

**Applicant Submission Template**

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| **Drug:**  | INN/Brand® |
| **Therapeutic indication:** |  |
| **NCPE HTA number:** |  |
| **Applicant Company:**  |  |
| **Submission checklist complete:** |  |
| **Applicant company representative:** | Name and email address |
|  | Signature |
| **Second company contact:** | Name and email address |
| **Date of submission:** |  |

**Version Control**

|  |  |  |
| --- | --- | --- |
| **Version/Date** | **Page** | **Description of key changes** |
| Version 3.0 07/03/23 | General | Heading restructureStandard table templates throughout |
|  | 8, 19 | State that the most recent data-cuts from both the intervention and comparator trials have been used |
|  | 19 | Model must be fit for purpose and can be efficiently interrogated by the NCPE Review Group |
|  | 22-24 | More detailed guidance on the presentation of survival analyses  |
|  | 23 | Requirement for the model to include the functionality to adjust relevant treatment effects or survival curves to account for alternative assumptions around persistence or durability of treatment effect. |
|  | 27 | More detail required on HRQoL analysis methods e.g. justification of mapping methods, use of appropriate statistical methods in the case of multiple observations from the same individuals |
|  | 29 | Clarification on vial-sharing |
|  | 31 | Guidance on the inclusion of companion diagnostic costs |
|  | 34 | Inclusion of explanatory text when results include negative ICERs |
|  | 35-36 | Clarification on the inclusion of cost-effectiveness thresholds |
|  | 42 | Appendix 1 update |

This document outlines the content and format of the written submission to the NCPE as part of a full pharmacoeconomic assessment. For further guidance on pharmacoeconomic methods, refer to HIQA Health Technology Assessment Guidelines ([www.hiqa.ie](http://www.hiqa.ie)), NCPE Requirements for conducting and reporting clinical evidence synthesis analysis and NCPE Guidelines for inclusion of drug costs in pharmacoeconomic evaluations ([www.ncpe.ie](http://www.ncpe.ie)). (1-4)Inclusion of commercial-in confidence information should follow guidance outlined in Appendix 3 of this Template. This document may be updated periodically. Please refer to www.ncpe.ie to obtain the most recent version prior to submission.

Double-sided printing should be used when preparing the completed Applicant template for submission. All pages in the submission, including appendices, should be numbered. While additional sub-headings may be included in the submission, do not otherwise alter the heading structure provided.

All files included in the submission should be named in accordance with the specified file-naming convention and saved in the specified format, as outlined in Table 1. The international non-proprietary name (INN) and NCPE HTA ID number (assigned to the assessment prior to the pre-submission meeting) should be included at the start of all filenames. **Please do not use all capital letters or use underscores in the filename.**

**Table 1 File naming convention and format**

|  |  |  |
| --- | --- | --- |
| Type of file | File naming convention | File format |
| Applicant template | <INN NCPE HTA Number Applicant Template> e.g. Aspirin 1901 Applicant Template | .docx and .pdf |
| Cost-effectiveness model | <INN NCPE HTA Number CEM> e.g. Aspirin 1901 CEM | .xlsx or similar |
| Budget impact model | <INN NCPE HTA Number BIM> e.g. Aspirin 1901 BIM | .xlsx or similar |
| References | <INN NCPE HTA Number references> e.g. Aspirin 1901 references | .ris |
| Submission checklist | <INN NCPE HTA Number Submission checklist> e.g. Aspirin 1901 Submission Checklist | .pdf |

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## Executive Summary

An executive summary consisting of no more than two pages should preface the document encompassing an overview of the submission and the main findings of the economic evaluation.

1. Disease and its management

*Where evidence is based on clinical opinion, include an appendix describing the methods of obtaining the opinion and the results, in full detail (see Appendix 1-Clinical Opinion).*

* 1. Description of the disease
* Provide a brief description of the disease/condition including an overview of the natural history of the disease, diagnosis, symptoms and clinical outcomes, causes or risk factors, disease-specific mortality etc. Important subgroups/subpopulations should also be defined and described.
* Summarise the epidemiology of the disease/condition, including the incidence and prevalence of the disease/condition in Ireland, in the general population and among relevant subgroups. Clearly indicate the source of epidemiological information and provide justification for its selection.
	1. Disease management
		1. Clinical guidelines
* Summarise Irish treatment/disease guidelines if available. Summarise other international guidelines which inform clinical practice and treatment choices in Ireland.
	+ 1. Standard of care in Ireland
* Describe how the disease/condition is managed in Ireland i.e. other available treatments, current standard of care and best practice. Standard of care is “routine care”, and reflects the most widely used interventions/treatment strategies in Ireland. Describe any variation in disease management, supported by data confirming how this was established. Include both licensed and unlicensed therapies where applicable.
1. Intervention under assessment
	1. Intervention
* Tabulate details of the intervention using the standard table template (Table title: Details of the intervention). Where applicable, this table should be populated directly from the EMA/competent authority website (Table Xa), and the Summary of Product Characteristics (SPC) (Table Xc).

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| --- |
| **Table X: Details of the Intervention** |
| Xa: Regulatory status [reference] |
| International non-proprietary name:  |  |
| Proprietary Name: |  |
| Therapeutic indication: |  |
| Currently designated an orphan medicine by the EMA: | Yes/No |
| Date of marketing authorisation: | [Date]*If applicable, include details of Conditional MA* |
| Other EMA/HPRA/FDA approved indication(s), or license extensions under EMA assessment (date of approval/status of assessment) | *Delete as appropriate:*EMA licensed indications:FDA licensed indications:EMA Indications under assessment:None |
| *Additional comment(s) on regulatory status may be added as narrative footnotes, in the following order a, b, c etc.* |
| Xb: Reimbursement status  |
| Requested reimbursement setting  | *Please select from the options and delete others*Hospital/National Drug Management SystemHigh Tech Drug Arrangement (HT)Community Drug Schemes (CDS)Oncology Drug Management System (ODMS)Other: *please specify* |
| Current reimbursement status | *Please select from the options and delete others*Not currently reimbursedReimbursed on [X] scheme for [Y] indication |
| Other reimbursed formulations |  |
| *Additional comment(s) on reimbursement status may be added as narrative footnotes, in the following order a, b, c etc.* |
| Xc: Description of drug |
| Formulation (pack size) |  |
| Dose and frequency |  |
| Route of administration  |  |
| Store in a refrigerator  | Yes/No |
| Duration of use | *If applicable, include details of response assessment recommendations and stopping criteria.* |
| ATC code  |  |
| Mechanism of action |  |
| Other  | *If applicable. Additional rows may be added for [Diagnostic testing], [Pharmacokinetics], [Dispensing/administration] etc. if, for example, specific tests or investigations are required for targeted therapy, specific pharmacokinetic aspects are of relevance, aseptic compounding or administration in a hospital setting is required etc* |
| *Additional comment(s) on the drug description may be added as narrative footnotes, in the following order a, b, c etc.* |

* 1. Place in therapy and comparators
* State the anticipated place in therapy of the intervention with respect to other available therapeutic options, lines of therapy and other aspects of clinical management, supported by data confirming how this was established. Outline any perceived advantages or disadvantages of the intervention over current standard of care. Do not include details of clinical efficacy in this section.
* Identify relevant comparators for the assessment of comparative effectiveness, cost-effectiveness and budget impact, supported by data confirming how this was established. The most relevant comparator(s) is that which is most widely used in clinical practice in Ireland in the target population. Technologies that do not have marketing for the indication defined may also be considered for the comparator if they are part of established clinical practice for that indication. Where such an unlicensed technology is used as the comparator, the evidence of efficacy and safety included in the assessment must be relevant to the unlicensed use.
* Provide details of any current use of the intervention in Ireland e.g. as part of a clinical trial or early access programme, or in an unlicensed capacity.
1. Clinical evidence

*All clinical efficacy and safety evidence included in the submission must be selected following a systematic literature review (SLR) to identify relevant data sources, and reported in accordance with* [*PRISMA*](http://www.prisma-statement.org/) *guidelines and the guidance set out in Appendix 2 of this template. The search date of the SLR must be no more than six months prior to the date of submission of the HTA. This applies to trials of both the intervention and comparators, where relevant for comparative effectiveness analysis. Justify the selection of specific sources. Wherever possible, clinical evidence should be based on an analysis of pre-specified endpoints when trial follow-up is complete, in accordance with national HTA guidelines (4). Results from the most recent data-cut(s) of the relevant clinical trial(s) must be provided. The submission of supplementary data after the initial submission date may result in realignment of timelines in line with the submission of new data. The NCPE Preliminary Review will always include a request to the Applicant to confirm if any additional evidence from relevant clinical trials of the intervention (and comparator, where relevant for comparative effectiveness analysis) has been published/become available, and a request to ensure that the most recent data-cut(s) from the trial(s) is included. This is particularly likely where marketing authorisation has been granted on the basis of interim analysis of clinical trial data, or where conditional marketing authorisation has been granted. Where evidence is based on clinical opinion, include an appendix describing the methods of obtaining the opinion and the results, in full detail (see Appendix 1).*

* 1. Clinical trials of the intervention
* Summarise the SLR process undertaken to identify and select relevant clinical trials of the intervention. This process should be described in detail in Appendix 2 following relevant NCPE Guidance.
* Summarise the clinical trial programme for the drug for the indication in question, including a summary table of trials conducted. Identify the pivotal trial(s) and indicate if it is ongoing and if so, when it is expected to be completed and, if applicable, when the next data-cut is expected. The pivotal trial(s) is typically that which formed the basis for marketing authorisation from the EMA (or other competent authority in the case of drugs approved by a decentralised/mutual-recognition procedure). Occasionally, some trials may not have been considered “pivotal” for the purposes of marketing authorisation, but may be pivotal to the decision-problem and should be also presented in detail (e.g. active comparator or targeted subgroup trials).
	+ 1. Clinical trial design and analysis
* Describe the relevant trial(s) in further detail, including a detailed description of the trial design and methodology, inclusion and exclusion criteria, treatments and concomitant medications and study endpoints (in particular the use of surrogate endpoints). Describe data analysis methods including the statistical approach to missing data and to specific trial design features e.g. crossover, switching, responder enrichment etc.
* Tabulate a summary of the relevant trial(s) design using the standard table template (Table title: [Trial name] trial design) and subsequent tables, as necessary if there is more than one relevant trial. The general structure of Table X.1 should be retained, though adjustments may be made for the sake of clarity and simplicity. Secondary and exploratory endpoints should be included if of key clinical relevance or of relevance for the economic evaluation.

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| **Table X.1: [Trial name] trial design** |
| **clinicaltrials.gov identifier: [#]** | **[Trial design e.g. Phase III, double-blind, randomised controlled trial]** |
| **Treatments** | **Key inclusion and exclusion criteria** | **Endpoints** |
| Intervention:[Drug1, dose, duration, stopping rules etc][n=X]Control:[Drug2, dose, duration, stopping rules etc][n=X][Other relevant details of treatments or procedures] |  | [Primary endpoint]:[Key secondary efficacy endpoint(s)]:[Health-related Quality of Life endpoint(s)]: |
| Abbreviations:*Additional comment(s) on the trial design may be added as narrative footnotes, in the following order a, b, c etc.* |

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| **Table X.2 [Trial name] trial design** |
| *Complete trial details as above* |

* + 1. Clinical efficacy results
* Provide a table (Table title: Baseline demographics and clinical characteristics) summarising the baseline demographics and clinical characteristics of the relevant trial(s) populations. Indicate if demographics and characteristics were balanced between the treatment arms or if any imbalances were observed.
* Provide details of participant flow in the relevant trials(s), including a CONSORT diagram(s).
* Provide the results of a Quality Assessment of the relevant trial(s), using a validated quality assessment tool, including risk of bias. This may be included as an appendix.
* Present clinical outcomes from the relevant trial(s) using the standard table template (Table title: [Trial name] clinical outcomes), and subsequent tables as necessary if there is more than one relevant trial. The general structure of the table template should be retained, though adjustments may be made for the sake of clarity and simplicity. Additional tables, in the same format, may be added for relevant subgroups. Indicate if the results pertain to an interim or final analysis of the trial data and, if applicable, when results of the final data analysis will be available. Ensure that the results of the primary and key secondary endpoint(s) are clearly shown for each study arm, in addition to relative effect measures and significance tests. Health-related quality of life measures should also be included, if available.

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| **Table X: Baseline demographics and clinical characteristics** |
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| [Abbreviations]Footnotes a, b, c etc. |

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| **Table X.1: [Trial name] clinical outcomes** |
| Date of [*interim/final*] analysis |  |
| Expected date of final analysis (if applicable) |  |
| **Outcome** | **[Drug]** | **[Comparator]** |
| [Primary endpoint] |  |  |
| [Key secondary endpoint(s)] |  |  |
| [HRQoL endpoint(s)] |  |  |
| [Abbreviations]Footnotes a, b, c etc. |

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| **Table X.2: [Trial name] clinical outcomes** |
| *Complete trial details as above* |

* Discuss the clinical efficacy results from the relevant clinical trial(s) in detail, including discussion of the limitations.
	+ - 1. Clinical efficacy results from other studies
* Provide details of other clinical evidence for the intervention which may be of relevance to the decision problem. This may include meta-analyses of study results, other non-pivotal randomised studies, observational studies, long term extension studies etc.
	1. Comparative effectiveness

*The comparative effectiveness of the intervention relates to its effectiveness relative to comparators of interest for the economic evaluation. Further consideration of comparative effectiveness may not be necessary if direct comparative evidence, versus comparators of interest, in the population of interest and for the clinical outcomes of interest, is available from the clinical trials of the intervention.*

* Discuss the background to and objectives of the comparative effectiveness analysis.
	+ 1. Comparative effectiveness analysis methods

*Refer to the NCPE requirements for conducting and reporting clinical evidence synthesis analysis for detailed guidance.*

* Summarise the SLR process undertaken to identify and select relevant data sources for the comparative effectiveness analysis.
* Summarise the SLR process undertaken to identify published comparative-effectiveness analyses for the intervention or comparators for the disease in question.
* This process should be described in detail in Appendix 2 following the relevant NCPE guidance.
* Provide a table (Table title: Overview of data sources included in comparative-effectiveness analysis) summarising the data sources identified by the SLR, highlighting those selected for inclusion in the analysis, including the trial name and design, treatments, outcomes, and other important characteristics.
* Provide a table (Table title: Overview of published comparative-effectiveness analyses) summarising the published comparative-effectiveness analyses identified by the SLR, highlighting the publication details, methodology and results

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| **Table X: Overview of data-sources included in comparative-effectiveness analysis** |
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| Abbreviations:Footnotes a, b, c etc. |

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| **Table X: Overview of published comparative-effectiveness analyses** |
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| Abbreviations:Footnotes a, b, c etc. |

* Identify and discuss any between-trial differences, particularly those which relate to potential treatment-effect modifiers or prognostic variables.
* Discuss the feasibility of conducting comparative- effectiveness analysis with the available data including a commentary on the relevance of the data sources to the decision problem, the similarity of the selected sources and the quality of the studies.
* Describe the analytical approaches used for the comparative-effectiveness analysis, including the approach to sensitivity analysis.
* The results of both a fixed effects and random effects analysis should be presented.
* If a population-adjusted method such as MAIC or STC is used in a connected network of evidence, the results of the standard non-adjusted network meta-analysis should also be presented for comparative purposes.
* Discuss the limitations of the comparative effectiveness analysis methods. Indicate if the robustness of analysis is limited by between-trial heterogeneity or poor quality, or other biases inherent in the analysis methods.
	+ 1. Results of comparative-effectiveness analysis
* Briefly summarise the results of previously conducted comparative-effectiveness analyses identified by the SLR.
* Tabulate the results of the Applicant’s analysis (Table title: Results of comparative-effectiveness analysis) including relative effects and associated measures of uncertainty for each treatment versus the common/reference comparator for each outcome, and for the intervention versus the comparator(s) for each outcome.

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| **Table X: Results of comparative-effectiveness analysis** |
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| Abbreviations:Footnotes a, b, c etc. |

* Discuss the comparative effectiveness results including the results of sensitivity analyses.
* Discuss the limitations of the comparative effectiveness results and any corresponding uncertainties.
* Provide a detailed description of the role of the results of comparative-effectiveness analysis in informing the treatment effectiveness inputs in the cost-effectiveness model.
	1. Clinical safety
* Provide details of the adverse events (AEs) occurring in the identified studies, in terms of absolute and relative statistical measures, specifying the population to which the results relate, and highlighting meaningful differences between the intervention and comparator(s).
* Summarise the key safety issues related to the intervention, and associated risk management requirements.
* Summarise the differences in safety profiles between the intervention and comparator(s) of greatest relevance to the decision problem, including results of any evidence synthesis analyses.
1. The decision problem: Population, intervention and comparators
	1. Model population
* Describe the population defined in the model, including mean age, gender breakdown and other indication-specific population characteristics. The population defined in the model should reflect the therapeutic indication, and may be further stratified into important subgroups as necessary. Provide justification if the primary modelled population does not reflect the licensed therapeutic indication.
* Populations or population subgroups should not be defined on the basis of response/non-response to treatment. This is more appropriately captured in the model using a treatment stopping-rule following response assessment.
* Discuss whether the model population characteristics are representative of the target population.
	1. Model intervention
* The intervention should reflect the licensed dose, frequency, route of administration, duration of use etc. as specified in the SPC.
* The dose and duration of treatment should reflect expected real-world clinical practice.
* Clearly describe and justify all parameters and any assumptions regarding dose intensity. Where a relative dose intensity (RDI, referring to the ratio of total dose delivered to the protocol-specified total dose over the total time course on treatment in a trial) is assumed to define the dose of the intervention, provide the details of the calculation of the RDI. Discuss the likelihood of clinical trial-observed doses being replicated in clinical practice, given the level and frequency of healthcare visits received in practice, and the similarity of clinical practice to strict clinical-trial protocols, particularly with regard to dose-reductions due to AEs.
* For treatments which have a variable but limited duration of treatment, please provide information on the expected mean duration of treatment and how this has been derived. For interventions modelled to continue for a discrete duration, duration of treatment should be based on the mean time-on-treatment (ToT) observed in mature clinical trials, as opposed to the median time. Where ToT data is not mature, parametric survival modelling may be required to estimate mean ToT. A systematic approach to the selection of appropriate statistical methods for survival analysis must be followed and described using, for example, the Model Selection Process Algorithm developed by the NICE Decision Support Unit (NICE TSD DSU 14) or other evidence-based guidance. If an exponential distribution for ToT is assumed then median/ln(2)=mean. This approach is not appropriate in cases where a stopping rule is applied as this may overestimate ToT (5). In addition, careful consideration should be given to any additional factors which may indicate a non-constant discontinuation rate. It is plausible that mean time-on-treatment will continue to increase over time until data is fully mature, and it is important that the most up-to-date data-cut from the trial is used to inform this analysis. If the source informing the mean duration of treatment is not fully mature this should be noted in the submission.
* Clearly describe and justify all parameters and any assumptions regarding treatment discontinuation. For long-term interventions, distinct short-term and long-term discontinuation rates may require definition, as short-term discontinuation rates derived from clinical trials may not be representative of long-term discontinuation rates. Short-term discontinuation rates are often influenced by AEs or loss of efficacy. Discuss the likelihood that AEs may diminish with extended use, or that those who continue the intervention long-term may be those in whom efficacy has been established, or in whom tolerance to AEs has developed. Conversely, the additional supports available to clinical trial participants may plausibly reduce the likelihood of discontinuation during the clinical trial, relative to real-world conditions. Discuss the likelihood of real-world discontinuation rates, with all assumptions verified using external data (e.g. from other similar, established interventions), where possible.
* If duration of treatment is determined by achievement of a clinical response, define this response, ensuring that it is clinically meaningful and captures sufficient benefit to justify continuing treatment. Clinical opinion is required to validate the clinical meaningfulness of the response definition, and the feasibility of its assessment in practice. Present scenario analyses in which alternative response definitions including partial response are explored.
* Clearly describe and justify all parameters and any assumptions regarding stopping rules. Stopping rules should reflect expected real-world clinical practice. The presence of a stopping-rule in a clinical trial does not justify its inclusion in the definition of the decision-problem if it is not expected to be implemented in clinical practice. The clinical evidence available for the intervention should correspond with the stopping-rule expected in clinical practice. Discuss the feasibility of implementing the stopping rule, based on the defined response criteria, in clinical practice. Scenarios in which the stopping rule is removed should be explored.
* Outline the approach taken to sensitivity analysis and scenario analysis in order to explore uncertainty in the definition of the intervention in terms of dose and duration. Probability distributions for each parameter in the model should be derived and used to propagate the associated uncertainty through the model. When more than one plausible data source is available, sensitivity and scenario analyses should be conducted to explore the impact of the alternative values.
* Tabulate the details of the intervention using the standard table template (Table title: Model intervention). All assumptions underpinning these details should be summarised (including those relating to dose reductions, response criteria, stopping rules, discontinuation rates or duration of treatment), using footnotes, with reference to the relevant section in the report where necessary. For treatments whose ToT is estimated from parametric survival modelling, the mean treatment duration should align with the area under the ToT curve in the cost-effectiveness model.

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| --- |
| **Table X: Model intervention** |
| Name  |  |
| Dose and frequency |  |
| Route of administration  |  |
| Duration of use and discontinuation |  |
| *Additional information on the source of data or basis for assumptions may be added as narrative footnotes in this row, in the following order a, b, c etc* |

* 1. Model comparator(s)
* The most relevant comparator(s) is that which is most widely used in clinical practice in Ireland in the target population. Unlicensed drugs may also be relevant comparators if they are part of standard of care. In certain dynamic therapeutic areas where treatment options are changing in response to emerging evidence, routine practice may differ from what is considered “best-practice”. In such circumstances, best-practice should also be considered among comparators.
* While the availability or quality of data on a comparator may affect the validity of the model results, this should not preclude its inclusion in the model.
* The definition of the comparator(s) should reflect the licensed dose, frequency, route of administration, duration of use etc. as specified in the SPC.
* The guidance as previously described for defining the dose and duration of the intervention also applies to the comparator(s).
* Outline the approach taken to sensitivity analysis and scenario analysis in order to explore uncertainty in the definition of the comparator(s) in terms of dose and duration. Probability distributions for each parameter in the model should be derived and used to propagate the associated uncertainty through the model. When more than one plausible data source is available, sensitivity and scenario analyses should be conducted to explore the impact of the alternative values.
* Tabulate the details of the comparator(s) using the standard table template (Table title: Model comparator(s)). All assumptions underpinning these details should be summarised (including those relating to dose reductions, response criteria, stopping rules, discontinuation rates or duration of treatment), using footnotes, with reference to the relevant section in the report where necessary.

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| --- |
| **Table X: Model comparator(s)** |
| Name  |  |
| Dose and frequency |  |
| Route of administration  |  |
| Duration of use and discontinuation |  |
| *Additional information on the source of data or basis for assumptions may be added as narrative footnotes in this row, in the following order a, b, c etc* |

* 1. Model perspective
* In accordance with national guidelines, the perspective of the publicly funded health and social care system in Ireland should be adopted when assessing costs. All health benefits accruing to individuals should be included in the assessment of outcomes. Broader perspectives may be explored in scenario analyses.
* State the perspective of the analysis and of any scenario analyses conducted.
1. Cost effectiveness

*All cost-effectiveness model inputs should be identified and selected following a systematic search to identify relevant data sources. The date of the systematic search must be no more than six months prior to the date of submission of the HTA. Inputs relating to treatment effects (including those relating to the baseline model) and health-related quality of life should be selected following a systematic literature review (SLR), and reported in accordance with PRISMA guidelines and the guidance set out in Appendix 2 of this template. The SLR should be conducted within the timelines outlined previously for clinical evidence, and include data from the most recent data-cuts of relevant clinical trials. For all other inputs, a description of the systematic search employed to identify relevant studies should be included. Justify the selection of specific sources.*

*Where evidence is based on clinical opinion, include an appendix describing the methods of obtaining the opinion and the results, in full detail (see Appendix 1-Clinical Opinion). Model inputs should be derived from an Irish population, where available.*

*Ensure that all parameter inputs included in the written submission align with those included in the submitted cost-effectiveness model.*

* 1. Model Structure
* The structure of the model should be no more complex than is necessary to faithfully represent the disease, the potential value of interventions, and to address the decision problem. Models are often submitted to the NCPE with unnecessarily complex structures and programming. This is often a consequence of the multinational re-use of the models which may limit the assessor’s ability to critically appraise within reasonable timeframes. It is the responsibility of the Applicant to ensure that the model is fit for purpose and can be efficiently interrogated by the NCPE Review Group. If either of these criteria are not met, a resubmission request may be made.
* While the availability or quality of data may affect the validity of the model results, this should not dictate the structure of the model. Sensitivity analyses may be conducted on aspects of the model for which no/poor data exist, or for which data is not yet available.
* Describe the type of model used, time horizon and cycle length. A lifetime horizon is generally most appropriate to capture all meaningful differences in costs and effects between alternatives considered. The inclusion of shorter time horizons should be justified and any potential bias explored in sensitivity analysis. The cycle length should be short enough that an outcome/event occurs at most once per cycle.
* State if a half-cycle correction was applied, and if not, provide justification for its omission.
* Describe the structure of the model, including the clinical outcomes which determine progression through the model, the mechanism by which patients progress through the model e.g. by transition matrices, survival curves etc., and the role of treatment effects in the model.
* If a state transition model was used, describe the health states and the pathway/possible transitions of patients through the various health states. Present the transition probability matrix.
* Describe the mechanisms by which costs and QALYs are differentially accrued across the treatment arms.
* Provide a graphical representation of the model structure.
* Provide the rationale for the model structure in terms of the natural course of the disease/condition and the clinical relevance/importance of model outcomes to patients.
* If surrogate outcomes were used in the model, with the intention of predicting a clinical outcome, they should be previously validated. There should be a robust, quantifiable evidence base for the relationship between the surrogate outcome and final clinical outcome(s) of relevance. This evidence should be specific to the population in question, and should extend to the relationship between the relative effects of the intervention on the surrogate outcome and relative effects of the intervention on the final outcome. This evidence should be provided and critically discussed in the submission.
* All structural assumptions should be fully described in tabular format. These assumptions should be justified and uncertainty explored in plausible scenario analysis.
* If the model structure includes a baseline model representing the natural history of the disease in question, or representing current standard-of-care, in order to predict outcomes for a best supportive care arm of the model, all inputs relating to the baseline model should be selected following an SLR to identify the most relevant data source. A detailed description of the data sources, analysis methods and assumptions used in the derivation of the baseline/natural history model/transition matrix is required (in line with guidance set out in Appendix 2).
* A comprehensive suite of quality assurance checks should be conducted and reported, to ensure the internal and external validity of the model. Provide details and results of all model verification, external validation and quality assurance exercises.

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| **Figure X: Model structure** |

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| **Table X: Model assumptions** |
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| *Additional information on the assumptions may be added as narrative footnotes in this row, in the following order a, b, c etc* |

* 1. Treatment effectiveness
* Describe the mechanism by which the intervention alters the disease course in the model.
* Describe the application of treatment effects in the model.
	+ 1. Data sources
* Identify and describe the data sources used to inform treatment effectiveness parameter input estimates for both the intervention and comparator(s). Include a summary of the SLR employed to identify relevant sources. A detailed description of the SLR may be provided in Appendix 2. The process of selecting data sources to inform model parameters should be transparent and unbiased. While RCTs are often the preferred source of data for treatment effectiveness inputs for economic models, the potential for valuable contributions from real-world observational studies should also be considered in certain circumstances e.g. when estimating effects of treatments used as part of treatment sequences, as commonly seen in autoimmune/inflammatory conditions.
* State if the most recent data-cuts from both the intervention and comparator trials have been used in the submission. If the most recent data-cuts have not been used, please provide justification for this omission.
	+ 1. Data analysis and parameter inputs
* Describe the analysis methods used to derive treatment effectiveness inputs for use in the model. Provide rationale and justification for the chosen analysis methods.
* If multiple studies are pooled to derive treatment effects for the model, the validity of pooling should be thoroughly justified. An assessment of study heterogeneity should also be conducted and reported. All baseline patient demographics and disease characteristics for the pooled and individual populations should be presented, together with a comparison of the populations and a discussion on the validity of pooling. Sensitivity analysis should be conducted to explore the impact of including/excluding certain trials from the pooled analysis.
* Where submissions include survival analysis of censored data, a systematic approach to the selection of appropriate statistical methods for extrapolation of survival analysis must be followed using, for example, the Model Selection Process Algorithm developed by the NICE Decision Support Unit (NICE TSD DSU 14) or other evidence-based guidance (5). A comprehensive justification of the chosen methods and exploration of the robustness of the model to those methods must be provided.
	1. Describe the approach to the selection of appropriate statistical methods.
	2. Tabulate the results of survival analysis for each model explored during the model selection process, highlighting the chosen base-case distributions and data sources for each outcome.
	3. Tabulate the survival predictions implicit in the base case at various timepoints, for example, 1 year, 2 years, 5 years, 10 years and 20 years.
	4. Where clinical opinion is used to assess the clinical plausibility of different modelling choices, this opinion must be obtained and reported in a transparent, robust and comprehensive manner in line with the guidance set out in Appendix 1.
* Where treatment effects are based (either entirely or partly) on Kaplan-Meier data, the model should include functionality allowing the assessor to select either the Kaplan-Meier data or the chosen survival model from the first cycle of the model.
* Where digitisation of Kaplan Meier curves is used for comparators, details of the methods, inputs and outputs of the digitisation process should be provided.
* Describe any assumptions made regarding the extrapolation, persistence or durability of treatment effects over the model time horizon and the evidence provided to support those assumptions. All assumptions regarding the persistence of treatment effects beyond that observed in clinical trials should be adequately justified.
* The model should include the functionality to adjust relevant treatment effects or survival curves to account for alternative assumptions around persistence or durability of treatment effects e.g. treatment effect waning.
* For all time-varying transition probabilities and/or rates used to model treatment effectiveness\*, the submitted electronic model and written submission should include the following:
	1. plots of the per-cycle transition probabilities or hazard rates (in the case of survival curves) over time
	2. Plots of the ratio of transition probabilities/hazard rates between treatment arms over time.

\***This should include the outcome of overall survival in any model that predicts a survival benefit, even where overall survival is not modelled explicitly** (e.g. in a [semi-]Markov model where death can occur from multiple health states). In partitioned survival models, plots of time-varying hazards for each treatment, and hazard ratios between treatments, should be provided for all survival curves affecting health state membership (e.g. progression-free survival and overall survival).

* The aforementioned plots may help reveal implausible patterns in treatment effects e.g. a treatment effect in the extrapolation period which is larger than the corresponding treatment effect in the observed period; a treatment effect which is maintained after all patients discontinue treatment, in the absence of clinical or biological plausibility. If implausible patterns in treatment effect are identified, the model should be constrained to ensure these patterns don’t occur. Please provide a discussion of any constraints imposed on the model in such cases.
* Please provide a measurement of the proportion of total QALYs gained, with the intervention versus the comparator, which were gained after the period for which data was directly observed in clinical trials of the intervention. Please also provide this measurement for life-years gained (LYG).
* Provide a table of key model assumptions relating to treatment effectiveness, including the rationale and justification for each assumption. If there is uncertainty regarding the clinical response definition, scenarios exploring alternative definitions or partial response, and associated treatment effects, should be explored.
* Outline the approach taken to sensitivity analysis and scenario analysis in order to explore uncertainty in treatment effectiveness.
* Tabulate the mean parameter values, data sources (i.e. named trial or specific analysis method) and ranges applied in probabilistic analyses and deterministic sensitivity analyses (Table title: Treatment effectiveness parameters used in the model), including justification for the chosen ranges and probability distributions. Probability distributions for each parameter in the model should be derived and used to propagate the associated uncertainty through the model. When more than one plausible data source is available, sensitivity analyses should be conducted to explore the impact of the alternative values.

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| **Table X: Survival analysis results** |
| *Additional information on the survival analysis results may be added as narrative footnotes in this row, in the following order a, b, c etc* |

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| **Table X: Survival analysis predictions** |
| *Additional information on the survival analysis predictions may be added as narrative footnotes in this row, in the following order a, b, c etc* |

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| **Table X: Treatment effectiveness assumptions** |
| *Additional information on the assumptions may be added as narrative footnotes in this row, in the following order a, b, c etc* |

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| **Table X: Treatment effectiveness parameters in the model** |
| *Additional information on the treatment effectiveness parameters may be added as narrative footnotes in this row, in the following order a, b, c etc* |

* + 1. Adverse treatment effects
* Clinically meaningful AEs which are likely to impact on costs and outcomes should be included among treatment effects in the model.
* Describe the criteria used to identify AEs for inclusion in the model. Clear justification of inclusion and exclusion criteria should be provided.
* Describe the data sources used to estimate the incidence of AEs for the intervention and comparator(s) and, if applicable, the comparative effectiveness of treatments on the incidence of AEs.
* It is preferable to base parameter inputs on a synthesis of relevant evidence e.g. network meta-analysis. If it is not feasible to estimate comparative effectiveness in terms of AEs e.g. if the AE profiles of interventions and comparators differ, the similarity of the data sources used to derive absolute adverse treatment effect estimates for different treatments should be discussed.
* Provide a table of AEs included in the model including the incidence/frequency of the event, and the data source.

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| **Table X: Adverse events included in the model** |
| *Additional information on the assumptions may be added as narrative footnotes in this row, in the following order a, b, c etc* |

* 1. Health-related quality of life
* The preferred submission type is a cost-utility analysis with the outcomes expressed in quality-adjusted life years (QALYs). All outcomes which impact on patients’ HRQoL should be included. State the primary health outcome of the model and describe the HRQoL parameters included in the model. Justify the inclusion or exclusion of selected benefits and harms (AEs) in the model.
	+ 1. Measurement and valuation of health-related quality of life
* Summarise the SLR process undertaken to identify and select relevant data sources for the comparative effectiveness analysis. An SLR is still required regardless of the availability of HRQoL from a clinical trial of the intervention. Include a summary of the SLR employed to identify relevant sources of HRQoL data. A detailed description of the SLR may be provided in Appendix 2. The process of selecting data sources to inform model parameters should be transparent and unbiased. If a utility value is identified from a secondary data source, the primary source should also be referenced.
* The clinical trial can sometimes be the most appropriate source of utility data, provided the population of interest were included, in sufficient numbers, and that the methods used to measure, obtain and gather the data were appropriate. However, the potential for large, population-based observational studies to yield more robust and meaningful values of relevance to patients outside of the clinical trial setting should be considered. All relevant data sources should be included in the SLR and the process of selecting data sources to inform model parameters should be transparent and unbiased.
* The EQ-5D-3L descriptive system is the preferred method of measuring HRQoL, with utilities derived from an EQ-5D-3L valuation set from a representative sample of the general population. Additional outcomes such as LYGs may also be presented.
* Describe the analysis methods used to derive the utility parameters used in the model. Provide rationale and justification for the chosen analysis methods.
* If a method other than the EQ-5D is used in the submission, its use should be justified and accompanied by a thorough description of the psychometric performance of the method, including evidence on its content validity, construct validity, responsiveness and reliability, derived from a synthesis of peer-reviewed literature. Where alternative methods are used, the recommendations outlined in the NICE DSU Report: “Measuring and Valuing Health-Related Quality of Life when Sufficient EQ-5D Data is not Available”, should be followed (6).
* Where mapping methods are used to convert data from other HRQoL measures to the EQ-5D, its choice should be justified, its statistical properties should be described and details of its derivation and validation should be provided. Sensitivity analyses should explore the impact of the choice of mapping algorithm and parameter uncertainty in the chosen algorithm.
* In cases where HRQoL data comprises of multiple observations collected from the same individuals at repeated intervals over the study period, statistical methods that account for the dependence between repeated measurements from the same individual should be used.
* Clearly detail and justify all assumptions regarding the application of utility values in the model.
* Outline the approach taken to sensitivity analysis and scenario analysis in order to explore uncertainty in health-related benefits and harms.
* Tabulate the mean parameter values, data sources and ranges applied in probabilistic analyses and deterministic sensitivity analyses (Table title: HRQoL utility values used in the model), including justification for the chosen ranges and probability distributions. Arbitrary intervals around the mean e.g. +/-20%, should be avoided wherever possible. If arbitrary intervals are necessary, they should be based on evidence as far as possible and should reflect a broad range of plausible parameter values. Probability distributions for each parameter in the model should be derived and used to propagate the associated uncertainty through the model. When more than one plausible data source is available, sensitivity analyses should be conducted to explore the impact of the alternative values.

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| **Table X: Utility values used in the model** |
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| Abbreviations:Footnotes a, b, c etc |

* 1. Costs
* Describe all costs captured by the model including intervention and comparator costs (drug acquisition, administration, monitoring etc.), adverse event, health state and other costs. All outcomes which impact on costs or healthcare resource use should be included. Justify the inclusion or exclusion of selected costs in the model. Direct costs relevant to the healthcare payer should be included in costs from the HSE perspective. Non-healthcare/wider societal costs, productivity losses associated with informal care, absenteeism from work etc. may be included in sensitivity analysis.
	+ 1. Intervention and comparator costs

*Costs included in this section should represent publicly available “list” prices. If a confidential patient access scheme (PAS) already applies to the intervention or if the Applicant has opted to propose a confidential PAS in the submission, supplementary confidential Tables should be included in this section, in addition to full details of the PAS and its current/proposed implementation.*

* The submitted model should clearly outline the component costs of the intervention and comparator(s). Each component of the total cost should be individually modifiable by the NCPE Review Group in the model, including the price-to-wholesaler (PtW) and all relevant rebates, mark-ups and fees.
* Refer to the Guidelines for Inclusion of Drug Costs in Pharmacoeconomic Evaluation when completing this section. (<http://www.ncpe.ie/submission-process/hta-guidelines/guidelines-for-inclusion-of-drug-costs/>).
* For treatments which have variable doses, or a variable but limited duration of treatment, ensure that that these estimates align with the information provided for the intervention and comparator in Section 4.2 (Model intervention) and 4.3 (Model comparator). Discuss the potential for variation in total costs depending on the dose/duration of treatments and explore this potential variation in sensitivity/scenario analyses.
* Vial sharing is generally not assumed for new therapies targeting small patient numbers, unless sufficient justification for this assumption can be provided. The practice of vial-sharing depends on the stability of the drug following initial vial manipulation and the feasibility of co-ordinating drug administration for sufficient patient numbers to eliminate wastage. The impact of vial-sharing on drug costs may be explored in sensitivity analyses.
* Complete the cost table template (Table title: Total drug cost per pack of [drug name] to the HSE)
* Complete the cost table template (Table title: Total comparative drug cost to the HSE for the intervention and comparator(s)). This table provides indicative summary costs based on model inputs. Where multiple presentations and strengths are available, a weighted average price may be appropriate. For treatments which have variable doses (e.g. based on weight, body surface area, age) it may be appropriate to use a mean dose. For treatments which have variable and/or limited durations of treatment it may be appropriate to use a mean duration. For treatments whose ToT is estimated from parametric survival modelling, the total drug cost per patient per treatment course should be based on the mean treatment duration calculated from the area under the ToT curve in the cost-effectiveness model.

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| **Table X: Total drug cost per pack of [drug name] to the HSE** |
|  | **Pack #1** | **Pack #2** | **Pack #3** |
| Strength  |  |  |  |
| Pack size  |  |  |  |
| Price to wholesalera (€) |  |  |  |
| Reimbursement scheme |  |  |  |
| Total drug costb per pack excluding pharmacy fees, excluding VAT (€) |  |  |  |
| Total drug costb per pack excluding pharmacy fees, including VAT (€) |  |  |  |
| [Abbreviations]aBased on the pricing application form (PAF) submitted to the HSE-CPU on [XX/XX/XXXX] OR \*Awaiting PAF OR \*PCRS price realignment fileb including relevant fees and Framework agreement rebate (specify rate applicable), excluding pharmacy feesc Footnote indicating that there is a 0% rate of VAT on oral medicines, if applicable e.g. “A commercial in confidence PAS is in place, not included in this table”d Footnote indicating that a PAS applies/is on offer, if applicable e.g. “A commercial in confidence PAS is in place, not included in this table” |

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| **Table X: Total comparative drug cost to the HSE for the intervention and comparator(s)** |
|  | **Total cost per patient per [year/treatment course**b**]**a |
|  | Including VAT (€) | Excluding VAT (€) | Source |
| [Drug] Pack#1 |  |  |  |
| [Drug] Pack#2 |  |  |  |
| [Drug] Pack#3 |  |  |  |
| [Comparator] |  |  |  |
| [Abbreviations]aIncluding all relevant fees and Framework agreement rebate (specify rate applicable)bFootnote explaining dose/duration assumptions (and clear justification) e.g. if cost per year has been replaced with cost per treatment coursec Footnote indicating that there is a 0% rate of VAT on oral medicines, if applicabled Footnote indicating that a PAS applies to a particular drug, if applicable e.g. “A commercial in confidence PAS is in place, not included in this table”e, f other assumptions as necessary |

* Administration and monitoring costs should be systematically identified, measured, and valued using Irish data wherever possible. Describe the measurement and valuation of administration and monitoring costs associated with the intervention and comparator(s).
* Clearly detail and justify all assumptions regarding the application of intervention and comparator costs in the model.
* Outline the approach taken to sensitivity analysis and scenario analysis in order to explore uncertainty in intervention and comparator.
* Tabulate the mean parameter values, data sources and ranges applied in probabilistic analyses and deterministic sensitivity analyses (Table title: HRQoL utility values used in the model), including justification for the chosen ranges and probability distributions. Arbitrary intervals around the mean e.g. +/-20%, should be avoided wherever possible. If arbitrary intervals are necessary, they should be based on evidence as far as possible and should reflect a broad range of plausible parameter values. Probability distributions for each parameter in the model should be derived and used to propagate the associated uncertainty through the model. When more than one plausible data source is available, sensitivity analyses should be conducted to explore the impact of the alternative values.
	+ 1. Healthcare resource use and costs
* Healthcare resource costs include all non-drug acquisition/drug-administration/drug-monitoring costs in the model.
* Healthcare resources should be systematically identified, measured, and valued following a review of literature and consultation with clinicians, where appropriate. A formal SLR is not required, due to the Irish-specific nature of the data required. Nevertheless, a transparent and systematic approach to the resource identification process should be followed. Identify and describe the data sources and analysis methods used to inform the cost parameters in the model, including a description of the systematic search employed to identify relevant studies. Provide the rationale for the choice of data sources.
* If a treatment decision is directly informed by the result of a specific companion diagnostic test (e.g. for the presence of a particular biomarker or gene expression etc.) which would otherwise not have been conducted, the cost of the test should be included in the intervention arm of the model. If the test is included in the existing standard panel of tests, it should not be included. All of the testing costs associated with defining the population should be included by means of an average test-cost per patient which takes into account the costs of a test (TestCost) for a patient with a positive test results, plus a proportionate cost for patients who have a negative test result based on the total tested population (=(total number of tests divided by total number of positive tests)\*TestCost).
* Describe any analysis methods used to derive the cost parameters used in the model. Provide rationale and justification for the chosen analysis methods.
* Where costs are based on data reported in the literature, particularly from countries other than Ireland, discuss the transferability of this data to the Irish target population. Describe the methods of converting costs from a different year or reported for a different country, using consumer-price-indices and purchasing-power-parity, as described in national HTA economic evaluation guidelines (4).
* Where costs are based on data collected during a clinical trial, describe the methods and results of the data analysis, and discuss the relevance of the trial protocol to standard practice in Ireland. Provide rationale for inclusion or omission of trial results in the model.
* Clearly detail and justify all assumptions regarding the application of costs in the model.
* Outline the approach taken to sensitivity analysis and scenario analysis in order to explore uncertainty in resource use and costs.
* Tabulate the mean parameter values, data sources and ranges applied in probabilistic analyses and deterministic sensitivity analyses (Table title: Healthcare costs used in the model), including justification for the chosen ranges and probability distributions. Probability distributions for each parameter in the model should be derived and used to propagate the associated uncertainty through the model. When more than one plausible data source is available, sensitivity analyses should be conducted to explore the impact of the alternative values.

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| **Table X: Healthcare costs used in the model** |
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| Abbreviations:Footnotes a, b, c etc. |

* 1. Discount rate
* State the discount rate applied to costs and benefits/harms. The discount rate is set by the Department of Finance (4% since August 2019). A range of discount rates should be applied in sensitivity analysis (0%-10%). (7)
	1. Parameter summary
* Tabulate all parameters used in the model including the mean value used for each parameter, the interval around the mean used in deterministic sensitivity analysis, the probabilistic distribution used to vary this parameter in probabilistic analysis (also specifying the parameters of this distribution), and the source of the data (Table title: Summary of parameters used in the model). Cross-reference parameter details to relevant sections in the written submission, and indicate the location of parameters in the electronic model.
* Indicate whether each parameter has been included in both probabilistic and deterministic analysis. Justify the exclusion of any parameter from probabilistic or deterministic analysis.

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| **Table X: Summary of parameters used in the model** |
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| Abbreviations:Footnotes a, b, c etc. |

1. Incremental cost-effectiveness analysis

*Cost-effectiveness results included in this section should represent publicly available prices. If a confidential patient access scheme (PAS) already applies to the intervention or if the Applicant has opted to propose a confidential PAS in the submission, supplementary confidential results tables should be included in this section.*

* 1. Incremental analysis of costs and benefits
* Tabulate total costs and outcomes, incremental costs and outcomes and incremental cost-effectiveness ratios (ICERs) using both probabilistic and deterministic analysis, for the full population and relevant subgroups using the table template (Table title: Incremental cost-effectiveness results). If more than one comparator is included, present ICERs for each pairwise comparison between the intervention and comparators, followed by a fully incremental analysis with exclusion of treatments subject to dominance and extended dominance. In situations where results include negative ICERs, include text alongside the ICER indicating the direction of the incremental costs and QALYs e.g. less costly and more effective, or more costly and less effective.
* Specify and justify the number of replications conducted for the probabilistic analysis. Probabilistic analysis should be based on a sufficiently large number of iterations that the expected values for costs and outcomes are stable (i.e. unlikely to vary substantially with increasing number of iterations). The ratio of the mean of the incremental probabilistic costs to incremental probabilistic QALYs should provide a stable estimate of the probabilistic mean ICER. It is inappropriate to base the mean ICER on the mean of the ICERs from each iteration.
* Discuss and explain the reasons for discrepancies between the deterministic and probabilistic results.
* Ensure that all results included in the written submission align with those included in the submitted cost-effectiveness model.

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| **Table X: Incremental cost-effectiveness results** |
| **Treatments**  | **Total costs (€)**  | **Total QALYs** |  **Incremental costs (€)** |  **Incremental QALYs**  | **ICER (€/QALY)** |
| [Comparator] | €XX,XXX | -.-- | - | - | - |
| [Intervention] | €XX,XXX | -.-- | €XX,XXX | 0-.-- | €XX,XXX |
| Abbreviations:Footnotes a, b, c etc |

* 1. Analysis of uncertainty
		1. Probability of cost effectiveness
* Present the results of the probabilistic analysis using a scatter-plot of simulated cost and effect pairs on the incremental cost-effectiveness plane, and cost-effectiveness acceptability curve.
* Tabulate the probability of cost effectiveness at a range of willingness to pay thresholds including €20,000 and €45,000/QALY (reflective of thresholds considered in previous HSE decisions) using the table template (Table title: Probability of cost-effectiveness for [intervention] vs [comparator]).

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| **Table X Probability of cost effectiveness for [intervention] vs [comparator] a** |
| **Threshold (€/QALY)** | **Probability of cost effectiveness** |
| 20,000 | X% |
| 45,000 | X% |
| a Results based on probabilistic analysis using X,XXX iterations |

* + 1. Sensitivity and scenario analyses
* Conduct sensitivity and scenario analyses for the full population and relevant subgroups. Present the results of sensitivity and scenario analyses in both tabular format and using a tornado diagram. Negative ICERs should not be included in tornado diagrams, as they are both meaningless and misleading without further explanation. In such cases, NMB can be included in the diagram. ICERs and NMBs should not be mixed in one diagram. Where ICERs are all positive, NMB should not be included in tornado diagrams.
* Discuss the key drivers of cost effectiveness.
* Discuss the uncertainty of the results.
* Ensure that all relevant information has been submitted, in the appropriate format, to allow the NCPE Review Group to re-run analysis and reproduce results.
	+ 1. Price-ICER analysis
* Present a price-ICER analysis over a range of intervention prices. These analyses may be carried out deterministically, provided the deterministic and probabilistic ICERs are similar (Table title: Results of price-ICER analysis). An estimate of the price reduction required for the intervention to be cost-effective, at thresholds considered in previous HSE decisions (i.e. €20,000/QALY and €45,000/QALY) should be included in the table. The price reduction should be implemented in the model by modifying the rebate component of the intervention cost, based on a percentage of the publicly available PtW. In Excel models, the rebate should be isolated to one cell to facilitate modification and should represent a total rebate, inclusive of the Framework Agreement rebate.
* If a PAS is in place for the comparator(s), the price-ICER analysis should include various comparator discounts within a plausible range.

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| **Table X: Results of Price-ICER analysis a** |
| **% reduction a in [intervention] PtW** | **ICER** |
| [X]% | €45,000/QALY |
| [Y]% | €20,000/QALY |
| 10% |  |
| 20% |  |
| 30% |  |
| 40% |  |
| 50% |  |
| *Abbreviations:*a Expressed as a total rebate (inclusive of the Framework Agreement Rebate) |

1. Budget-impact analysis

*Budget-impact analysis (BIA) results included in this section should represent publicly available prices. If a confidential patient access scheme (PAS) already applies to the intervention or if the Applicant has opted to propose a confidential PAS in the submission, supplementary confidential results tables should be included in this section.*

* The BIA must be conducted using the NCPE Budget Impact Model Template (available at <http://www.ncpe.ie/submission-process/submission-templates/budget-impact-model-template/>).
* The gross drug-BIA includes drug-acquisition costs of the intervention (inclusive of fees, margins, rebates and VAT, as applicable). For drug-combination regimens, the drug-acquisition costs of the intervention should include all drugs included in the regimen. Costs associated with administration of the drug should not be included here. The net drug-BIA may include potential drug-acquisition cost offsets anticipated from changes in the utilisation of other drugs. All assumptions regarding the magnitude and persistence of cost-offsets in clinical practice should be justified for the net drug-BIA.
* The “Eligible population” should directly reflect the prevalence and incidence of the disease in Ireland, and be specific to the population covered by the Marketing Authorisation. All other assumptions such as diagnostic availability, levels of testing, treatment uptake and market share should be factored into “Proportion treated”.
* Costs in the BIA should correspond with those applied in the cost-effectiveness model, including the same assumptions regarding dose, frequency, duration etc. The duration of treatment should reflect expected real-world clinical practice. Guidance outlined in Section 4.2 Model intervention, should be followed for the BIA also. For continuous treatments, partial calendar years are not acceptable in BIAs due to uncertainty in the exact date or month of introduction to the market. In line with data inputs for the cost-effectiveness model, estimates of ToT for interventions expected to continue for a discrete duration should be based on the mean treatment duration observed in the relevant trial(s). This duration may be very uncertain if clinical trial data is immature i.e. a substantial proportion of the population are still receiving the intervention by the end of follow-up. If data is immature, it is likely that the mean treatment duration for the trial population will be underestimated. In such cases, the most plausible prediction of treatment duration should be the estimated mean from the area under the ToT curves in the cost-effectiveness model.
* Describe the data sources used to estimate the eligible and treatment population numbers.
* Clearly detail and justify all assumptions regarding the estimation of the numbers of patients in the eligible and treated populations, and regarding the costs of the intervention and comparator(s) in the BIA.
* All assumptions underpinning the definition of the intervention/comparator(s) should be fully justified and explored in sensitivity/scenario analyses. Discuss the potential for an increase/decrease in patient numbers/costs based on new indications/competitors, including generic/biosimilar alternatives, emerging in the next five years.
* All parameters which impact total drug cost should be accounted for appropriately in deterministic sensitivity analyses. Outline the approach taken to sensitivity analysis and scenario analysis in order to explore uncertainty in the BIA estimates due to potential variation in eligible and treatment population numbers, and total drug costs.
* Complete the standard table template (Table title: Drug-budget impact analysis). Costs in the Drug-BIA table should be limited to drug costs only.
* Indicate if any additional non-drug costs or cost-offsets are expected due to changes in healthcare resource utilisation. An additional table may be included to represent any additional non-drug costs or cost-offsets which are expected due to changes in wider healthcare resource utilisation e.g. administration costs, companion diagnostic costs etc.
* Alternative prices may be included in a sensitivity analysis. If a PAS or confidential discount is in place for a comparator, include a plausible range of prices in sensitivity analysis.

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| **Table X: Drug-budget impact analysis a, b**  |
| **Population** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **5-year cumulative**  |
| Eligible populationc |  |  |  |  |  |  |
| Proportion treated (%) |  |  |  |  |  |  |
| Treated population |  |  |  |  |  |  |
| Gross drug-budget impact |  |  |  |  |  |  |
| Including VAT (€) |  |  |  |  |  |  |
| Excluding VAT (€) |  |  |  |  |  |  |
| Net drug-budget impact |  |  |  |  |  |  |
| Including VAT (€) |  |  |  |  |  |  |
| Excluding VAT (€) |  |  |  |  |  |  |
| [Abbreviations][a Including all relevant fees and Framework Agreement rebate (specify the rate of rebate applicable)][b Footnote indicating that there is a 0% rate of VAT on oral medicines, if applicable][c Provide a definition of the “eligible population” for the purposes of the BIA][d Footnote indicating that a PAS applies to a particular drug, if applicable][e, f other assumptions as necessary] |

1. International HTA
* Complete the standard table template (Table title: International HTA) including the status of HTAs conducted by the specified agencies, the level of reimbursement, any restrictions on reimbursement, and any PASs which may apply.

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| **Table X: International HTA** |
| **Organisation**  | **Recommendation/Status (date)** |
| NICE, UK |  |
| SMC, Scotland |  |
| NIHDI, Belgium |  |
| ZIN, Netherlands |  |
| AIHTA, Austria |  |
| CADTH, Canada |  |
| PBAC, Australia |  |
| ICER, US |  |

1. Conclusion
* Provide an overview of the main findings of the submission including a discussion of the uncertainty of the results.
1. References
* Format all references in the Vancouver style, and list at the end of the submission. Verify that all in-text references correspond to the final reference list prior to submission.
* Where a reference is used to support specific evidence e.g. data point or other piece of information, the primary data source should be referenced. The relevant line/table/section should be highlighted in colour within the primary reference source.
* Submit electronic full-text copies and an RIS formatted file of all references. Website links alone are not sufficient due to the potential for web addresses to change over time. Screenshots should be provided as “full-text” copies in these cases. The title of each individual reference file should begin with the corresponding reference number in the submission. The number of full-text references should match the number of references in the submission.
1. Appendices
* Appendix 1: Clinical opinion, should be submitted if any evidence in the submission is based on expert opinion. The information provided in A1: “NCPE Guidance on the use of expert opinion as supporting evidence in the Applicant submission”, should be used to guide completion of A2: “Template for reporting of clinical opinion in Applicant submissions to the NCPE”.
* Appendix 2: Systematic literature review, should describe all SLRs conducted as part of the submission. Information provided in this appendix should follow “NCPE Guidance on conducting and reporting on the systematic literature search used to identify evidence on clinical efficacy and safety evidence, in addition to economic model inputs”, located at the end of this document.
* Appendix 3: Confidential information, requires completion of a Confidential Information template if the submission contains confidential information. Information provided in this appendix should follow the “NCPE Guidance on the submission of commercial/academic-in confidence information”, located at the end of this document.
* Summary of product characteristics, EPAR, additional information and other supporting documentation may be submitted as appendices, as appropriate.
* Each individual appendix should appear as an individual heading within the main table of contents or within a separate table of contents for appendices alone.

## Appendix 1: Clinical opinion

**A1: NCPE Guidance on the use of clinical opinion as supporting evidence in the Applicant submission**

**A2: Template for reporting of clinical opinion in Applicant submissions to the NCPE**

**A1: NCPE Guidance on the use of clinical opinion as supporting evidence in the Applicant submission**

Healthcare professionals are important stakeholders in HTA and clinical opinion from doctors, pharmacists, nurses and other allied health professionals can be used to inform a range of aspects of a HTA submission. Clinical opinion may be a qualitative expression of an individual’s judgement (6) for example opinion on the appropriate target population, comparators (through establishing existing standard of care and the place in therapy of the intervention) and aspects of the intervention including dose, clinical response and duration. Qualitative clinical opinion may be used to validate model structure and assumptions. Qualitative clinical opinion provides valuable input into the NCPE assessment and is required in all Applicant submissions. Clinical opinion may also be a quantitative expression of judgement used to define point estimates of key economic model parameters and characterise uncertainty (6).

In general, data inputs in economic models should be based on empirical data from high quality, methodologically rigorous studies which are designed to minimise the effect of bias. Where such data is lacking, clinical opinion may be needed to supplement or support observed data. If quantitative clinical opinion is used, its inclusion should be justified in the HTA submission.

Experts should have advanced clinical or practical experience relevant to the issues in question. All studies or exercises used to obtain clinical opinion should be well-designed to minimise bias, and reported with clarity and transparency. All background information provided to experts should be consistent with the evidence provided in the NCPE submission. Applicant submissions which include clinical opinion should provide details of the process used to obtain the opinion, using the following template.

**A2: Template for reporting of clinical opinion in Applicant submissions to the NCPE**

*This document outlines the content and format required when reporting on methods of obtaining clinical opinion for use in submissions to the NCPE, and on the results of these methods. All sections of the template must be included in the submission. While additional sub-headings may be included in the submission, do not otherwise alter the heading structure provided.*

1. **Details of experts who participated**
* Outline the criteria used for selecting the clinical experts.
* Complete Table A1 with the details of the experts who participated. Names of participating experts will not be included in NCPE reports or made publicly available.
* A declaration of potential conflicts of interest from each expert who provided opinion should be included in the reference pack.

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| **Table A1: Participating experts** |
| Name | Position | Date opinion obtained | Reference number\* |
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| *\*Potential conflict of interest declaration* |

1. **Background information provided to the clinical experts**

Provide the background information that was provided to the experts. Background information may include, but is not limited to, invitations, slides of presentations or literature references provided to clinicians.

1. **Methods used to obtain opinion**
* Describe all methods used to collect opinion (e.g. opinion collected via group discussion or collected individually through interviews or questionnaires).
* Provide a full description of all questions asked. Depending on the method used, this may be outlined here in full or provided as a reference e.g. a questionnaire, interview/discussion guide etc.
1. **Responses**
* Provide the individual responses received for each question. In the case of a group discussion, a summary of the responses may be provided but this should be accompanied by the transcript or minutes of the discussion.
* Describe the analytic approach used to collate the opinion, including the variability in opinion. Where quantitative expert opinion has been used to inform a model input parameter, all of the data used to derive the parameter in addition to a description of the mathematical method or process used to aggregate the data is required. Where qualitative opinion has been obtained, highlight when consensus or conflict is identified. State how many experts made consensus or conflicting statements.
1. **Other sources of clinical opinion used in the submission**
* If clinical opinion has been derived from other published sources, clearly reference the source e.g. page numbers in published NICE submissions/reports etc. The use of any such opinion should be validated for the Irish setting.
1. **Checklist of items required for Appendix 1**

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| **Table A2: Checklist of items required for Appendix 1\*** |
| *Please confirm that the background information, questions used to obtain clinical opinion, and the associated responses, have been included in the submission. Where more than one method is used, indicate the inclusion of questions and responses from each method.*  |
|  | **Background information is included in the submission** |
| Background information (describe information presented or provided to clinical experts e.g. slides, literature references) |[ ]
|  | **Questions are included in the submission** |
| Method 1 (describe method as applicable e.g. interview, questionnaire etc.) |[ ]
| Method 2 (describe method as applicable e.g. interview, questionnaire etc.) |[ ]
|  | **Responses are included in the submission**  |
| Method 1 (describe method as applicable e.g. interview, questionnaire etc.) |[ ]
| Method 2 (describe method as applicable e.g. interview, questionnaire etc.) |  |
| \* Additional rows may be added to this table as required |

## Appendix 2: Systematic literature review

**NCPE guidance on conducting and reporting on the systematic literature search used to identify evidence on clinical efficacy and safety evidence, in addition to economic model inputs.**

Studies for the efficacy and HRQoL inputs of the model should be identified and selected following a systematic review of the published peer-reviewed and grey literature, in addition to any relevant unpublished data available to the Applicant. Provide a clear description of the data sources used, and the search strategies used for all electronic databases.Database searches must be conducted within **six months** of the date of HTA submission. Applicant submissions should provide details of the search process **including the following elements**:

1. A breakdown of each of the PICOS elements (i.e. population, interventions, comparators, outcomes, study design) used in the search. The elements should correspond with the decision problem outlined in the Applicant Submission
2. Details of all electronic databases searched including years of coverage and the platform used
3. Details and justification of any date limits applied to the search strategy
4. Details and justification of any other limits applied to the search strategy (study/publication type, languages etc)
5. References for any validated search filters used in the strategy
6. Date that searches were undertaken
7. The full search strategies used, including the number of hits per line, for each individual database.
8. Details of sources searched to identify grey literature (conference proceedings, trial registries)
9. Details of the search strategies or key words used to identify grey literature
10. Details of study selection criteria including inclusion and exclusion criteria
11. A PRISMA flow chart that details the number of studies identified and excluded from electronic databases and grey literature sources
12. Details of studies excluded at the full text review stage (with reasons for exclusion)
13. Complete reference list of included studies

Where applicants are undertaking a clinical evidence synthesis more detailed reporting is required, refer to the document “NCPE requirements for conducting and reporting clinical evidence synthesis analyses” for further guidance.

## Appendix 3: Confidential information

In the interests of transparency of NCPE recommendations, all efforts should be made to ensure that information included in the Applicant Submission can be included, without redaction, in NCPE Assessment Reports and is publishable in NCPE summaries.

It is recognised, however, that certain information may be requested to be considered confidential, either by the Applicant, or other parties contributing to the Assessment. This type of data should be kept to a minimum in submissions. If confidential information is included in an Applicant Submission, it should be highlighted in yellow in all relevant documents. Submissions which include confidential information **must include a completed Table A4.1**, identifying all confidential information contained in the submission and the specific reason for identifying information as confidential. It is not acceptable to identify any information as “Academic-in-confidence” as the NCPE does not consider data contained in HTA reports to be academic-in-confidence. This is in line with the International Committee of Medical Journal Editors (ICMJE), which does not consider results or data contained in health technology assessment or regulatory agencies’ reports to be duplicate publication (10). If there are other reasons why unpublished data should remain confidential, this should be highlighted, together with an indication of the date on which this no longer applies. This requirement should not preclude the submission of any clinical data of relevance to this assessment. All information included in Table A4.1 will be reviewed by the NCPE Review Group. Any information which is not considered to warrant confidentiality will be highlighted by the NCPE Review Group. Any information accepted as confidential by the NCPE Review Group, and subsequently included in the NCPE Assessment Report, will be highlighted as such. Confidential information will not be included in the NCPE Assessment Summary.

*Types of information which* ***may*** *be considered confidential*

Detailed information must be provided to justify the identification of information as confidential in Table A4.1. Types of information which may be considered confidential include the following:

* Price discounts/rebates submitted as part of PAS proposals.
* Cost-effectiveness model and budget-impact model outputs, estimated under the terms of a PAS.

*Types of information which* ***may not*** *be considered confidential*

* Information which is already in the public domain.
* Drug price (as outlined in Table 3)\*.
* Cost-effectiveness input parameters, except where the information is considered confidential under the circumstances described above.
* Cost-effectiveness results including ICERs, incremental costs and QALYs, probabilities of cost effectiveness etc\*.
* Budget impact estimates including estimates of eligible patient population, treated patient population, gross drug-budget and net drug-budget impact\*.

*\*With the exception of prices, and cost-effectiveness and budget-impact model outputs, calculated/estimated under the terms of a PAS.*

**Table A4.1: Confidential information included in the Applicant Submission**

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| **Page and line number** | **Specific reason for confidentiality** | **Date/milestone after which information may not be regarded as confidential** |
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1. Guidance for submitting electronic models
* Microsoft Excel 2019 (or earlier versions) is the preferred software for NCPE submissions. Contact the NCPE in advance of submission if alternative software packages, including Excel 365, are considered for submission. Contact the NCPE in advance of submission if a micro-simulation model is going to be submitted. Ensure that all relevant information has been submitted, in the appropriate format, to allow the NCPE Review Group to re-run analysis and reproduce results.
* A Technical Specification Document should be submitted along with the cost-effectiveness model. The information in this report should include but not be limited to, guidance for model-users on how to use/adapt the model, and detail on the basic functioning, background calculations, and underlying assumptions of the model structure. At a minimum, the document should:
1. define the role and describe the content of each tab of the Excel spreadsheet
2. describe which cells/inputs are modifiable and which are not. Any inputs which are non-modifiable should be sufficiently justified.
3. list and describe all of the macros used in the model and define their relationship to the various tabs of the spreadsheet. Where macros call other procedures/macros, a VBA map should be included to show the order and relationship between them.
4. provide exact changes required in the model for any scenario analyses presented. These changes should include:
	1. changes to any cell values on the worksheets
	2. changes to any dropdown menus
	3. changes to any VBA code required.
5. include the model runtime, for example for a PSA or micro-simulation to run to convergence, for a given machine specification (e.g the runtime on the computer used by the Applicant).
	1. Cost-effectiveness model
* The Applicant must submit a fully executable electronic copy of the cost-effectiveness model, ensuring that the model structure and all parameter values are as specified in the written submission.
* In Microsoft Excel models, all parameter values directly feeding into the deterministic and probabilistic calculation of costs and benefits should be listed in consecutive rows on a single worksheet.
* Disaggregated probabilistic results i.e. all simulated cost and effect pairs, should be presented in the model, in addition to summary measures.
* Trace graphs should be presented to visually demonstrate the long-term distribution of patients across health states.
* As described in more detail in Section 5.2.2, specific plots are required for all time-varying transition probabilities and/or rates used to model treatment effectiveness. These include plots of the per-cycle transition probabilities or hazard rates (in the case of survival curves) over time, in addition to plots of the ratio of transition probabilities/hazard rates between treatment arms over time. These plots should be included as model outputs.
	1. Budget-impact model
* The NCPE Budget Impact Model Template (available at <http://www.ncpe.ie/submission-process/submission-templates/budget-impact-model-template/>) should be used to conduct the budget impact analysis. Budget Impact Models other than the NCPE template are not accepted.
* The budget impact model should be fully executable so that the NCPE Review Group can easily examine the impact of a change in any of the parameters to the budget impact.
	1. Spreadsheet best practice
* Please ensure that all intermediate calculations between the input parameters and the final matrices (transitions, patients, costs, QALYs etc) are clearly shown on the spreadsheets.
* Workbooks, cells, and tabs should all be unhidden and modifiable.
* Value restrictions should not be placed on cells.
* Tabs should be appropriately named and correspond with those in the Technical Specification Document.
* Key cells and ranges should be named in order to provide clarity.
* Formulae that have been copied down for multiple rows should not change in the middle of a column, without clear indication.
* Nested IF statements or cells with nested min/max functions should be kept to a minimum. The exact values used in each possible scenario should be made clear to the Review Group.
* Any irrelevant or unused tabs or inputs in the model should be removed.
* Ensure the integrity of all calculations employed in each model before submission.
	1. VBA programming guidelines
* Code that is not being used in the model should not be included in the submitted model.
* Code should be as concise and efficient as possible.
* All VBA procedures that are being used for a button should all be in the same module where possible. Functions and other commands that are being used for multiple buttons should be kept together in a separate module.
* There should be a brief description at the beginning of each procedure to explain what it is intending to do.
* Commenting should be included throughout each procedure.
	1. Microsimulation models
* Provide notice at the pre-submission meeting if you plan on submitting a micro-simulation model.
* A VBA map should be included in the submission which details the order of all macros or procedures used throughout the model, and how these macros relate to one another.
* Random seeds should be set so that results can be reproduced by the NCPE review group.
* Key intermediary calculations e.g. transition probabilities at each time point, should be presented as a print out or in graphical format where possible.
* It is particularly important to provide the results of scenario analyses in micro-simulation models due to the potentially long runtime for replication.

## References

1. Health Information and Quality Authority. Guidelines for the Budget Impact Analysis of Health Technologies in Ireland. Dublin, Ireland: HIQA, 2018. .

2. Health Information and Quality Authority. Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland. Dublin, Ireland: HIQA, 2019.

3. Health Information and Quality Authority. Guidelines for Stakeholder Engagement in Health Technology Assessment in Ireland. Dublin: 2014.

4. Health Information and Quality Authority. Guidelines for the Economic Evaluation of Health Technologies in Ireland. Dublin, Ireland: HIQA, 2020.

5. Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available from <http://www.nicedsu.org.uk>.

6. Rowen D, Brazier J, Wong R, Wailoo A. Measuring and valuing health-related quality of life when sufficient EQ-5D data is not available. NICE DSU Report. 2020. Available from <http://www.nicedsu.org.uk>.

7. Department of Public Expenditure and Reform. Circular 18/2019: Update of the Public Spending Code (PSC): Central Technical References and Economic Appraisal Parameters. Dublin, Ireland: Department of Public Expenditure and Reform; 2019. Available from: <https://assets.gov.ie/20001/35c13bbd055a4a09961a4ec59c93c798.pdf>.

8. Iglesias CP, Thompson A, Rogowski WH, Payne K. Reporting Guidelines for the Use of Expert Judgement in Model-Based Economic Evaluations. PharmacoEconomics. 2016;34(11):1161-72.

9. Australian Government Department of Health. Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee (PBAC Guidelines), version 5.0. .

10. International Committee of Medical Journal Editors. Updated ICMJE recommendations (May 2022). July 2022. <https://www.icmje.org/news-and-editorials/updated_recommendations_may2022.html>.