



METHODOLOGICAL GUIDELINES

FOR ECONOMIC EVALUATION
STUDIES OF HEALTH TECHNOLOGIES

Methodological Guidelines

for Economic Evaluation Studies
of Health Technologies

Version	Description of changes	Date of publication
1.0		12/12/2019

Suggested citation: Perelman J, Soares M, Mateus C, Duarte A, Faria R, Ferreira L, Saramago P, Veiga P, Furtado C, Caldeira S, Teixeira MC, Sculpher M (2019): Methodological Guidelines for Economic Evaluation Studies. INFARMED - National Authority of Medicines and Health Products, I.P., Lisbon. Available online at www.infarmed.pt

Authors

Julian Perelman

Escola Nacional de Saúde Pública, Universidade Nova de Lisboa and Comissão de Avaliação das Tecnologias da Saúde (INFARMED, I.P.) (coordination)

Marta Soares

University of York and Comissão de Avaliação das Tecnologias da Saúde (INFARMED, I.P.) (coordination)

Céu Mateus

Lancaster University and Comissão de Avaliação das Tecnologias da Saúde (INFARMED, I.P.)

Ana Duarte,

University of York and Comissão de Avaliação das Tecnologias da Saúde (INFARMED, I.P.)

Rita Faria

University of York and Comissão de Avaliação das Tecnologias da Saúde (INFARMED, I.P.)

Lara Ferreira

Universidade do Algarve and Comissão de Avaliação das Tecnologias da Saúde (INFARMED, I.P.)

Pedro Saramago

University of York and Comissão de Avaliação das Tecnologias da Saúde (INFARMED, I.P.)

Paula Veiga

Universidade do Minho and Comissão de Avaliação das Tecnologias da Saúde (INFARMED, I.P.)

External expert

Mark Sculpher, University of York (coordination)

Institutional Reviewers

Claudia Furtado, INFARMED, I.P.

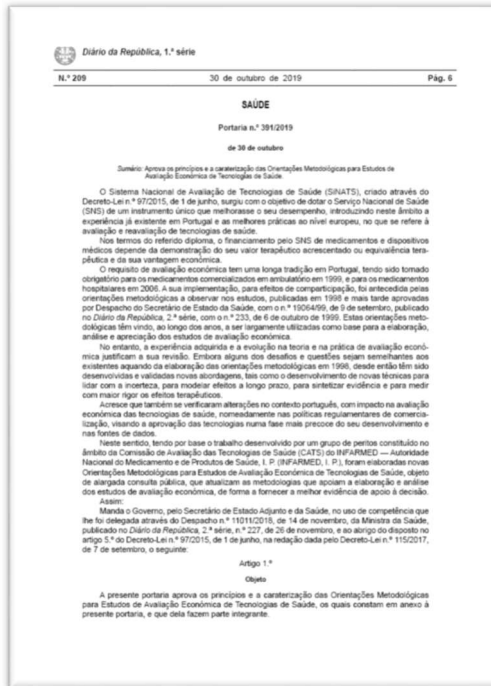
Maria do Céu Teixeira, INFARMED, I.P.

Sónia Caldeira, INFARMED, I.P.

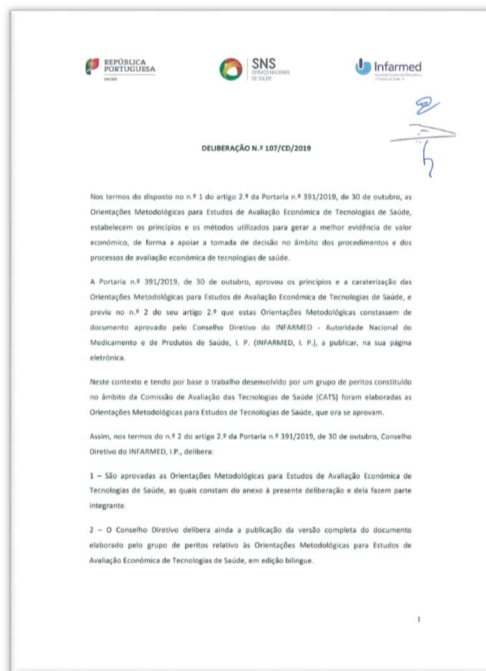
Maria do Céu Machado, INFARMED, I.P.

Rui Santos Ivo, INFARMED, I.P.

Sofia de Oliveira Martins, INFARMED, I.P.



Ordinance No. 391/2019, of 30 October
Francisco Ventura Ramos, Secretary of State Assistant and of Health
- XXI Government - Portuguese Republic



Resolution nº107/CD/2019
Dr. Rui Santos Ivo, President
Dr. António Faria Vaz, Vice-President
Dr.ª Cláudia Belo Ferreira, Vowel

List of Contents

List of Contents	5
List of Tables	6
Abbreviations	7
I. Synopsis	8
II. Introduction	11
1. Principles of appraisal	14
2. Comparators	16
3. Population and subgroups	18
4. Evaluation of treatment effect.....	20
5. Time horizon	22
6. Analytical techniques.....	23
7. Perspective	24
8. Identification, measurement and valuation of costs.....	26
9. Measurement and valuation of health effects.....	28
10. Study design and modelling methods.....	30
11. Evidence, or assumptions, related to other model parameters	34
12. Information provided by experts.....	36
13. Quantitative analyses of primary data to support modelling	39
14. Decision uncertainty and identification of further evidence needs.....	42
15. Validation.....	46
16. Discount rate.....	48
17. Presentation of cost-effectiveness results	49
18. Uncertainty and further evidence collection supporting decision making on targets for re-appraisal.....	51
19. Budget Impact Analysis.....	53
20. Ethical and procedural aspects	55
References	56
Annexes.....	60

List of Tables

Table A1. Guidelines for elicitation.....	60
Table A2. Characterisation of the sources of uncertainty.....	61
Table A3. List of criteria for collection of further evidence.....	62

Abbreviations

ATV	Added Therapeutic Value
AUC	Area Under the Curve
BIA	Budget Impact Analysis
CATS	Health Technology Assessment Commission (Comissão de Avaliação de Tecnologias de Saúde)
CE-CATS	Executive Commission of the Health Technology Assessment Commission (Comissão Executiva da Comissão de Avaliação de Tecnologias de Saúde)
DATS	Health Technology Assessment Directorate (Direção de Avaliação de Tecnologias de Saúde)
EVPI	Expected Value of Perfect Information
EVPPi	Expected Value of Partially Perfect Information
HTA	Health Technology Assessment
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-effectiveness Ratio
ITT	Intention-to-Treat
MA	Marketing Authorisation
MAIC	Matching-Adjusted Indirect Comparisons
NHS	National Health Service
OS	Overall Survival
PartSA	Partitioned Survival Analysis
PFS	Progression-Free Survival
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
SINATS	National Health Technology Assessment System (Sistema Nacional de Avaliação de Tecnologias de Saúde)
STC	Simulated Treatment Comparisons
VAT	Value Added Tax

I. Synopsis

The following Table shortly summarises all guidelines, in relation to the base case to be used in the economic evaluation.

1. Principles of appraisal

The recommendations detailed here aim to guide the development of economic evaluation studies, and also to guide the appraisal of the economic evidence submitted by companies. In appraising the evidence, its adequacy, scope, and quality, should be considered, with a view to identify the results on economic value results that are more relevant and valid to support decision making.

2. Comparators

The economic evaluation should compare the new technology to all other health care options relevant to the disease or clinical condition in focus, as defined in the scope of the pharmacotherapeutic evaluation and considered in the pharmacotherapeutic recommendation by the Health Technology Assessment Commission (CATS).

3. Population and subgroups

The economic evaluation should assess the new technology in the entire target population and in relevant subgroups, as defined in the scope of the pharmacotherapeutic evaluation and considered in the pharmacotherapeutic recommendation by CATS.

4. Evaluation of treatment effect

The economic evaluation should be based on the assessment of all effectiveness evidence contained in the CATS pharmacotherapeutic recommendation. However, there may be additional methodological and evidence requirements for the assessment of the economic value of the technology.

5. Time horizon

The time horizon used for the cost-effectiveness model should be sufficiently long to include all important differences in costs and consequences of all technologies under comparison.

6. Analytical techniques

We recommend that cost-effectiveness studies are carried out with the consequences expressed as Quality-Adjusted Life Years (QALYs). Health consequences should not be expressed in monetary terms.

7. Perspective

The perspective on costs for the reference case should be that of the National Health Service (NHS). The perspective on consequences should consider all health effects for current patients.

8. Identification, measurement and valuation of costs

All health care resources relevant to the analysis should be identified. Detailed information on the health care resources used (measured in physical units) and how they are valued (unit prices or costs) should be reported separately.

9. Measurement and valuation of health effects

The EQ-5D-5L is the preferred measure for assessing health-related quality of life, with Portuguese tariffs.

10. Study design and modelling methods

The submission should include a full description of how the model reflects the natural course of the disease and the impact of treatment(s) on the disease, health outcomes and health costs. The choice of modelling approach should always be justified. If it is possible and reasonable to apply different approaches, it is preferable to implement the simplest approach (parsimony principle).

11. Evidence, or assumptions, related to other model parameters

Evidence that relate to model parameters and assumptions should be identified using a systematic and explicit process, and the quality and appropriateness of each source for the context of care should be carefully considered.

12. Information provided by experts

When no empirical evidence on a parameter of interest exist, or its representativeness in the context of the target population is uncertain, the opinions of experts can be elicited.

13. Quantitative analyses of primary data to support modelling

Statistical analyses conducted to inform model parameters that have not been fully published in peer reviewed literature should be documented in a statistical appendix.

14. Decision uncertainty and identification of further evidence needs

Parameterised and non-parameterised uncertainties should be systematically evaluated and explicitly characterised. This should be performed using sensitivity analysis and scenario analysis.

15. Validation

Validation should focus on all the elements of the model development. It should highlight the transferability and generalisability of model predictions to the Portuguese context.

16. Discount rate

All costs and consequences should be discounted at 4% per year.

17. Presentation of cost-effectiveness results

All interventions should be evaluated together using a full incremental analysis.

18. Uncertainty and further evidence collection supporting decision making on targets for re-appraisal

The results of the analyses of uncertainty should inform a list of priorities on further evidence needs, which will aim to substantiate formal requests for evidence collection, to be submitted at the re-appraisal stage.

19. Budget impact analysis

Budget impact analysis (BIA) must adopt the NHS perspective, and consider the costs related to the intervention and the comparator(s) selected in the economic evaluation.

20. Ethical and procedural aspects

The complete list of authors and their affiliations, the list of financing entity(ies), and a statement on the contribution of each entity and author to the study should be submitted.

II. Introduction

a. Background

The National Health Technology Assessment System (SiNATS) was created by Decree-Law 97/2015, of 1 June, and aimed at providing the National Health Service (NHS) with a unique instrument to improve its performance. It considered the experience in the economic evaluation of drugs existing in Portugal since the 1990s and best practices at European level concerning the appraisal (and re-appraisal) of health technologies.

According to this Decree-Law, the reimbursement of drugs and medical devices by the Portuguese National Health Service (NHS) is conditional on demonstrating not only added therapeutic value (or therapeutic equivalence) but also value for money (art.14). These requirements also apply for the public financing of prescription drugs acquired by entities under the supervision of the member of the Government responsible for the health area (art. 25). The economic evaluation of health technologies is, therefore, clearly highlighted in the Portuguese legislation as a principle to be used in public financing, with possible extensions of its use in price negotiation and in supporting the development of therapeutic guidelines.

The requirement of economic evaluation has a long tradition in Portugal. It was first made compulsory for drugs dispensed in the community in 1999 and then for those dispensed in hospitals in 2006. Preceding its implementation for financing purposes, the first "Guidelines for economic drug evaluation studies" were published in 1998 and were authored by Emilia Alves da Silva, Carlos Gouveia Pinto, Cristina Sampaio, João António Pereira, Michael Drummond, and Rosário Trindade. These were later approved in law by Order No. 19064/99, of 9 September, of the Health Secretary of State. This work was amongst the first methodological guidelines for the economic evaluation of drugs produced in Europe and was, thus, an innovative and precursory document. For over 20 years, these methodological guidelines have supported the preparation, analysis and appraisal of economic evaluation studies.

However, the experience gained since and recent developments in the theory and practice of economic evaluation justify its revision. Although some of the challenges and issues are similar to those existing in 1998 when the first methodological guidelines were developed, new approaches have been developed and validated since, such as new techniques to handle uncertainty, to model long-term effects, to synthesise evidence and to more accurately measure treatment effects.

Also, the Portuguese context changed over time in ways that impact on the economic evaluation of health technologies. Of relevance are the multiple budget constraints imposed in recent years, prompting the need for budget impact analyses and for the re-appraisal of approved drugs. There are also new regulatory policies that enable certain technologies being marketed earlier in the evidence development pathway when there is still significant uncertainty over their clinical and cost-effectiveness. This meant that it became critical to create incentives for post-financing evidence collection and to define clear principles for re-appraisal. Finally, there was a need to incorporate in the guidelines methodological advances in sources of evidence that are specific to the Portuguese context, related mainly to costs and quality of life evaluation.

Following the publication of Ordinance No. 391/2019, of 30 October, approving the principles and a brief description of the methodological guidelines for economic

evaluation studies of health technologies in Portugal, this more detailed document is here presented which makes recommendations on the methodology of economic evaluation in order for the best evidence to be used in support the decision making.

b. Objective

This document presents the guidelines for economic evaluation of new health technologies, including drugs and medical devices. However, these guidelines are more focused on therapeutic innovations, since at the time of their preparation, the methods and process of appraisal of medical devices was still at an early stage of development, still requiring prior adoption of clinical guidelines to measure their effectiveness.

c. Team

According to the statutes of INFARMED, I.P., the Health Technology Assessment Commission (CATS), which supports the Health Technology Assessment Directorate (DATS) created by Decree-Law 97/2015, of 1 June, began operating in June 2016. The remit of CATS is, within the scope of the SiNATS, to issue advice and recommendations, appraise economic evaluation studies and propose appropriate measures to public health and NHS interests regarding health technologies.

INFARMED's Board of Directors (BoD) invited Prof. Julian Perelman, as vice-chair and economist of the Executive Committee of CATS (CE-CATS), to constitute a working group to review the Methodological Guidelines for economic evaluation studies of health technologies. The working group included the eight economists who were part of the CATS when this review process was started. The choice of the CATS economists is explained essentially for two reasons: 1) they had experience on a number of economic evaluation appraisal processes submitted for the funding of drugs and had thus faced, in practice, the challenges that could benefit from extended guidance; 2) as those undertaking the evaluations, they were aware of the need of harmonisation to ensure consistency across appraisals.

Also invited to coordinate the scientific development of the guidelines was Prof. Mark Sculpher, from the University of York, United Kingdom, an internationally recognised academic with an outstanding record in the economic evaluation of health technologies.

d. Methods

With a view to updating the methodological guidelines published in 1998, the revision process started with the listing of topics to be included in the new guidelines in accordance with the most recent advances in this field. The list of topics was circulated and discussed among authors, until a consensual list was reached. Then, each topic was allocated to a group of at least two persons according to their personal interests and expertise. Each group was then asked to produce a short overview (of maximum 4,500 words) highlighting the relevance of the topic, describing the results of a brief literature review on the topic, and listing possible options for guidance. Note that the literature review consisted of: a summary of the 1998 Portuguese methodological guidelines; a summary of the content of the guidelines from other countries and the most recent developments on the topic identified in publications with peer review. This work was

largely facilitated by the review of European guidelines produced by the European Network for Health Technology Assessment - EUnetHTA [1], of which the INFARMED, I.P. takes part since 2006. Each group was also asked to identify their preferences on how the guidelines should be revised and formulated, in the light of their findings.

After this preparation stage, a two-day meeting with all the authors was held in Lisbon in April 2018. Each group briefly presented their literature review and arguments on whether and how the guidelines should be revised. Each topic was extensively discussed until a consensus was reached. The content of the meeting was recorded and Prof. Joana Alves (Escola Nacional de Saúde Pública, Universidade Nova de Lisboa) produced minutes, which were used in the next stage of the process.

After that meeting, the authors produced a first version of the guidelines, which included for each topic a one-line summary, a short summary (maximum 150 words), and the full contents of the guideline (maximum 1,000 words). This first version was extensively commented by the coordination team and the external expert, and sent back to authors, who revised their documents in accordance to the suggestions and comments received. The revised version of all chapters was then compiled and organized into a single document, which was sent for revision to the members of the CE-CATS not directly involved in the process (Dr. José Vinhas and Dr. António Melo Gouveia), in particular of the chapters devoted to the evaluation of treatment effects, in order to ensure its agreement with the therapeutic guidelines. After including their suggestions, the coordinators sent the revised version to all authors, for a final and complete revision, and approval of the complete document. The final document was discussed and revised by the INFARMED, I.P.'s Board of Directors and the Assistant Secretary of State for Health, Dr. Francisco Ramos.

In May 2019, the final document was subject to public consultation. To this end, a group of entities and individuals was contacted to provide their opinions on the proposal for the methodological guidelines. Written comments were received from the following entities and individuals: Lisbon Cerebral Palsy Association (APCL), Portuguese Pharmaceutical Industry Association (APIFARMA), Portuguese Association of Generics and Biosimilar Medicines (APOGEN), National Association of Pharmacies (ANF), Portuguese Chapter of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Council of Rectors of Portuguese Universities (CRUP), Exigo Consultores, Mais Participação Melhor Saúde, Portuguese Pharmacists' Association, Portuguese Medical Association, Central Administration of the Health System, I.P. (ACSS), and Professor Pedro Pita Barros (Universidade Nova de Lisboa). Upon receipt of these comments, a discussion session was organized at the INFARMED I.P. on July 19, 2019, with the presence of the aforementioned entities, two of the authors of this document, the CE-CATS, the Executive Board of the INFARMED, I.P., and the Assistant Secretary of State for Health.

1. Principles of appraisal

The recommendations detailed here aim to guide the development of economic evaluation studies, and also to guide the appraisal of the economic evidence submitted by companies. In appraising the evidence, its adequacy, scope, and quality should be considered, with a view to identify the results on economic value that are more relevant and valid to support decision making. To determine economic value, it is essential to compare the gains for health resulting from the new technology with the additional costs it may entail for the NHS.

Given that circumstances influencing the economic value may change over time (e.g. price reductions), the guidance detailed here considers a dynamic evaluation process, informing not only a first appraisal but also possible re-appraisals. Such dynamic appraisal process also lends itself to be used to promote activities for developing new evidence aiming to reduce uncertainty in the results. This means that uncertainty should be explicitly considered in the evaluation process. Therefore, all evidence should be appraised in terms of remaining uncertainty (focusing not only on clinical effectiveness, but also on cost-effectiveness and budget impact), with a view to identifying a list of significant uncertainties.

1. These Methodological Guidelines specify the principles and methods used to produce evidence of the economic value to support decision making in the reimbursement/funding process.
 - 1.1. The guidance detailed here is to be used both by companies in preparing the evidence to be submitted to the INFARMED, I.P., and by the independent experts in appraising the evidence submitted.
 - 1.2. The Methodological Guidelines are intended to support the appraisal of the economic evidence submitted. In appraising the evidence, its adequacy, scope, and quality should be considered, with a view to identify the results of the economic value of health technologies that are more relevant and valid to support decision making. It is important to recognise that the evaluation conditions may change over time (e.g. changes to the price of health technologies, new comparators emerging, or new evidence becoming available), meaning that the magnitude of economic value may also change. Therefore, the appraisal process should be dynamic and should inform not only the first appraisal but also the renegotiations of financing conditions (re-appraisal).
 - 1.2.1. Uncertainty typically results from the fact that the studies on which the decision is based are sampled studies. However, uncertainty may also be associated with other aspects, such as the assumptions of the model, the lack of representativeness of the evidence regarding the context of the decision, or the poor quality of the evidence, thus introducing the possibility of bias. Uncertainty in the evidence-base may result in uncertainty in the final decision itself, thus introducing the possibility that the decision made is not the right one, with consequences for the patients' health. Thus, when there is significant uncertainty, additional evidence should be encouraged in

order to mitigate against the source(s) of that uncertainty and to allow for a timely review of the decision (in re-appraisal), thus avoiding potential negative consequences for future patients (this topic will be further discussed in Section 14).

- 1.2.2. Uncertainty may also result from the external validity of the evidence being questionable. In this case, health outcomes and/or costs related to the use of the technology in the Portuguese context should be confirmed. Such evidence should be considered at the re-appraisal stage.
- 1.3. At all stages of the appraisal (including re-appraisals) it is essential to identify all relevant sources of uncertainty (i.e. those that may have significant implications). The decision-making process should adequately judge the uncertainties identified and possibly consider the conduct of future additional studies that deal with the uncertainties identified. However, it is important to recognise that once a technology is available in clinical practice, it may not be possible to conduct a new randomised clinical trial (RCT) (that generates comparative evidence), and therefore the ability to obtain relative efficacy information may become limited. In this and other cases, it is important to consider whether there is a possibility that the intended research will not be conducted and will not be reported (this topic will be further discussed in Section 14).
- 1.4. It is worth recognising that the level of uncertainty and the relevance of uncertainty, and therefore the need for additional research, depend on the price of the technology being evaluated. Uncertainty reaches the highest level at the price for which the technology becomes cost effective (i.e. when the incremental cost-effectiveness ratio (ICER) equals the "cost-effectiveness threshold" value (see Section 14)). Lower prices lead to a reduction of uncertainty in the decision, and if the price reduction is sufficient, the collection of additional evidence may no longer be justified.
2. The appraisal process aims to identify the evidence on (expected) health effects and costs (expected) for the NHS associated with the (new) technology, in relation to relevant alternatives, as well as to describe the uncertainty and identify its sources.
3. Decision making requires weighing the expected gains in health of the new technology against the additional costs it may entail for the NHS.
 - 3.1. To support contract negotiations, all analyses submitted by the company must calculate the opportunity costs using cost-effectiveness threshold ranges between 10,000 EUR per quality-adjusted life year (QALY) and 100,000 EUR per QALY.
 - 3.2. When submitting the cost-effectiveness evidence, the company sets a price for the technology under evaluation. However, the final price is only determined after negotiation. Therefore, and to usefully inform the decision-making process, the evaluation should identify the price at which the technology becomes cost-effective for the threshold ranges mentioned in the preceding paragraph.

2. Comparators

The economic evaluation should compare the new technology to all other health care options relevant to the disease or clinical condition in focus, as defined in the scope of the pharmacotherapeutic evaluation and considered by CATS.

Relevant comparators are all therapeutic alternatives available in Portugal and may include therapeutic sequences, inactive therapeutic options, non-therapeutic active treatment options, and include alternative rules to start-stop the new technology.

When the most efficient alternative is clearly established, the comparison can be made with only this one.

1. The selection of comparators is made during the scoping stage, conducted by CATS, i.e. prior to the evaluation of the pharmacotherapeutic and economic evidence. At this stage, the selection of comparators should be inclusive, and all potentially relevant comparators should be identified.
2. The economic evaluation is comparative, since the incremental costs and consequences of a new technology depend on the costs and consequences of the alternative(s) with which it is compared. Restricting the comparators ex ante may exclude the most efficient technology, leading the NHS to opt for technologies with excessive incremental costs for their incremental consequences.
3. Comparators should include all the options that could be taken to manage the disease in the absence of the new technology [2-5]. When considering an intervention as a comparator, no claims are being made about their effectiveness. Hence, an intervention should be included as a comparator even if it is thought that it may be less beneficial than the new technology.
4. The standard of care may comprise of various technologies and/or interventions. The economic evaluation must compare the new technology with all relevant comparators in a fully incremental analysis, where each is included individually rather than blended into a single comparator.
5. When the most efficient alternative is clearly established, the comparison can be made with only this one. In justifying comparing the new technology against a single alternative, the criterion used to measure efficiency, and the result of this measurement, should be clearly stated.
6. In a blended comparator, the comparator technologies are considered together. The average of the costs and consequences of each comparator technology, weighted by their relative proportion in the blend, are used to define the costs and health consequences of the blended comparator. Blended comparators are not recommended given that these will not be as cost-effective as the most cost-effective technology in the blend.
7. All strategies (or technologies) that are licensed for the target population and any subgroups, or that are not licensed but are being used in clinical practice (well established off-label use) should be included as comparators.
8. Non-active management (or do nothing) options include best supportive care and watchful waiting. Best supportive care aims to improve or maintain patients' quality of life, not intending to cure or

halt disease progression. Watchful waiting consists of monitoring patients until treatment is warranted. These options should be included as relevant comparators, if deemed by the CATS to be an option in clinical practice in Portugal for the management of the target disease of the new technology.

9. Sequencing refers to situations where the technology is provided after treatment failure with a previous technology. Treatment sequences most often occur in chronic conditions where treatment intensification or treatment withdrawal is intended due to lack of efficacy or toxicity (e.g. diabetes, rheumatoid arthritis, psoriasis) and in evaluations of oncology drugs, particularly in early-stage cancer [6]. Modelling treatment sequences may be important to allow quantifying long-term outcomes, and define the line of treatment at which the new technology is best placed. For example, a sequence starting with a less effective and cheaper technology then moving on to a more effective and costlier technology may achieve similar benefits at lower costs. Alternative sequences of comparator interventions and, where relevant, sequences including the new technology in different treatment regimens should be considered, if such is in line with the CATS pharmacotherapeutic recommendation.
10. Start-stop rules refer to the criteria to decide to start or stop a technology in a given patient. The consideration of start-stop criteria can improve cost-effectiveness by obtaining health benefits at lower cost, for example, when treatment is continued only in those patients who have responded or when the new technology is temporarily stopped during remission and restarted if the condition exacerbates. Start-stop rules should be included as alternative options for the use of the new technology, if it is in line with the CATS pharmacotherapeutic recommendation.

3. Population and subgroups

The economic evaluation should assess the new technology in the entire target population and in relevant subgroups, as defined in the scope of the pharmacotherapeutic evaluation and considered in the pharmacotherapeutic recommendation by CATS.

Subgroup analyses should be conducted when there is evidence of heterogeneity in the target population that may determine cost-effectiveness. Additional subgroups may be considered in the context of the economic evaluation, provided that they are duly justified. Heterogeneity may relate to differences in the effectiveness of the new technology, differences in its costs, baseline risk of events or progression, and other model parameters that affect the costs or the health benefits of the new technology compared to its comparators.

1. In the evaluation of new technologies, the target population consists of the population for which funding is requested, i.e., the target population should reflect the group of individuals in whom the new technology is intended to be used [3]. Economic evaluation should assess the new technology in the target population and any relevant subgroups for which the CATS has concluded that there is an Added Therapeutic Value (ATV).
2. Patients within the target population may differ in ways that determine the magnitude of the health benefits achieved from a technology or its total costs. If the differences in benefits or costs can be explained by characteristics known at the time of deciding which technology to use, these characteristics can be used to define 'subgroups' of patients [7].
3. If a new technology is cost-effective in some subgroups but not in others, reimbursing it in the entire target population represents a net loss of health. Subgroup analysis ensures that the new technology is only made available to the patients in whom it is cost-effective.
4. Subgroup analyses should be conducted when there is evidence of heterogeneity in the target population that may determine cost-effectiveness. Hence, additional subgroups may be considered in the context of the economic evaluation, provided that they are duly justified. The heterogeneity may relate to differences in the effectiveness of the new technology (i.e. modification of treatment effect), differences in its costs, baseline risk of events or progression, and other model parameters. Differences observed in any of these parameters constitute a valid reason for the subgroup analyses as cost-effectiveness will be affected.
5. The presence of heterogeneity is difficult to establish, particularly as studies showing differences between potential subgroups have typically not been designed to identify such differences causally or are powered to generate definitive conclusions. Hence, the justification for subgroups needs to be supported by not only empirical evidence but also a robust clinical or cost-effectiveness rationale.
6. Any practical or process implications of identifying the subgroup a patient belongs to, such as the application of a diagnostic test, should be considered in the cost-effectiveness analysis.

7. Despite subgroup analyses being recommended, the definition needs to be made carefully:
 - 7.1. Subgroups defined on the basis of treatment effect modification must have been pre-specified in the scoping process, and their relevance must be appraised within the clinical evaluation process. In these subgroups, the cost-effectiveness analysis can use a subgroup-specific relative treatment effect.
 - 7.2. Subgroup analyses not based on treatment effect modification may be important for the economic evaluation if the differences amongst subgroups affect cost-effectiveness even if they do not affect relative efficacy. For example, parameters such as baseline risks, treatment costs, or Health-Related Quality of Life (HRQoL) may differ between subgroups and affect the cost-effectiveness outcomes. A clinical rationale, supported by robust and relevant evidence, is required to quantify the assumed differences. The analysis of subgroups which were not assessed and accepted in the pharmacotherapeutic assessment should assume that the relative treatment effect is equal to that of the entire target population, i.e. no modification in the treatment effect.
 - 7.3. If the marketing authorisation (MA) refers to a subgroup of the regulatory trial, the treatment effect to be considered should refer to this subgroup and not that of the entire population. In addition, a sensitivity analysis should be presented that uses the treatment effect from the entire population.
8. Subgroup analyses should report separate results for all subgroups, even those for whom the technology may not be cost-effective.

4. Evaluation of treatment effect

The economic evaluation should be based on the assessment of all effectiveness evidence contained in the CATS pharmacotherapeutic recommendation. However, there may be additional methodological and evidence requirements for the assessment of economic value of the technology.

Differences between the evidence used, analysed and reviewed by the CATS to define the ATV and the evidence used in the economic evaluation have to be appropriately justified.

Where available, evidence from randomised clinical trials (RCTs) should be used to evaluate and quantify the effectiveness of the interventions of interest. The use of evidence from non-randomised studies is permitted to: (i) inform scenario analysis when non-randomized trials are conducted in the Portuguese context, even in the presence of RCTs; (ii) inform the reference case when there is no evidence produced in RCTs, accompanied by a sensitivity analysis that varies the effect parameter up to the value corresponding to the assumption that the new technology has no effect; (iii) based on the time extrapolation of the treatment effect beyond the follow-up period of randomized controlled trials, complemented by a sensitivity analysis to alternative assumptions about the duration of the treatment effect; (iv) and to inform disconnected networks of evidence. Preference is given to non-randomized studies conducted in Portugal.

Adequate methodologies such as meta-analysis or network meta-analysis should be used to quantitatively synthesise effectiveness evidence. The use of evidence synthesis methods requires an appropriate assessment of the quality of the studies and of heterogeneity of the results across studies.

1. This section relates to the quantification of the effectiveness of alternative interventions in the economic model, including the quantification of uncertainty about these values (e.g. expressed through standard error or confidence interval).
2. The principles and methodologies applied should follow the guidelines for pharmacotherapeutic evaluation prepared by the CATS and approved by the Board of Directors of the INFARMED, I.P. However, there may be additional methodological and evidence requirements needed to quantify the treatment effect(s) in the economic model. Differences between the evidence used, analysed and reviewed by the CATS to define the ATV and the evidence used in the economic evaluation should be duly justified.
3. For the quantification of an intervention's effectiveness, all available relevant evidence should be considered, preferably evidence from RCTs. However, the use of evidence from non-randomized trials may be permitted in the following circumstances:

- To inform scenario analyses, when non-randomized studies are conducted in the Portuguese context, even in the presence of randomized studies.
 - To inform the reference case, when there is no evidence of RCTs, accompanied by sensitivity analysis in which the effect value varies up to the value corresponding to the hypothesis of absence of effect of the new technology. This sensitivity analysis will allow to understand the impact on the costs and health consequences in case the non-randomized trial evidence is biased in favour of the new technology.
 - As a basis for the temporal extrapolation of the treatment effect beyond the follow-up of the RCTs, complemented with a sensitivity analysis to alternative assumptions about the duration of the treatment effect.
 - To inform disconnected evidence networks (see point 8 below).
4. All evidence considered should be critically appraised. The limitations of the evidence-base, and attempts to adjust for these, should be described as fully as possible and its implications appropriately reflected in the analysis of uncertainty.
 5. Where the effectiveness evidence focuses on intermediate (or surrogate) endpoints, it is necessary to justify its association to final outcomes as implemented in the model, in accordance with CATS recommendations (see Section 10).
 6. As per the guidelines on pharmacotherapeutic evaluation prepared by the CATS and approved by the Board of Directors of the INFARMED, I.P., when more than one source of information is identified, the studies should preferably be summarized together, using appropriate methodologies such as meta-analysis or network meta-analysis.
 7. The validity of the results of the synthesis should be discussed in context of the validity of the individual studies that feed onto it and the potential risk of publication bias, again in line with the pharmacotherapeutic evaluation performed by the CATS.
 8. When the evidence base includes only randomized studies but has at least two disconnected elements (disconnected network), other approaches may be taken in order to link the separate network elements. These include, by order of preference: (i) broadening the evidence network to consider 2nd and 3rd order indirectness [8]; (ii) broadening the evidence base to include, for example, other populations (e.g. bring adult data to inform an evaluation on treatments for children); (iii) introduce assumptions on treatment effects (e.g. equivalence or exchangeability); or (iv) use of unanchored adjustment methods (unanchored) (Matching-Adjusted Indirect Comparisons- MAIC, or Simulated Treatment Comparisons – STC), observational data, or elicited expert opinion to inform the missing relative treatment effect(s) of technologies. The results of such analyses should be interpreted with caution.
 9. When evidence of effectiveness includes single-arm observational studies, population-adjusted indirect comparison methods may be used (MAIC or STC), providing that full justification is given and that best methodological practice is followed. Its results should be interpreted with caution.

5. Time horizon

The time horizon should be sufficiently long to include all important differences in costs and consequences of all technologies under comparison. The time horizon must be identical for costs and consequences. Shorter time horizons may be considered if consequences and costs occur over a short period, but this choice must be clearly justified.

1. The time horizon used in the cost-effectiveness model should be sufficiently long to include all important differences in costs and consequences of all technologies under comparison, including any intended and unintended effects related to the treatment or the condition. In general, a lifetime time horizon is the most appropriate approach not only for chronic diseases but also for acute conditions where there may be effects over mortality or long-term disability.
2. The time horizon must be identical for costs and consequences, so that equal weight is given to each dimension.
3. Time horizons longer than the patients' lifetime will only be accepted as sensitivity analysis. These could be relevant, for example, in treating infectious diseases where transmission to others is possible (those not included in the initial population and who may live longer than this initial population). Although this is theoretically relevant, modelling such very long-term effects present additional (and likely substantial) uncertainty.
4. Sensitivity analyses (see Section 14) can consider alternative time horizons shorter than lifetime.

6. Analytical techniques

We recommend that cost-effectiveness studies are carried out with the consequences expressed as Quality-Adjusted Life Years (QALYs). QALYs are preferred because they: (i) incorporate Health-Related Quality of Life (HRQoL); (ii) account for the patients' perspective and society's preferences; (iii) allow the comparison of different treatments for different diseases; and (iv) have been widely adopted by national health technology assessment agencies. Health consequences should not be expressed in monetary terms.

1. Health consequences may be expressed as follows:
 - In clinical units, obtained directly from clinical studies, including surrogate outcomes;
 - Using composite measures that combine gains in life expectancy and HRQoL, usually using quality-adjusted life years (QALY).
2. Expressing health consequences as QALYs is recommended, because it: (i) systematically incorporates HRQoL; (ii) accounts for patients' perspective and society's preferences; (iii) allows comparing different treatments for different diseases using a common metric, and in this way allowing appropriate consideration for the opportunity cost of financing a new technology; and (iv) are the most common measure in the economic evaluation literature, and have been widely used by national health technology assessment agencies.
3. Note that instruments that enable QALY calculation may not always be available in relevant randomized clinical trials. In this case, the use of other forms of evidence is recommended (see Section 12), rather than expressing consequences in units other than QALYs.
4. Decisions must be taken that are the most appropriate in the health sector; that is, the objective of health technologies assessment is to enhance population health, taking into account the available budget in the health sector. Therefore, cost-benefit analyses with consequences expressed in monetary terms are not accepted.
5. Costs should be evaluated in accordance with the principles mentioned in Sections 7 and 8, regardless of the technique of analysis.

7. Perspective

The perspective on costs for the reference case should be that of the NHS. The perspective on consequences should consider all health effects for current patients. The incremental cost-effectiveness ratio (ICER) should be calculated according to this perspective, which forms the basis for decision-making.

Costs and/or savings falling in other public and/or private costs sectors may be quantified and presented in a scenario analysis but should not be included in the ICER. The quantification of the costs and/or savings not ascribed to the NHS budget should be described in detail and disaggregated as follows: costs and/or savings for other sectors of the State (not ascribed to the NHS budget); and costs and/or savings for the patient, caregivers and relatives. The submission can also present and quantify the impact on the working capacity of the patient, caregivers and relatives, measured in terms of days, and the consequences for health and quality of life for caregivers and relatives.

1. The perspective is the viewpoint from which the intervention's and comparator's costs and consequences are evaluated. The definition and explanation of the perspective that is adopted is fundamental to economic evaluation, since it defines which resources and consequences should be included in the analysis.
2. In the reference case, the perspective on costs should be that of the NHS. The perspective on consequences should consider all health effects for current patients. This approach aims for reimbursement decisions to maximise the population health according to the availability of NHS resources, thus providing support for resource allocation decisions within the NHS. By contrast, the societal perspective implies the ability to quantify, and aggregate, health benefits gained and health benefits lost due to opportunity costs across the various sectors, which would be extremely complex [10].
3. The evaluation in the reference case should focus on current patients and exclude any consequences or costs for future patients (e.g., those infected by current patients), families and informal caregivers.
4. Clinical consequences or costs (and/or savings) falling in other public and/or private costs sectors may be quantified and presented in a scenario analysis. The nature and relevance of these costs should be clearly justified and supported by sufficient and adequate evidence. However, these should not be included in the reference-case ICER and no additional ICER including these should be presented. The quantification of the costs and/or savings not ascribed to the NHS budget should be described in detail and disaggregated as follows: costs and/or savings for other sectors of the State (not ascribed to the NHS budget); costs and/or savings for the patient, caregivers and relatives; and clinical consequences for caregivers and relatives.

5. The impact on the working capacity of the patient, caregivers and relatives, measured in terms of days, as well as the consequences for health and quality of life for caregivers and relatives, can also be presented.

8. Identification, measurement and valuation of costs

All health care resources relevant to the analysis should be identified. Since the preferred perspective is that of the NHS, all costs falling on the NHS budget and relevant to the technology under assessment should be described. Detailed information on the health care resources used (measured in physical units) and how they are valued (unit prices or costs) should be reported separately. The information on the use of these resources should be based on Portuguese clinical practice. If this is not possible, and analyses are based on international data, these resource use should be validated by national experts, considering national clinical practice.

National published sources (as Portuguese NHS tariffs) are preferred for valuing resources. The use of other sources has to be justified. For the purposes of the evaluation, unit costs are to include the Value Added Tax (VAT) and be adjusted for inflation when necessary.

1. The identification of health care resources is as relevant as the measurement of effectiveness. However, much less attention is given to this topic in comparison to what happens with effectiveness data, even though the estimation of treatment costs is a fundamental element in the calculation of the ICER [11].
2. Health care resources to be considered must be aligned with the NHS perspective, i.e., only costs accruing to the NHS budget must be considered.
3. However, social care costs, such as long-term care or palliative care, when financed by the NHS, should be considered in the reference case.
4. Costs that are unrelated to the disease, such as future unrelated costs of remaining alive should be left out of the analysis. This type of cost should not be included in the analysis because it may penalize treatments that increase survival, by the inclusion of costs that are unrelated to the disease.
5. Detailed information on the health care resources used (measured in physical units) and how they are valued (unit prices or costs) should be reported separately.
6. Regarding treatment costs, detailed information is to be provided on:
 - The price of the drug package, pharmaceutical form specifying the number of tablets, vials, etc. in the pack, dosages, etc., and any other relevant information;
 - The price of the comparator(s), pharmaceutical form specifying the number of tablets, vials, etc. in the pack, dosages, etc., and any other relevant information;
 - Recommended treatment (dosage, number of administrations, duration, etc.);

- Cost per tablet, vial, etc., and total costs per month and/or per cycle;
7. The calculation of the units of drugs required should consider losses (wasted), for example due to dosing schedules.
 8. The identification of relevant health care resources should be based on national practice, either through direct data collection or by making use of national published sources. If expert panels are used to gather information, this should be explicitly stated, and these panels should follow the rules set out in Section 12.
 9. If international data are used to account for health care resource consumption, expert panels of local professionals must be used to validate results. Further guidance on this topic can be found in the section on expert opinions (Section 12).
 10. Unit costs or prices should be based on national published sources. Health care resources should be valued with unit costs or prices derived within the NHS. Published official tariffs for the NHS are preferred, as they are valid proxies of unit costs in this context. The use of other sources of unit prices or costs must be clearly justified and subject to sensitivity analysis.
 11. When using NHS tariffs, the most recent version in use by the NHS is the one that should be selected for the purposes of valuing resources.
 12. Unit prices or costs should be those effectively paid by the NHS. Therefore, VAT should be included. Patient co-payments or user charges are to be excluded.
 13. With the exception of NHS tariffs, all prices and costs should be adjusted for inflation at the observed rate if these are more than two years old at the time of submission of the economic evaluation study. Data on inflation should be obtained from official sources like the Instituto Nacional de Estadística and correspond to the annual average of the Consumer Price Index except housing.
 14. If the time horizon of the economic analysis is over one year, all costs have to be discounted (See Section 16).

9. Measurement and valuation of health effects

The EQ-5D-5L is the preferred measure for assessing health-related quality of life (HRQoL), with Portuguese tariffs. If information is not available based on the EQ-5D-5L, and as long as there is no mapping algorithm, the EQ-5D-3L with the Portuguese tariff can be used to calculate the QALYs. Other preference-based generic measures can also be used but their choice must be justified. When using other instruments, Portuguese tariffs should also be used if available.

If HRQoL was not measured in the clinical studies used to evaluate treatment effectiveness, EQ-5D or other preference-based generic data can be sourced from: (i) the literature; (ii) other observational studies; (iii) surveys designed for this purpose. In the absence of relevant utility data from one of the aforementioned generic preference-based measures, mapping data to the EQ-5D may be used alternatively from other disease-specific or generic preference-based instruments of HRQoL. When presenting mapped utilities, a clear description should be presented of the mapping algorithm and of the study on which the mapping function was based on. Algorithms published in peer-reviewed international journals are preferred.

1. Health effects should be expressed in QALYs. Changes in quantity and quality of life should be reported separately along with a clear explanation of how these measures were combined, the assumptions made and the methods used to estimate the QALYs.
2. HRQoL measurements should be elicited from relevant patient populations.
3. The EQ-5D-5L [12] is the preferred measure to assess HRQoL. Portuguese tariffs should be used [13]. If the information is not available based on the EQ-5D-5L, the mapping algorithm for the Portuguese tariffs should be used as soon as it is published. However, while the mapping algorithm is not available, the EQ-5D-3L [14] can be used with the Portuguese tariffs [15]. If the EQ-5D is not available, other generic preference-based measures such as SF-6D [16-18] or HUI (HUI 1, HUI 2 or HUI 3) [19-21] may also be used, but their choice should be justified.
4. When they exist, the published Portuguese tariffs should be used [18]. In the absence of the Portuguese tariffs (i.e. when another preference-based instrument is used such as the HUI), it is possible to use preference-based tariffs from international studies, subject to a critical analysis of their quality. However, the population from which the preferences are derived should be clearly described along with their relevance to the Portuguese context.
5. If HRQoL was not measured in the clinical studies used to evaluate treatment effectiveness, EQ-5D or other preference-based generic data can be sourced from: (i) the literature; (ii) other observational studies; (iii) surveys designed for this purpose.

6. When obtained from the literature, the methods of data identification should be clear, systematic, detailed and transparent, and the justification for choosing a particular data set should be clearly explained, in accordance to Section 4. When HRQoL measures are obtained from observational studies, these should be fully described and the quality of the evidence, as well as its suitability to the Portuguese context, should be discussed. When HRQoL is obtained from surveys designed for this purpose, these should be fully described and the study design justified, and its suitability to the context under study should be discussed. In any of these situations, the data should be adapted to the context under analysis and the methods of adaptation should be fully described and justified.
7. In the absence of relevant utility data from one of the aforementioned generic measures, mapping data to the EQ-5D may be used alternatively from other disease specific or generic preference-based instruments of HRQoL. When presenting mapped utilities, a clear description should be presented of the mapping algorithm, of the study on which the mapping function was based on, and a clear justification of the relevance of the measure to the relevant population. The selected measure must be fit for purpose, that is, it should accurately describe the health states arising in the disease in question. Details should be provided regarding the derivation, validation and relevance of any psychometric instrument used along with a description of its supporting published evidence. This type of analysis implies that utility evidence used in the cost-effectiveness model is likely to be associated with an increased uncertainty level. In addition, algorithms published in peer-reviewed international journals are preferred.
8. When the EQ-5D is seen as not suitable, empirical evidence on the lack of content validity and/or lack of sensitivity to change for the EQ-5D should be provided, demonstrating that key dimensions of health assessment are missing. In these cases, other measures may be used, including new dimensions developed to add/supplement existing preference-based generic instruments (e.g. bolt-ons), which should be clearly justified.

10. Study design and modelling methods

The economic evaluation typically requires decision analytic modelling. Modelling allows combining multiple data sources and facilitates meaningful temporal extrapolation, which is often required. Model conceptualisation is an important step of the evaluation. Therefore, the submission should include a full description of how the model reflects the natural course of the disease and the impact of treatment(s) on the disease, health outcomes and health costs; a full description of the sources of information considered and the assumptions made (with their rationale) and a full list of the parameters.

Different approaches can be used to implement cost-effectiveness analytic models, from decision trees evaluated in a cohort to individual simulation models. These approaches have different strengths and limitations and different levels of complexity and transparency. The choice of modelling approach should always be justified, using available evidence to support the adequacy of alternative assumptions and their implications (such as for extrapolations). If it is possible and reasonable to apply different approaches, it is preferable to implement the simplest approach (parsimony principle).

1. There are two alternative approaches to evaluating cost-effectiveness: within trial analysis and decision modelling. Within trial analysis is rarely an appropriate study design for economic evaluation [22]. Decision modelling, contrarily to within trial analyses, allow multiple data sources (primary and/or secondary) to be combined and facilitate extrapolation and are the most commonly used approach. Decision analytic modelling involves describing the natural course of the disease and how interventions affect it using a series of health states or events.
2. Specifying a cost-effectiveness model typically involves several stages. For the purposes of these methodological guidelines, the stages were defined as follows:
 - 2.1 Conceptualisation: the process of translating the decision problem into a model with a given structure [2, 23].
 - 2.2 Parameterisation: the process of selecting, analysing and manipulating the relevant data so that it can be used to define the model.
 - 2.3 Implementation: the process of building the model in a software platform.

Model conceptualisation and parameterization

3. The process of model conceptualisation, which aims to design an appropriate model structure, requires knowledge about the disease, its impact on patients, and its management by the health care system as well as knowledge about the effects of the new technology and its comparators (e.g. which transitions are affected by the intervention in the cost-effectiveness model and the time profile of such effects; how to extrapolate to the longer term).
4. The cost-effectiveness model should be relevant to the decision of reimbursement of the new technology and should be credible regarding the impact of the new technology and its comparators on patients and on the health care system [24, 25].
5. The description of the model conceptualisation aims to ensure the transparency of the model's structure and its assumptions and aims to facilitate its critical appraisal. This description should be brief and include [26-28]:
 - 5.1 The sources of evidence that informed model conceptualisation (e.g. literature review of previous cost-effectiveness models, review of literature on the disease, discussions with clinical experts, etc.).
 - 5.2 The summary description of the natural course of the disease, its impact on HRQoL and other health outcomes, and the impact of the new technology and its comparators on the patients. In other words, a summary of the consequences of the disease and its progression, and what outcomes are affected by the new technology and its comparators.
 - 5.3 The summary description of how the health care system manages the disease, the resources involved and the impact of the new technology and its comparators on the progress of the disease, HRQoL, on resources and/or costs.
 - 5.4 The description, in text and in a diagram, of the model structure. It is important that the diagram and text describe how the model assumes that the new technology and its comparators act in the disease (e.g., improve quality of life in health state X; decrease the risk of progression to health state Y; etc.).
 - 5.5 A list of the assumptions of the model, together with their rationale.
6. It is important that the parameterisation of the economic model is made explicit using:
 - 6.1 A diagram representing the health states considered and transitions allowed between them,
 - 6.2 A description of the model, and
 - 6.3 A list of all parameters required to implement the model structure, highlighting all treatment related parameters. All assumptions underpinning the model and extrapolations should be clearly identified, particularly in what concerns the duration and magnitude of treatment effects.

Model implementation

7. The most common types of models used for cost-effectiveness evaluation include decision trees, state-transition models, or models based on discrete events. Decision trees define a set of alternative pathways in the disease and their probability. The state-transition models evaluate possible transitions between health states, and their speed, to determine the average time spent in each health state. Models based on discrete events are defined based on the time between events, in order to determine the average time between events. Although most cost-effectiveness models use one or the other of these approaches, there may be situations where a hybrid model is adopted. In addition, the models can be evaluated in cohort or using simulation. Cohort formulations are the most commonly used approach to modelling in economic evaluation (decision trees or Markov models). Cohort formulations evaluate proportions of a cohort of patients. Alternatively, individual patient simulation models evaluate health state transitions or event history patient-by-patient, using enough simulations to allow obtaining mean results with sufficient precision.
8. Different modelling approaches have different strengths and limitations and different levels of complexity and transparency, which have been described in the published literature [29-31]. Each approach is also associated with particular assumptions; for example, Markov cohort models use the Markov property which imposes independence of past events. Such assumptions are simplifying and allow for a more efficient and simpler implementation, which highlights the trade-off between simplicity and transparency required in adopting increasingly complex modelling approaches. It is important to recognise that there are ways of circumventing the simplifying assumptions associated with cohort models, typically using more complex model structures, like tunnel health states. In practice, these changes in the structure model may lead to increased implementation burden, and may make these simpler modelling approaches less clear and transparent.
9. The modelling approach should be always justified, using available evidence to support the (in)adequacy of alternative assumptions. The modelling approaches chosen should not limit the feasibility of conducting a rigorous assessment of uncertainty. When alternative approaches can be reasonably applied, it is preferable to implement the simplest one (parsimony principle). There are a number of 'good practice' guidelines on modelling (e.g. Caro, Briggs [23]), and topic-specific guidance documents [32, 33] that should be followed.
10. Recent economic evaluations, mainly in advanced or metastatic cancers, have used a modelling approach different from those identified above, namely the partitioned survival analysis (PartSA) or area under the curve (AUC) modelling [34, 35].
 - 10.1 This approach cannot be considered a state-transition model as transitions between health states are not explicitly modelled. Instead, the PartSA approach uses, independently, data on multiple endpoints from a clinical study. The first outcome used is overall survival (OS), and others are composite, including both an intermediate outcome (such as progression) and the final survival outcome – typically progression free survival (PFS).
 - 10.2 The strengths and limitations of PartSA have only recently been formally considered [32]. PartSA approaches fail to take into account information on intermediate endpoints in extrapolations of the final OS endpoint. On the one hand, a PartSA model facilitates the exploration of different parametric survival functions, and allows applying equal hazard rates between different treatments after a set time-point. On the other hand, given the inability to reflect the conceptual links between

intermediate and final endpoints, these models do not allow for an adequate set of sensitivity analyses. For example, they do not allow the absence of treatment effect to be considered after disease progression.

- 10.3 It is important to recognise that an important role of modelling is that it permits extrapolation of costs and health consequences over a longer time horizon. Therefore, where PartSA models are used, the plausibility of its extrapolations should be judged and justified carefully, using not only evidence from pivotal clinical trial data on post-progression survival (for example considering multistate modelling [32]), but also including relevant long-term external evidence. It is necessary to demonstrate clinical plausibility for any post-progression treatment effects.

11. Evidence, or assumptions, related to other model parameters

An economic model often integrates multiple sources of evidence or assumptions that relate to parameters (other than relative effectiveness), such as probabilities and other state-transition parameters, health-related quality of life weights, unit costs for resource evaluation, disease incidence and prevalence. Evidence that relate to these parameters and assumptions should be identified using a systematic and explicit process, and the quality and appropriateness of each source for the context of care should be carefully considered. The evidence used in the model should be clearly described, and the omission of evidence sources identified in the systematic review should be justified.

1. This section relates to evidence on other parameters (besides relative effectiveness) or assumptions of the cost-effectiveness model. This includes, for example, probabilities and other transition or rate parameters as well as evidence on health-related quality of life weights, resource consumption or costs, correlations, incidence and prevalence. It also includes evidence used in support of assumptions underlying the model design and structure, for example, mechanistic evidence that could be used to justify assumptions of long-term benefit of a particular treatment.
2. Evidence, data sources and/or assumptions used to support each model parameter should be listed and justified. Particular detail should be provided on the assumptions and/or evidence used to support treatment effect extrapolations.
3. It is important that there is a systematic process (not necessarily comprehensive) for the identification of evidence [36, 37] and that the quality and relevance of the evidence identified is justified. External sources of evidence should be sought for, even where primary data on the quantity(ies) of interest is available from the pivotal trial.
 - 3.1 Evidence on some parameters is more difficult to be assumed generalisable across different contexts of health care – for example, costs and resource use are often specific to the health care system. In this case, submissions should explicitly attempt to identify evidence relevant to the Portuguese context. This can be done by conducting a specific search on national journals and can be complemented by consulting with recognized experts that may help identifying relevant published (or unpublished) literature as well as relevant primary data sources, if existing. Where available, evidence from the Portuguese context should be compared to evidence from other contexts, with appropriate consideration for quality, quantity and relevance.

- 3.2 The quality of the evidence should be appraised considering the research question. For example, it is generally considered that the best study design for quantifying health care resource use includes prospective data collection within a long-term naturalistic setting. In its absence, retrospective analysis of existing data sets (including routine data) can be used alternatively.
4. The exclusion of evidence identified in the systematic review should be justified. If multiple sources retain relevance, these need to be considered either using scenario analyses or by synthesising the different sources together using appropriate analytical methods [38]. Where there is evidence about a parameter that can be described as a function of other parameters, the inclusion of this evidence should be undertaken using multiparameter evidence synthesis (rather than calibration) [39].

12. Information provided by experts

When no empirical evidence on a parameter of interest exists, or its representativeness in the context of the target population is uncertain, the opinions of experts can be elicited. Gathering experts' opinions should be based on a structured and explicit process based on a set of methods defined in these guidelines (reference methods).

In reporting, the experts consulted should be identified and potential conflicts of interest stated.

1. When no empirical evidence is available to quantitatively characterize a parameter of interest to be included in the model or in the budget impact analysis, or when there is a need to justify or integrate the findings of existing empirical research to the population and context of the Portuguese NHS, the opinion of experts - a process called elicitation - can be used in the model. In order to incorporate this evidence into the model, experts should be asked to express their opinions quantitatively.
 - 1.1 Where any empirical evidence exists (being either sparse and/or not totally generalisable to the Portuguese context), this evidence cannot be ignored in the elicitation. Thus, such evidence should be provided to the experts before they are asked to elicit (so they can integrate it in their judgements). Through elicitation, experts may be asked to directly express the parameter of interest or, alternatively, to elicit differences between the context of interest and the estimates presented in the literature.
 - 1.2 The parameters of the model may not be elicited directly. Instead, other quantities related to the parameters of interest can be elicited. For example, probabilities can be elicited to inform an odds parameter. The quantities elicited should be justified and should be observable to experts. They should also be fit-for-purpose and ensure mathematical coherence with other parameters of the model, respecting the structure of the cost-effectiveness model [40].
 - 1.3 The future collection of empirical evidence should be considered for all elicited parameters (see Section 18).
2. To appropriately quantify the expected economic value and decision uncertainty, and to help decision makers take stock of the uncertainty level on the quantities of interest, it is important that uncertainty in knowledge is elicited from experts.
 - 2.1 Between-expert variation is common in health care, and it may arise from genuine heterogeneity in the population experts draw upon to formulate their judgements. Hence, to describe current beliefs over a particular parameter of interest, the views of multiple experts are desired. These are then typically pooled to form a single distribution (to be used in the economic model). It is desirable that between-expert variation is appropriately reflected in the uncertainty in the pooled distribution. The implications of between-expert variation for cost-effectiveness should also be assessed in the scenario analyses.

3. There is no methodological consensus on the elicitation of probability distributions, but there are some widely accepted guiding principles [41, 42].
 - 3.1 It is desirable that the process is transparent and tries to minimize biases and heuristics [41, 43]. Elicitation exercises should be designed, conducted, analysed and reported in a structured and explicit way. Thus, the protocol, a summary of the conduct of the elicitation process (e.g. who facilitated the exercise, any deviations to protocol accompanied by justification, etc.) and results of the exercise should be clearly reported.
 - 3.2 In what concerns expert selection:
 - 3.2.1 Experts are typically professionals with substantive expertise on the questions of interest. All criteria used for experts' selection and for panel composition must be explicitly described, listed and justified. The degree of expertise should be justified for each expert, for example, by mentioning the years of clinical experience and/or the scientific publication record of the experts. Experts should have the skills necessary to be able to elicit the quantities required. It is important that concepts such as probabilities (to the depth required by the method of elicitation used), uncertainty (how to represent it and its distinction from variability and heterogeneity), and potential biases and heuristics (and how these can be avoided) are communicated to the experts before elicitation.
 - 3.2.2 The composition of the panel of experts, including the names and affiliations of the individual experts, should be included in the study. Experts must declare their conflicts of interest, which must be annexed to the submission.
 - 3.2.3 The expert panel should represent, as much as possible, the range of possible views/settings, e.g. should represent different clinical contexts and different clinical practices. Methodologically there is no consensus on the number of experts needed for an accurate elicitation. However, we recommend that at least 5 experts are used.
 - 3.2.4 Anonymised responses from each of individual expert need to be supplied as well as group results pooled across all experts. The pooled estimate should be used in the reference case, and differences between experts in the values provided should be presented and explained (it may be useful to ask the individual experts to provide rationales for the elicited values). The implications of between-expert differences to cost-effectiveness should be quantified using sensitivity analyses.
 - 3.3 Given the decision-making context, assuring consistency in the methods used across appraisals is important. Thus, this methodological guideline defines a set of methods of elicitation as a reference case, which should be used in all submissions (see Table A1, in the appendix). Note that as new evidence emerges on methodological options for elicitation, the reference case should be redefined.
 - 3.4 Companies are encouraged to also submit data collected using other methodologies as long as this does not compromise obtaining valid estimates for the reference case. These scenarios will be considered where justified appropriately. For example, in scenario analysis the opinions of individual experts may be weighted using calibration to generate analytical weights for each individual expert [44]. Or group distributions can be obtained via a Delphi-type process [45], but only after the individual elicitation that is required for the reference case. The use of methods aimed at achieving

consensus is discouraged, since the interaction between experts is difficult to manage, even in the presence of an experienced facilitator [46].

13. Quantitative analyses of primary data to support modelling

The parameterization of economic evaluation models often requires statistical analysis to be performed on individual patient level data. Good methodological practice is crucial to guarantee that the evidence used to parameterise the models is of good quality and that the underlying parameter uncertainty is duly reflected. Statistical analyses conducted to inform model parameters that have not been fully published in peer reviewed literature should be documented in a statistical appendix. Data sources for each parameter should be listed and all assumptions justified.

1. Cost-effectiveness model parameterization often requires statistical analyses to be performed on individual patient level data. Statistical analyses conducted to inform the model parameters that have not been fully published in peer reviewed literature should be documented in a statistical appendix.
2. Thus, data sources for each parameter should be listed and all assumptions justified.
3. All analyses should be described in sufficient detail to allow assessing their appropriateness to inform the model. Where the information below is not available¹ in full elsewhere, this should be included in an appendix to the submission. This includes:
 - 3.1. A full description of the dataset(s) and rationale for selecting data sources where multiple options are available;
 - 3.2. A full description of the methods and results of analyses, including:
 - Rationale for the selection of the statistic model used (e.g. fixed effects vs. random effects models) and rationale for covariate selection;
 - Assessment of model validity, which may include examination of residuals, summary of statistical adequacy measures, hypothesis testing and, where external data is available, validation on alternative datasets;
 - Assessment of the missing data mechanism, identification and justification for the method for handling missing data and a discussion of any potential impact of missing data on the estimates;
 - The statistical software code to produce all the analyses;
 - The results of all analyses, including point estimates and associated variance;

¹Summaries included in conference proceedings and other short form publications are not considered full publications since they do not have the necessary level of detail to assess the suitability to inform the model parameters. Where only short form publication is available, the submission of a statistical appendix is still required.

- Descriptions of how the estimates obtained have been used in the cost-effectiveness model, and how uncertainty and associated correlation has been accounted for.
- 3.3. The reporting requirements described in the previous point have been structured into a checklist [47, 48] that can be used to both guide the analysis protocol and check that the analysis is reported transparently.
 4. Some types of regression analysis frequently applied in model parameterization merit special attention. Requirements specific to statistical analyses used to estimate transition probabilities and survival rates, and to map utility values are described next.
 5. For the calculation of transition probabilities, including survival analysis, it should be considered that:
 - 5.1. The values (deterministic analyses) and distributions (probabilistic analyses) assumed to describe transition probabilities in the cost-effectiveness model should be clearly identified. The data sources from which they were derived should be described and justified, as well as the methods used to derive them. The methods used should comply with good-practice guidelines [49]. Transition probabilities should be estimated for a reference intervention. Transition probabilities for the other interventions covered in the appraisal should be estimated by applying the relative treatment effects (Section 4) to the reference transition probabilities. Where possible, appropriate, and taking into account the evidence, to apply relative treatment effects, these should be correctly applied considering the relationship between the relative effectiveness measures (such as hazard ratios), transition probabilities and any other assumptions (such as proportional hazards). Where the use of relative treatment effects is not appropriate, the proposer must duly justify the alternative approach.
 - 5.2. When data relevant to the Portuguese context exists, these should be incorporated considering their quality. Any external sources of data used to adjust the probability estimates must be described and explicitly detail the methods of adjustment and required assumption(s).
 - 5.3. For the specific case of probabilities derived from a survival or time-to-event analysis, the selection of survival models should follow a systematic approach as proposed by Latimer and colleagues [50, 51]. The submission should provide sufficient detail to ascertain that model selection followed the process algorithm and that the uncertainty in the survival data was comprehensively explored. The analysis of alternative structural assumptions around the use of survival data is of particular importance where follow-up time over which survival data were collected is very short compared to the time horizon over which the data are extrapolated, which introduces considerable uncertainty.
 - 5.4. If the existing methodological guidelines in survival analysis significantly change over the next few years in response to specific situations not covered in models with parametric survival distributions [50], supplementary guidance will be published in order to cover the relevant methodological developments.
 - 5.5. Although regression methods for survival analysis of randomized clinical trials data should be applied to intention to treat (ITT) data, some trial protocols allow for treatment switching or crossover from the control to the experimental arm at predefined events. The switching between treatment arms will bias the estimates of

treatment effect if no adjustments are performed. The statistical analysis by which this adjustment is performed should follow the analytical framework proposed by Latimer and Abrams [52] and documented so as to demonstrate that it has been correctly implemented. Available statistical methods to account for treatment switching rely on strong assumptions [52], and hence the ITT analysis should always be presented alongside the treatment switching adjusted analysis.

6. Whenever possible, regression analysis on HRQoL should control for differences in baseline utility [53]. Where multiple observations per patient have been collected over time, longitudinal models should be used to control for potential heterogeneity within and between participants.
7. Mapping of HRQoL
 - 7.1. In the cases where mapping is accepted as an option for obtaining utility estimates (see Section 9), the submission should be explicit about the mapping method and the sources of evidence used, so that the validity and reliability of the approach taken can be assessed.
 - 7.2. Only validated mapping algorithms that have been published in peer review journals are accepted.

14. Decision uncertainty and identification of further evidence needs

Parameterised and non-parameterised uncertainties should be systematically evaluated and explicitly characterised. This should be performed using sensitivity analysis and scenario analyses for a range of plausible values and key sources of uncertainty identified. Probabilistic sensitivity analysis (PSA) should be used to assess parameter uncertainty. The expected value of perfect information (EVPI) should also be evaluated in order to appropriately quantify the consequences of uncertainty and the value of additional future research.

1. Given that assessments of the effectiveness and/or cost-effectiveness of a particular technology are based on evidence or assumptions that are themselves uncertain, it is important for the cost-effectiveness model to:
 - 1.1. Explicitly characterize all uncertainties in the appraisal (see Section 14.1);
 - 1.2. Quantify the level of decision uncertainty, i.e., quantify the likelihood that the ICER will be above the indicated cost-effectiveness thresholds (see Section 14.2);
 - 1.3. Evaluate the expected consequences of overall uncertainty to the NHS (see Section 14.3), and
 - 1.4. Identify which additional evidence could be valuable in informing re-appraisals, i.e. to identify the key sources of uncertainty and the value of future research to mitigate such uncertainties (see Section 14.4).
2. Given that items 1.2 to 1.4 of this section depend on price, analyses should consider range of prices for the new technology including prices at which the ICER is equal to the range of plausible values of the cost-effectiveness threshold (see Section 1) (unless the proposed price is already below it). Note that the level of decision uncertainty and the value of additional evidence are highest at prices equal to the cost-effectiveness threshold; hence, lower prices will result in reduced uncertainty levels.

Explicit characterisation of uncertainty in the cost-effectiveness model

3. There are two alternative ways of representing uncertainty within cost-effectiveness models:
 - 3.1. The first refers to uncertainty represented in the model using probability distributions on parameters. Typically, the description of uncertainty comes from the evidence used to estimate the parameter being itself uncertain. A description of parameter uncertainty is achieved using a statistical distribution. Other uncertainties, such as structural uncertainties, can also be parameterised [see [54], [55] and [56]]. Where feasible, uncertainties should be parameterised.

- 3.2. The second case relates to uncertainties that cannot be (easily) parameterised. This may relate to (structural) assumptions in analysis (e.g. different ways to categorise health states, alternative assumptions on the extrapolation of treatment effects, alternative statistical distributions used to describe the course of the disease, or alternative data sets on the health-related utility associated with the disease or intervention in question). It may also relate to the choice of data sources, where different sources may retain relevance but are judged inappropriate to pool together. Such uncertainties are typically represented using alternative scenarios.
4. All stochastic model parameters should be considered uncertain (for example, the price of the new technology is a deterministic parameter and should not be subject to uncertainty). The type of distribution used to describe uncertainty should be dictated by the nature of the parameter and/or any associated assumption used in the estimation method [57]. The extent of correlation between individual parameters (for example, the variance/covariance matrix for coefficients estimated within a regression analysis, or the natural correlation in Network Meta-Analysis) should be considered and reflected in the probabilistic sensitivity analysis (PSA) [58]. Any correlation could be an uncertainty parameter, itself. Formal ways to deal with correlation include the Cholesky decomposition of the variance-covariance matrix [59] or the paired use of simulations obtained by Monte Carlo method via Markov Chains. The values chosen for distribution parameters should be presented, explained and justified with reference to the supporting evidence and any assumptions used.

Quantification of the level of uncertainty

5. The level of decision uncertainty imposed by parameterised uncertainties can be evaluated using a simple extension of the cost-effectiveness models, called PSA. PSA requires that 1) distributions describing the uncertainty in the stochastic model parameters (inputs) are assigned; 2) Monte Carlo sampling of these distributions; 3) the model is applied to each sample; and 4) the results of the model (outputs) are recorded. The distribution thus obtained for the model outputs describes the uncertainty about cost-effectiveness.
6. The impact of non-parameterised uncertainties should be represented using separate analyses looking at a comprehensive range of plausible scenarios [60, 61].
 - 6.1. Where feasible, PSA should be run within each scenario to generate probabilistic ICERs. The PSA applied to a specific scenario indicate the potential benefits of collecting additional evidence when only this scenario is regarded as credible. However, when more than one scenario might be credible and carry some 'weight', there will be uncertainty between as well as within scenarios. The 'weighting' of scenarios can be made explicit by assigning probabilities to represent how credible each is believed to be [62, 63].
7. The results of the level of decision uncertainty should be presented for a range of cost-effectiveness threshold values (see Section 1), using a table of probabilities of each alternative being cost-effective or using cost-effectiveness acceptability curves [CEACs, that show the probability of the new technology to be cost-effective (y-axis) over different cost-effectiveness thresholds (x-axis) [48].
 - 7.1. The computational methods and/or platform/software package chosen to implement an appropriate cost-effectiveness model may present challenges to conducting PSA. The use of model structures that limit the feasibility of performing PSA should be clearly

justified. The choice of a 'preferred' model structure or software platform should not result in the failure to adequately characterise uncertainty.

Quantification of the consequences of uncertainty

8. To ascertain the potential consequences of uncertainty, a simple extension of PSA can be used, called the expected value of perfect information (EVPI) [59, 64]. The EVPI is evaluated per patient, but it is important that this is scaled up to reflect the population eligible for the treatment in the health system - the population EVPI. This represents the expected losses to the health system resulting from uncertainty, and it is considered significant when it is higher than the costs of the further research needed to mitigate such uncertainty.
 - 8.1. The estimates of the eligible population used to scale up the EVPI should be consistent with those presented in the budget impact analyses. However, these should consider taking into account that the technology is to be used within the NHS for a maximum of 10 years, which may be reduced if other sources of uncertainty resolve over time.
 - 8.2. Estimates of EVPI (and population EVPI) should be evaluated for the range of cost-effectiveness threshold values (see Section 1) and for a range of prices for the new technology. These estimates should be presented using both monetary units (net monetary benefits) and health units (net health benefits). The aim of these analyses is to identify the range of prices of the new technology for which research is valuable, considering alternative cost-effectiveness threshold values.
9. Where uncertainties are represented as scenarios, it is not appropriate to take a simple weighted average of the expected consequences of uncertainty across these scenarios. Such simple weighted average may underestimate or overestimate the combined consequences of uncertainty within and between scenarios [62, 63]. The correct estimate requires that weights, based on the probability of each scenario being true, be applied directly to the output from PSA rather than to the mean values. Although this process does not require additional simulation and is quick and easy to implement, it does require either that the probabilities are made explicit in advance or that estimates be presented for a range of probabilities [62, 63].

Identification of key sources of uncertainty and the feasibility and value of future research

10. It is essential to identify the specific sources of uncertainty that are significant, as it is on these uncertainties that additional research is justified.
 - 10.1. The simplest analyses that can support the identification of significant sources of uncertainty is univariate (one-way), best- or worst-case and multivariate (e.g. two-way) sensitivity analysis. The variation ranges used in such analyses should be based on plausible values for the parameters and represent uncertainty. However, it is important to recognise that these analyses are not entirely informative. This is because they do not consider remaining parameters as uncertain; and also, they do not inform of the significance of the source of uncertainty examined. However, given their simplicity, these should always be implemented and the results provided.

- 10.2. Estimates of partial EVPI (EVPPI) could also be used for key parameters (or groups of parameters). The EVPPI essentially aims at identifying uncertain parameters/scenarios that contribute most to overall decision uncertainty [57, 60, 61], and also whether data collection on specific research questions is worthwhile (comparing the population EVPPI to the expected cost of obtaining such evidence).
 - 10.3. For uncertainties represented as scenarios, there will be uncertainty between as well as within each of the scenarios. The analysis in 10.2 can also be used to identify the expected consequences of uncertainty associated with the alternative scenarios themselves, i.e., what might be gained if the evidence could immediately distinguish which scenario was 'true'.
11. Once significant uncertainties have been identified, a list of priorities for future research must be set. For such, the following factors should be considered:
- 11.1. Feasibility of the research being conducted, in particular when the technology is recommended for use in the health system;
 - 11.2. If there are significant irrecoverable costs incurred from introducing the technology in the health system that may alter the cost-effectiveness in case the decision is reversed in the future (see Section 1);
 - 11.3. Possibility of changes in circumstances over time that could alter the value of the evidence. For example, the introduction of generic medicines (associated with significant price reductions), the emergence of new comparators, upstream changes in patient care, or relevant ongoing studies and research. It is important to consider when these changes are expected to occur in the future (see point 8 of this section).

15. Validation

Model validation is crucial to demonstrate that the model results are reliable, credible and transferable to the Portuguese context. Validation should be conducted on all elements of model development, including the conceptual model, selection of input data, electronic model implementation and model outcomes. Model validations should also highlight the transferability and generalisability of model predictions to the Portuguese context. For that, experts may be used. The validation can be restricted to the specific parameters of the Portuguese context, provided that the model has been validated as part of the assessment by other regulatory authorities.

1. Model validation is crucial to build confidence on the outputs of a decision model. It should also provide information on whether the model: (i) performs its stated purpose; (ii) is the right model to answer the decision problem; and (iii) has been implemented correctly [65].
2. The process used in the validation of the model and its results should be described in the submission. An example of a validation process that could be used is the one developed by the Assessment of the Validation Status of Health-Economic Decision Models (AdViSHE) Study Group [66], although its use is not mandatory.
3. For models that have been validated by other regulatory European agencies for the same decision problem, item 2 above may cover only the validation of parameters and assumptions specific to the Portuguese context.
4. The description should include the validation of:
 - 4.1. The conceptual model;
 - 4.2. The input data;
 - 4.3. The computerised model (including the software-aided implementation code); and
 - 4.4. The model outcomes.
5. In addition, the computational code developed for the electronic model should be annotated to facilitate its inspection and guarantee transparency.
6. The face-validity of input data and model results should be assessed in relation to the Portuguese context (see elicitation, Section 12). This process should involve comparing the model results with external empirical data (e.g., observational data), and any differences should be identified and justified. Where empirical evidence directly relevant to the Portuguese context is not available, expert opinion can be used to provide insight into the transferability of outcomes to the Portuguese context.
7. Experts should seek to identify any significant differences between the model outcomes and what would be expected in the Portuguese clinical practice. Where differences are

identified, uncertainties may be quantitatively elicited using a formal elicitation process. Further research on these quantities should be considered.

16. Discount rate

As there is no official value in Portugal to support investment decisions with public funding, it is decided to follow the practice of several European countries, by reducing the rate in use. Thus, all costs and consequences should be discounted at 4% per year.

1. The discount rate represents the opportunity cost for the society to use the health care resources available at the time, since they could have been used -invested- in other areas of the economy and with a positive rate of return.
2. In order to ensure comparability, costs and consequences should refer to the same time period.
3. In Portugal, the annual discount rate used for public investments has been approximately 4 to 5 % over recent years [67]. As there is no official value in Portugal to support investment decisions with public funding, it is decided to follow the practice of several European countries, by reducing the rate in use. Thus, all costs and consequences should be updated at an annual rate of 4%.

17. Presentation of cost-effectiveness results

All interventions should be evaluated together using a full incremental analysis. Results should be probabilistic estimates for the reference case, scenarios and subgroup analyses. Disaggregated results by health state and cost category should be presented by health state and cost category (e.g. technology acquisition and management costs, adverse event monitoring, etc.). If there are more than two interventions being compared, their costs and expected results and any relevant incremental ratios should be calculated sequentially. This approach requires the identification of both interventions that lie at the cost-effectiveness frontier and those that are not (i.e. those that are subject to dominance or extended dominance).

In order to support decision making, the economic evaluation should carry out a scenario analysis on the price of the new technology for the whole target population and relevant subgroups covered by the assumptions of the base case, and for each scenario analysis, including the scenarios suggested by the CATS experts.

1. The results should be reported as ICERs (i.e. the difference in expected costs between two interventions to be divided by the difference in the expected health outcomes). If there are more than two interventions being compared, their costs and expected health outcomes and any relevant incremental ratios should be calculated sequentially. This approach requires the identification of interventions that lie in the cost-effectiveness frontier and that of others that are not (i.e. those subject to dominance or extended dominance).
2. In non-linear decision models, probabilistic methods provide the best estimates of costs and expected consequences. Expected cost-effectiveness results derived from the PSA are preferred, and should be presented for reference case, scenarios and subgroups analyses. In cases where the lack of linearity does not result in a considerable difference between probabilistic and deterministic results, the submission may present probabilistic results for the reference case only and deterministic results for the remaining analyses.
3. The company must present cost-effectiveness results using their proposed list price when submitting the economic evaluation study. The results presented should include the ICER (based on incremental analysis) and the results on the total expected costs and health outcomes of the interventions under comparison. These results should be presented with and without discounting, if appropriate.
 - 3.1. The results of the key analyses (reference case, and relevant scenarios and subgroups analyses) should also be presented in aggregate and disaggregated format (by health state). A table should be presented that includes estimates of life years gained, proportions dead (at different time points) and the frequency of selected clinical events predicted by the model. Cost estimates should be presented by cost category (e.g. technology acquisition and administration costs, adverse events monitoring, etc.).

Disaggregated results may be provided only for the reference case (minimum requirement) and the decision not to provide results in this format for the remaining analyses should be justified.

4. To support decision making, it is important to identify the price at which the ICER of the new technology is equal to the cost-effectiveness threshold. Alternative thresholds between 10.000 EUR and 100.000 EUR per QALY gained should be considered. This price is identified by conducting a univariate sensitivity analysis on the price of the new technology, holding all other parameters constant. This analysis should also be conducted for all subgroups considered, and for each scenario analysis.
 - 4.1. Decision-making will be informed by the comparison of the health costs and consequences of the widespread use in the entire target population (higher volume at a lower price) with those resulting from restricted use in more cost-effective subgroups (lower volume at a higher price).
5. To support the quantification of uncertainty, it is important to identify the price at which the EVPI is no longer significant. Such analysis should consider the range of alternative thresholds between 10.000 EUR and 100.000 EUR per QALY gained. As previously, this price is identified by conducting a univariate sensitivity analysis on the price of the new technology, holding all other parameters constant. This analysis should also be conducted for all subgroups considered, and for each scenario analysis.

18. Uncertainty and further evidence collection supporting decision making on targets for re-appraisal

The results of the analyses of uncertainty should inform a list of priorities on further evidence needs, which will aim to substantiate formal requests for evidence collection, to be submitted at the re-appraisal stage. Such evidence could include the analyses of existing databases, the reporting of ongoing studies (e.g., extensions of RCT) or new data collection.

1. The results of the analyses of uncertainty (see Section 14) should be used to derive a list of priorities for further evidence needs, which will aim to substantiate formal requests for further evidence collection (to be submitted at the re-appraisal stage). The evidence gathering activities considered here could include the analyses of existing databases, the reporting of ongoing studies, or new data collection. Where it is not possible to quantify uncertainty, for example, in the case of potential bias due to the use of a non/comparative clinical trial, i.e. with a single arm study, this source of uncertainty should always be identified as relevant for the production of additional evidence.
2. Based on the effectiveness and cost-effectiveness evidence submitted, a single table should list the key sources of uncertainty by order of importance. Table A.2 attached presents an example of such a table.
 - 2.1. The Table should list the sources of uncertainty (column 1), reference previous sections detailing how each has been identified (column 2), identify the feasibility of further evidence collection (column 3); describe summarily the optimal study design (column 4), and identify whether any other study is being conducted and, if so, when is it expected to report (column 5). Considering all the evidence produced in the submission, the company should also complete the checklist referred to in Table A3 attached, which has been adapted to reflect the specificities of the Portuguese price regime (based on direct price negotiation).
3. One of the checklist items refers to irrecoverable costs to the NHS. These costs and their importance in this context have been detailed in [68] and a brief summary is presented next:
 - 3.1 Irrecoverable costs are costs that, once committed, cannot be recovered should decision is revised at a later date. These can comprise investment expenditure (on equipment, facilities or to train staff). Even in the absence of investment expenditure, most new technologies offer a 'risky investment profile', where initial per patient treatment costs exceed the immediate health benefits and accumulated 'gains' only compensate 'losses' after some considerable time.

- 3.2 Under decision uncertainty, an approval decision might be reconsidered after relevant additional evidence results are available. If significant irrecoverable costs have been committed, it may be better to withhold approval of the technology (avoiding the commitment of irrecoverable resources) until the uncertainty is resolved.
4. Re-appraisal may also be relevant when the evaluation conditions change in a way that can alter the earlier assessment of economic value of the intervention. This may include, for example, modification of the price of the technology or its comparators, marketing of a new comparator, modification of upstream health care, or new clinical evidence or relevant to determining the economic value of the intervention or comparators. In these cases, it is pertinent that the company resubmit evidence of effectiveness and cost-effectiveness, when relevant.

19. Budget Impact Analysis

Budget impact analysis (BIA) focuses on the financial consequences of adopting an intervention. The BIA must adopt the NHS perspective, and consider the costs related to the intervention and the comparator(s) selected in the economic evaluation. If the new intervention replaces or adds to the current one, scenarios must be presented about the path of substitution of the current practice. The BIA must consider the current population to be treated, based on the prevalence, and the new cases to be treated in the future, based on the incidence, in accordance to the pharmacotherapeutic evaluation. The BIA must be limited to a two-year or more time horizon, depending on the health technology. The costs of the new therapy must also be presented separately.

1. Budget impact analysis (BIA) complements the economic evaluation and should not substitute it. Economic evaluation incorporates costs and consequences, while BIA solely focuses on the financial consequences of adopting a given intervention. However, in a context of limited public resources for health, knowing these financial consequences is crucial for budget planning and forecasting.
2. Given that BIA is expected to inform NHS decision-making, the analysis should adopt the NHS perspective. If relevant, a State perspective can also be considered, e.g., if the disease involves costs or savings for the social security system. In any case, the BIA must be presented separately for the NHS and the other sectors of the State.
3. The BIA must compare current practice with clinical practice after the adoption of the new intervention. Hence, it must consider the costs related to the comparator(s) selected in the economic evaluation. If the new technology is intended to replace current practice, realistic scenarios should be presented, in a transparent way, about the pathway towards substitution of current practice. In particular, alternative scenarios must be presented regarding the pathway of adoption by health professionals and patients' adherence to treatment.
4. The BIA must consider the target population to be treated (based on the prevalence), and any new cases to be treated over time (based on the incidence of the disease). The estimates about the number of cases to be treated should refer to the approved indication, and should consider progression of the disease (e.g. possibility of cure/remission, recurrence, or increase in severity). Estimates about the number of cases to be treated may be based in any relevant sources, including epidemiological sources, registries, administrative data, and in last instance, expert opinion. These estimates must correspond to those presented in the pharmacotherapeutic evaluation.
5. The BIA must provide highly reliable estimates of real costs that will be supported by the NHS, which can be used for budget planning in the short run. This is why the BIA should have a limited time horizon, in order to avoid the uncertainties of long-term modelling,

about epidemiologic changes, clinical history of the disease, adoption pathway of the therapy, and possible emergence of new therapies. Thus, the BIA should be limited to a two-year time horizon. Hence, discounting can be deemed as negligible, and should not be considered in the analysis.

6. The costs to be included must be in accordance with the adopted perspective. Thus, the costs related to productivity losses are not included, contrary to costs supported by the NHS and the State. All health resource consumption should be presented separately, in particular the costs related to the new technology. Fixed costs related to human resources or equipment should not be included if these are not directly related to the technology and if these would be supported even in its absence. Transfers to other levels of decision, in particular from the NHS to the State, should be included.

20. Ethical and procedural aspects

The complete list of authors and their affiliations, the list of financing entity(ies), and a statement on the contribution of each entity and author to the study should be submitted. Potential conflicts of interest due to funding source, collaborations, or outside interests should be stated.

The credibility of the study must be guaranteed through ensuring that the rules of independence and authorship have been followed. Thus, the following details must be provided:

- Complete list of authors, with their affiliation(s);
- Statement of potential conflicts of interest due to funding source, collaborations, or outside interests, by each external expert who contributed to the study, e.g., through participation in elicitation processes;
- Statement of the entity(ies) that funded the study, of all entities that contributed to the development of the study, and of each author contribution to the study.

References

1. European Network for Health Technology Assessment (EUNETHTA). Methods for economic evaluation - a guidelines based on current practice in Europe. 2015.
2. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes: Oxford university press; 2015.
3. Owens DK SJ, Sculpher MJ, Salomon JA. Designing a Cost-Effectiveness Analysis. In: Press OU, editor. Cost-Effectiveness in Health and Medicine. Oxford: Oxford University Press; 2016.
4. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: A report of the ISPOR-SMDM modeling good research practices task force–2. *Medical Decision Making*. 2012;32(5):678- 89.
5. (NICE). NifHaCE. Guide to the Methods of Technology Appraisal. London: 2013.
6. Zheng Y, Pan F, Sorensen S. Modeling treatment sequences in pharmacoeconomic models. *Pharmacoeconomics*. 2017;35(1):15-24.
7. Sculpher M. Subgroups and heterogeneity in cost-effectiveness analysis. *Pharmacoeconomics*. 2008;26(9):799-806.
8. Caldwell DM, Dias S, Welton NJ. Extending treatment networks in health technology assessment: how far should we go? *Value in Health*. 2015;18(5):673-81.
9. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for population-adjusted indirect comparisons in health technology appraisal. *Medical Decision Making*. 2018;38(2):200-11.
10. Claxton K, Palmer S, Sculpher M, Walker S. Appropriate perspectives for health care decisions. Discussion Paper 2010.
11. Raikou M, McGuire A. Estimating costs for economic evaluation. *The Elgar Companion to Health Economics*. 2006:429.
12. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*. 2011;20(10):1727-36.
13. Ferreira PL, Antunes P, Ferreira LN, Pereira LN, Ramos-Goñi JM. A hybrid modelling approach for eliciting health state preferences: the Portuguese EQ- 5D-5L value set. *Quality of Life Research*. 2019; 28(12):3163-75.
14. Brooks R, Group E. EuroQol: the current state of play. *Health Policy*. 1996;37(1):53-72.
15. Ferreira LN, Ferreira PL, Pereira LN, Oppe M. The valuation of the EQ-5D in Portugal. *Quality of Life Research*. 2014;23(2):413-23.
16. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002;21(2):271-92.
17. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care*. 2004:851-9.
18. Ferreira LN, Ferreira PL, Pereira LN, Brazier J, Rowen D. A Portuguese Value Set for the SF-6D. *Value in Health*. 2010;13(5):624-30.
19. Torrance GW, Boyle MH, Horwood SP. Application of multi-attribute utility theory to measure social preferences for health states. *Operations Research*. 1982;30(6):1043-69.
20. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system: Health Utilities Index Mark 2. *Med Care*. 1996:702-22.
21. Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, et al. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. *Med Care*. 2002;40(2):113-28.
22. Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? *Health Econ*. 2006;15(7):677-87.

23. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices— overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–1. *Medical Decision Making*. 2012;32(5):667-77.
24. Caro JJ, Eddy DM, Kan H, Kaltz C, Patel B, Eldessouki R, et al. Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value in Health*. 2014;17(2):174-82.
25. Tappenden P. Problem Structuring for Health Economic Model Development. *Encyclopedia of Health Economics*. 2014;3.
26. CADTH. Guidelines for the Economic Evaluation of Health Technologies: Canada, 4th edition. Ottawa: 2017.
27. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment. *Pharmacoeconomics*. 2006;24(4):355-71.
28. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS)— explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value in Health*. 2013;16(2):231-50.
29. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Medical Decision Making*. 1993;13(4):322-38.
30. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. *J Health Serv Res Policy*. 2004;9(2):110-8.
31. Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. *Health Econ*. 2006;15(12):1295-310.
32. Woods B SE, Palmer S, Latimer N, Soares M. NICE DSU Technical Support Document 19: Partitioned survival analysis for decision modelling in health care: a critical review. 2017.
33. Davis S, Stevenson M, Tappenden P, Wailoo A. NICE DSU Technical support document 15: Cost-effectiveness modelling using patient-level simulation. Sheffield, United Kingdom: University of Sheffield. 2014.
34. Hoyle M, Peters J, Crathorne L, Jones-Hughes T, Cooper C, Napier M, et al. Cost-effectiveness of cetuximab, cetuximab plus irinotecan, and panitumumab for third and further lines of treatment for KRAS wild-type patients with metastatic colorectal cancer. *Value in Health*. 2013;16(2):288- 96.
35. Hornberger J, Rickert J, Dhawan R, Liwing J, Aschan J, Löthgren M. The cost- effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective. *European Journal of Haematology*. 2010;85(6):484-91.
36. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technology Assessment*. 2004;8(36), 1-58
37. Kaltenthaler E, Tappenden P, Paisley S. Reviewing the evidence to inform the population of cost-effectiveness models within health technology assessments. *Value in Health*. 2013;16(5):830-6.
38. Saramago P, Manca A, Sutton AJ. Deriving input parameters for cost- effectiveness modeling: taxonomy of data types and approaches to their statistical synthesis. *Value in Health*. 2012;15(5):639-49.
39. Dias S SA, Welton NJ, Ades AE. NICE DSU Technical support document 3: Heterogeneity: subgroups, meta-regression, bias and bias adjustment. 2011.
40. Soares MO, Sharples L, Morton A, Claxton K, Bojke L. Experiences of Structured Elicitation for Model-Based Cost-Effectiveness Analyses. *Value in Health*. 2018, 21(6): 715-723
41. O'Hagan A, Buck CE, Daneshkhah A, Eiser JR, Garthwaite PH, Jenkinson DJ, et al. *Uncertain judgements: eliciting experts' probabilities*: John Wiley & Sons; 2006.
42. Kadane J, Wolfson LJ. Experiences in elicitation. *Journal of the Royal Statistical Society: Series D (The Statistician)*. 1998;47(1):3-19.

43. Montibeller G, Shaw D, Westcombe M. Using decision support systems to facilitate the social process of knowledge management. *Knowledge Management Research & Practice*. 2006;4(2):125-37.
44. Colson AR, Cooke RM. Expert elicitation: using the classical model to validate experts' judgments. *Review of Environmental Economics and Policy*. 2018;12(1):113-32.
45. Authority EFS. Guidance on expert knowledge elicitation in food and feed safety risk assessment. *EFSA Journal*. 2014;12(6):3734.
46. Montibeller G, von Winterfeldt D. Individual and group biases in value and uncertainty judgments. *Elicitation: Springer*; 2018. 377-92.
47. Kearns B, Ara R, Wailoo A, Manca A, Alava MH, Abrams K, et al. Good practice guidelines for the use of statistical regression models in economic evaluations. *Pharmacoeconomics*. 2013;31(8):643-52.
48. Kearns B, Ara R, Wailoo A. A review of the use of statistical regression models to inform cost effectiveness analyses within the nice technology appraisals programme. 2012.
49. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. *Value Health*. 2012 Sep- Oct;15(6):835-42.
50. Latimer N. Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. School of Health and Related Research, University of Sheffield, 2011.
51. Latimer NR. Survival analysis for economic evaluations alongside clinical trials— extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. *Medical Decision Making*. 2013;33(6):743-54.
52. Latimer N, Abrams K. Adjusting survival time estimates in the presence of treatment switching: National Institute for Health and Care Excellence (NICE), London; 2014.
53. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ*. 2005;14(5):487-96.
54. Bojke L, Claxton K, Sculpher M, Palmer S. Characterizing structural uncertainty in decision analytic models: a review and application of methods. *Value in Health*. 2009;12(5):739-49.
55. Strong M, Oakley JE, Chilcott J. Managing structural uncertainty in health economic decision models: a discrepancy approach. *J R Stat Soc C-Appl*. 2012;61:25-45. .
56. Jackson CH, Bojke L, Thompson SG, Claxton K, Sharples LD. A framework for addressing structural uncertainty in decision models. *Med Decis Making*. 2011 Jul-Aug;31(4):662-74.
57. Briggs A, Sculpher M, Claxton K. *Decision modelling for health economic evaluation*: OUP Oxford; 2006.
58. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. *Value in Health*. 2012;15(6):835-42.
59. Strong M, Oakley JE. An efficient method for computing single-parameter partial expected value of perfect information. *Medical Decision Making*. 2013;33(6):755-66.
60. Ades AE, Claxton K, Sculpher M. Evidence synthesis, parameter correlation and probabilistic sensitivity analysis. *Health Econ*. 2006 Apr;15(4):373-81.
61. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ*. 1999 Jun;18(3):341-64.
62. Walker S, Sculpher M, Claxton K, Palmer S. Coverage with evidence development, only in research, risk sharing, or patient access scheme? A framework for coverage decisions. *Value in Health*. 2012;15(3):570-9.
63. Claxton K, Palmer S, Longworth L, Bojke L, Griffin S, Soares M, et al. A comprehensive algorithm for approval of health technologies with, without, or only in research: the key principles for informing coverage decisions. *Value in Health*. 2016;19(6):885-91.

64. Strong M, Oakley JE, Brennan A. Estimating multiparameter partial expected value of perfect information from a probabilistic sensitivity analysis sample: a nonparametric regression approach. *Med Decis Making*. 2014 Apr;34(3):311-26. PubMed PMID: 24246566. Pubmed Central PMCID: PMC4819801.
65. McCabe C, Dixon S. Testing the validity of cost-effectiveness models. *Pharmacoeconomics*. 2000;17(5):501-13.
66. Vemer P, Ramos IC, Van Voorn G, Al M, Feenstra T. AdViSHE: a validation- assessment tool of health-economic models for decision makers and model users. *Pharmacoeconomics*. 2016;34(4):349-61.
67. Ordinance No. 13 208/2003 (Series II). Portuguese Official Gazette No. 154 — July 7, 2003.
68. Claxton KP, Palmer SJ, Longworth L, Bojke L, Griffin S, McKenna C, et al. HTA report

Annexes

Table A1. Reference methods of elicitation of expert opinion

Component	Reference methods
Experts	Substantive expertise or experience, and training in elicitation techniques and methods (normative skills)
Quantities elicited	Observable quantities to the experts, elicited under uncertainty
Approach to elicitation	Individual elicitation (with no, or limited, interaction between experts)
Method	Chips and bins (preferred)*
Aggregation	Linear pooling with equal weighting of experts
Delivery	Face-to-face where possible to allow a facilitator to deliver training to the expert

*The 'chip and bins' method (histogram or probability grid) is often used in cost-effectiveness analyses [40.Soaes MO, Sharples L, Morton A, Claxton K, Bojke L. Experiences of Structured Elicitation for Model-Based Cost-Effectiveness Analyses. Value in Health. 2018]. It is a fixed interval elicitation method using a graphical presentation, a grid, which defines a high number of intervals (usually up to 20) within reasonable bounds of the quantity of interest. The expert is then asked to distribute a fixed number of chips across these intervals (bins). The more chips are placed in a given bin, the stronger the individual's belief that the true value for the quantity of interest lies in that bin.

Table A2. Characterisation of the sources of uncertainty

Source of uncertainty		Further research focussing on the source of uncertainty			
	Description (by order of importance)	Reference to submission	Is further research possible with approval? If not, why?	Brief description of the design of the research	Is relevant evidence being collected? When is it expected to report?
1	Extrapolation of relative treatment effects	Scenario analyses	Comparative research is only possible if approval is conditional on the research	<p><u>Design</u>: RCT <u>Patient population</u>: as per MA <u>Outcomes</u>: survival <u>Follow-up</u>: Long term (at least 5 years) <u>Technologies</u>: standard of care vs. Treatment <u>Proposed sample size</u>: 50 patients per arm would return a standard error for the HR of 0.05</p>	An extension study to the pivotal RCT will report in Jan 2019 presenting a follow-up of 5 years.
2	Relevance of considering a health state	Scenario analyses	There is already a body of mechanistic evidence on whether the health state	It is not clear what study design could answer this research question	No
3	Representativeness of the HRQoL data source	Scenario analyses	Yes	<p><u>Design</u>: Cross-sectional, observational <u>Patient population</u>: patients in different health states, representative of the Portuguese care context <u>Outcomes</u>: EQ-5D for health state <u>Technologies</u>: standard of care or treatment <u>Follow-up</u>: <u>Proposed sample size</u>: 20 patients per health state would return a standard error of 0,05</p>	No
4	Monthly patient costs for the Portuguese NHS of caring for post-progression patients	Univariate analysis and EVPPI	Yes	<p><u>Design</u>: Observational, retrospective or prospective <u>Patient population</u>: patients in different health states, representative of the Portuguese care context <u>Outcomes</u>: resource use/costs for health state <u>Technologies</u>: standard of care or treatment <u>Follow-up</u>: 3 months (retrospective or prospective)</p> <p><u>Proposed sample size</u>: 20 patients per health state would return a standard error of 0,05</p>	There is a registry of NHS patients that collects resource use, but access has not

Table A3. List of criteria for collection of further evidence

	Avaliação	
1	Quais os preços a que o RCEI da tecnologia é igual a um intervalo de limiares de custo-efetividade (RCEI a variar entre 10.000 e 100.000 EUR por QALY)	[Apresentar tal informação para o caso de referência, mas também para cenários importantes]
2	Are there significant irrecoverable costs?	
3	What is the price range of the new technology for which further research is worthwhile?	[Evaluate population EVPI estimates for a range of drug prices, comparing the EVPI with the potential costs of collecting additional evidence]
4	Is additional evidence collection possible if the technology is approved?	[Consider the research priorities in Table A.2 above, and the feasibility of the research]
5	Will other sources of uncertainty resolve over time?	[Consider the possibility of changes in circumstances that could significantly alter the value of future evidence. For example, check when the drug's patents and comparators expire, or check whether potential comparators are under clinical evaluation in phase II or III studies]
6	At what price ranges are the benefits of research greater than its costs?	[Identify the benefits and costs of further research, considering not only that such evidence takes time to collect (therefore can only benefit future patient cohorts) and also that other sources of uncertainty may resolve over time (considering point 5)]

Adapted from Claxton et al. [68]



Parque de Saúde de Lisboa, Av. do Brasil 53
1749-004 Lisboa, Portugal

www.infarmed.pt
infarmed@infarmed.pt