Norwegian population are shown in "Tools for severity calculation and age adjustment", available at NOMA's website. Expected remaining QALYs are based on mortality data for the Norwegian population sourced from Statistics Norway [81] and age specific HSUV.

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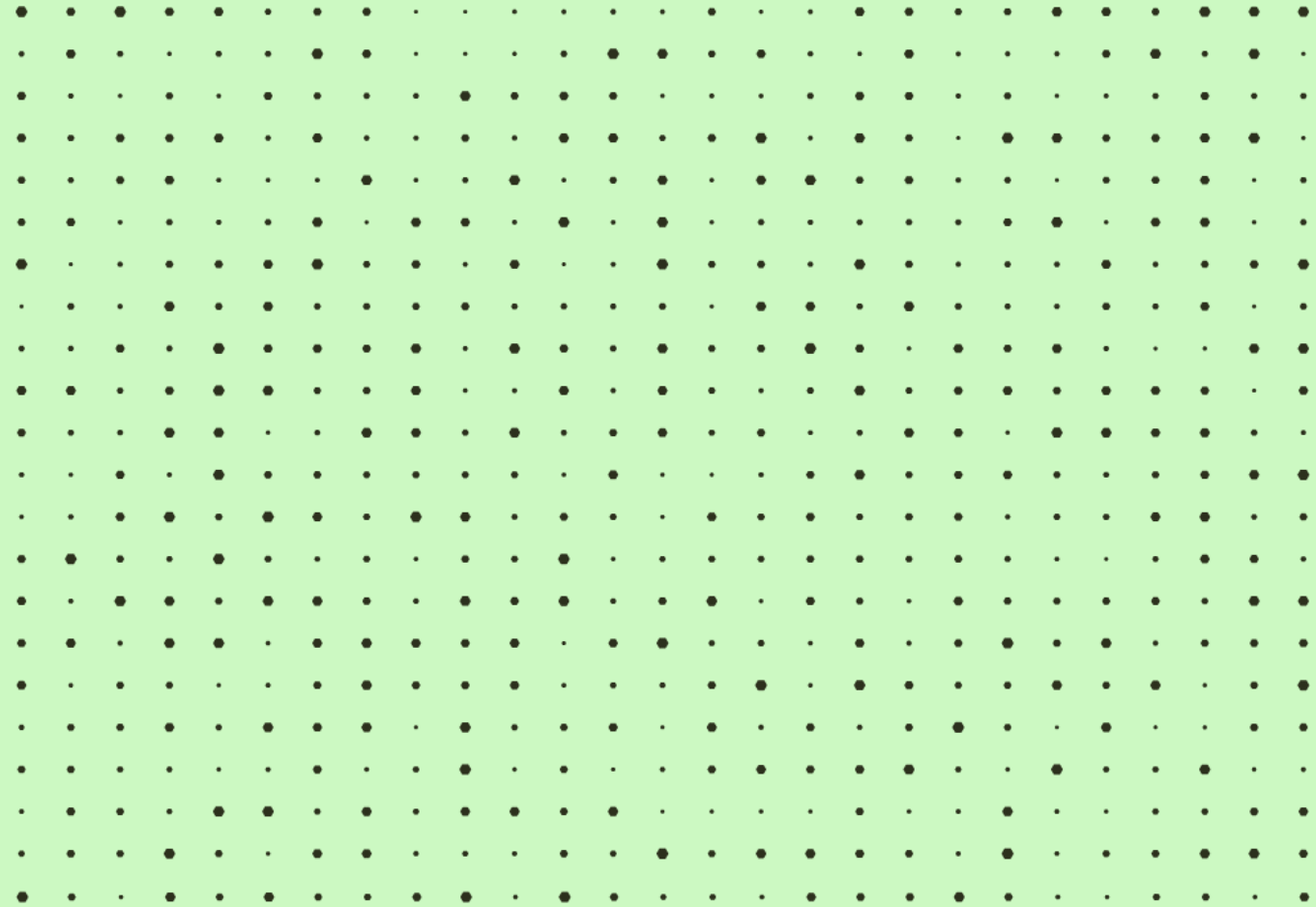
# Log of updates

## Submission Guidelines for
## Single Technology Assessment of Medicinal Products

Guidelines valid from 01.01.2018
Last updated 01.07.2025



| Time of update | Updates |
|---|---|
| **15.10.2018** | Ch. 11.5.2: The final two sentences in 11.5.2 are deleted while awaiting the result of a clarification of which measures should be considered as treatment or prevention when calculating absolute shortfall in single technology assessments.<br><br>Ch. 13.1.1: An elaboration of how expenditures on individual reimbursement usually is estimated. In line with this the footnotes in tables 1 and 2 are deleted. The cells in the upper row in table 2 are changed from including «zeroes» to be left blank.<br><br>Ch. 13.2: In line with the changes in Ch. 13.1.1, additional sentences are added in the last three paragraphs in Ch. 13.2. |
| **20.05.2020** | Introduction chapter: New paragraph on vaccines, infectious diseases control and prevention and antimicrobial resistance, with referrals to notes published at NOMA's web site.<br><br>Ch. 6.1.6: The chapter is deleted, and partly replaced by chapter, 6.3 (new)<br><br>Ch. 6.3: New chapter on Real World Data. Some parts of the text are from the previous ch. 6.1.6, and other are new.<br><br>Ch.7: Specifications about requirements for literature search and requirements for comparisons of health state utility values (HSUVs) in the actual STA vs other relevant STAs.<br><br>Ch. 7.1: New chapter with specifications on documentation requirements for HSUVs. The chapter structure of the rest of chapter 7 has thus been changed. The chapter numbers have increased by one in the chapters following ch.7.1.<br><br>Ch. 7.2 (previously 7.1): In paragraph 2 there are new clarifications with respect to EQ 5D 3L vs EQ 5D 5L, as well as for instruments for children/youth.<br><br>Ch. 7.3 (previously 7.2): Most of paragraph 2 is reframed, mentioning a new Norwegian tariff (15D)<br><br>Ch. 9.4: Specifications on discount rates in health economic analyses with time horizon longer than 40 years.<br><br>Appendix 2.2.1:<br>In the first paragraph second and third sentence are new/partly new:<br>«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:"<br><br>The points following this paragraph are, with a couple of exceptions, partly new and partly reframed.<br><br>Appendix 2.2.3:<br>A box is added in the figure 1 – with the following text: «Compare plot of smoothed hazard from the study data with the smoothed hazard from the |

| | |
|---|---|
| | parametric functions and assess the graphical sand choose the most appropriate parametric functions."<br><br>Appendix 3: The numbers in the examples and the references in the text, figure and table are adjusted – corresponding to the updates in appendix 4.6 (see below).<br><br>Appendix 4.1-4.4: The numbers in the examples and the references in the text, figure and table are adjusted – corresponding to the updates in appendix 4.6 (see below).<br><br>Appendix 4.6: Text is updated. The table «Expected remaining QALYs and HSUV in the general population" is updated. The update is based on HSUVs for the general population in Norway in Stavem et al 2018 and mortality data from Statistics Norway for 2019. |
| **18.10.2021** | Appendix 2 moved to chapter 6.2<br><br>Updated references |
| **01.10.2023** | New table of content and structure of the entire guideline.<br><br>Introduction replaced with foreword.<br><br>Chapter 2 Technology – added as new chapter.<br><br>Chapter 4 Documentation of population, intervention, comparator, and outcomes (PICO) – added as new chapter.<br><br>Chapter 5 Information retrieval and selection of relevant documentation – revised and additions included in previous chapter on literature search.<br><br>Chapter 6 Documentation of relative efficacy by direct comparative studies – revised completely.<br><br>Chapter 7 Documentation of relative efficacy through evidence synthesis – new chapter.<br><br>Chapter 8 Extrapolation of relative efficacy - specifications in the text for clarification<br><br>Chapter 9 Treatment switching - revised completely.<br><br>Chapter 10 Use of real-world data – new text.<br><br>Chapter 11 Documentation of health-related quality of life – revisions and additions to the text<br><br>Chapter 12 Health economic analyses – revised.<br><br>Chapter 14 Uncertainty – revised completely.<br><br>Chapter 15 Budget impact – revised completely.<br><br>Appendices – Text is revised and included in the main body of the document.<br><br>Appendix - Examples – added as new appendix. |

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| | References - updated |
| **10.05.2024** | Updated with new name/logo and new visual profile (as of 01.01.2024 the Norwegian Medicines Agency became the Norwegian Medical Products Agency). Updated hyperlinks. |
| **24.02.2025** | Added new Chapter: 1.2 Notification of planned submission |
| **02.07.2025** | Chapter 11 and appendix updated.<br>Updated with EQ-5D-5L utility values from the Norwegian general population. Level adjustment of utility values used in the cost-effectiveness modelling included, calibration of severity based on level adjustment obsolete and removed.<br><br>Clarification of certain minimum standards for the submission of documentation throughout the Guideline. |