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ISPOR Report

Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force

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ABSTRACT

Health economic evaluations are comparative analyses of alternative courses of action in terms of their costs and consequences. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement, published in 2013, was created to ensure health economic evaluations are identifiable, interpretable, and useful for decision making. It was intended as guidance to help authors report accurately which health interventions were being compared and in what context, how the evaluation was undertaken, what the findings were, and other details that may aid readers and reviewers in interpretation and use of the study. The new CHEERS 2022 statement replaces the previous CHEERS reporting guidance. It reflects the need for guidance that can be more easily applied to all types of health economic evaluation, new methods and developments in the field, and the increased role of stakeholder involvement including patients and the public. It is also broadly applicable to any form of intervention intended to improve the health of individuals or the population, whether simple or complex, and without regard to context (such as healthcare, public health, education, and social care). This Explanation and Elaboration Report presents the new CHEERS 2022 28-item checklist with recommendations and explanation and examples for each item. The CHEERS 2022 statement is primarily intended for researchers reporting economic evaluations for peer-reviewed journals and the peer reviewers and editors assessing them for publication. Nevertheless, we anticipate familiarity with reporting requirements will be useful for analysts when planning studies. It may also be useful for health technology assessment bodies seeking guidance on reporting, given that there is an increasing emphasis on transparency in decision making.

Keywords: cost-benefit analysis, economic evaluation, guidelines, methods, microeconomic analysis, reporting, standards.

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Background

Economic evaluations of health interventions are comparative analyses of alternative courses of action in terms of their costs and consequences. They can provide useful information to policy makers, payers, health professionals, patients, and the public about choices that affect health and the use of resources. Economic evaluations are a particular challenge for reporting because substantial information must be conveyed to allow scrutiny of study findings. Despite a growth in published economic evaluations[1-3] and availability of reporting guidance,[4] there is a considerable lack of standardization and transparency in reporting.[5,6] There remains a need for reporting guidance to help authors, journal editors, and peer reviewers in their identification and interpretation.

The goal of the original Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement[4] was to recommend the minimum amount of information required for reporting of published health economic evaluations. The statement consisted of a 24-item checklist and Explanation and Elaboration Task Force (TF) Report.[4] CHEERS was intended to help authors provide accurate information on which health interventions are being compared and in what context, how the evaluation was undertaken, what the findings are, and other details that may aid readers and reviewers in interpretation and use of the study. In doing so, it can also aid interested researchers in replicating research findings. Some checklist items (eg, title, abstract) were also included to aid those researching economic evaluation literature. The CHEERS statement consolidated previous health economic evaluation reporting guidelines[7-18] into one current, useful reporting guidance.

The CHEERS statement overview was copublished by 10 journals that frequently publish economic evaluations in healthcare.[19-28] It has since been endorsed by other journals and health research organizations, such as the UK National Institute for Health Research[29] and the International Society for Medical Publication Professionals.[30] CHEERS is recognized by the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network[31] as a reporting guideline for main study types in health research, along with the Consolidated Standards of Reporting Trials (CONSORT),[32] the Strengthening the Reporting of Observational Studies (STROBE),[33] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[34]

Since the original publication of the CHEERS statement, there have been several developments that have motivated an update. These included feedback on perceived limitations of CHEERS, including criticism of its neglect of addressing reporting of cost-benefit analyses (CBAs).[35] CHEERS has also been observed to be used inappropriately, as a tool to assess quality of methods, for which other tools exist[36] rather than the quality of reporting.[5] It has also been used as a tool to quantitatively score studies in systematic reviews, an approach that could mislead readers and reviewers[37] given that it has not been designed for this purpose.

There have also been methods developments in economic evaluation motivating an update. This includes an update of methods proposed by the Second Panel on Cost-Effectiveness in Health and Medicine ("Second Panel"), which contained a number of new recommendations concerning the perspective of economic evaluations, the classification of costs and benefits in a structured table, and the inclusion of related and unrelated healthcare costs in added years of life.[38] Health technology assessment (HTA) bodies have also updated their guidance on conducting and appraising economic evaluations.[39,40]

Other developments include an increasing calls for the use of Health Economic Analysis Plans[41] and the use of open-source models.[42-46] The latter may be of particular importance because published economic evaluations are increasingly available in journals with broad data sharing policies. The increased use of and guidance for economic evaluations to support policy decisions in immunization programs[47,48] and global health in lower- and middle-income countries[49] have also motivated an update. There has also been an increase in the number of economic evaluations that attempt to capture consequences extending beyond health outcomes, such as equity and distributional effects.[50,51]

Finally, the increased role of stakeholder participation in health research and HTA, including patients and the public, suggests the need to recognize a broader audience.[52-54] All of these developments suggest that the scope of guidance for reporting economic evaluations should be expanded and updated.

The objective of this "Explanation and Elaboration" TF Report is to describe the CHEERS 2022 reporting guidance in detail. This includes under what circumstances CHEERS should and should not be used ("Scope") and how it should be used ("How to Use CHEERS"). The main body of the article describes the rationale for recommending each reporting item with evidence (if available) and a rationale to support the recommendation and accompanying examples to facilitate its appropriate use.

Approach

In January 2020, a new ISPOR Good Practices TF was approved, with the objective of revising and updating the CHEERS statement and to improve the CHEERS checklist and accompanying Explanation and Elaboration document. The process of revising CHEERS followed that of the ISPOR Good Practices TF Reports[55] and guidance developed by the EQUATOR Network,[56] where the CHEERS 2022 update is also registered. Original CHEERS TF members were invited to participate, and additional members were nominated and invited by TF members based on their specific areas of expertise, geographic region, or work environments. An informal review of reporting guidelines published since CHEERS was undertaken, and new items were proposed and consolidated along with the existing CHEERS checklist. In parallel with this, a TF was convened and a group of patient and public involvement and engagement (PPIE) contributors was formed to review the consolidated checklist and provide suggestions on language and the need for additional items. The draft checklist was finalized by CHEERS TF members.

TF members then nominated experts in economic evaluation and those with perspectives in journal editing, decision making, HTA, and commercial life sciences to participate in a modified Delphi Panel ("Delphi") process. Panelists along with the PPIE contributors were subsequently invited to participate by email and directed to a web-based survey. Feedback from each round of the Delphi process was discussed by TF members, who ultimately finalized the item list based on the input provided. A guiding principle in the development of CHEERS 2022 is that economic evaluations made available publicly should be understandable, interpretable, and replicable to those who use them.

A complete Guidance for Reporting Involvement of Patients and the Public Version 2 (GRIPP2) checklist is featured in Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.10.008. The protocol for the Delphi process and panel composition, size, response rates, and analytic approach can be found in Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.10.008.

The CHEERS 2022 Explanation and Elaboration

Scope

The CHEERS 2022 statement is intended to be used for any form of health economic evaluation.[57] This includes analyses that only examine costs and cost offsets (ie, cost analysis) or those that examine both costs and consequences (eg, cost-effectiveness analysis [CEA]/cost-utility analysis [CUAs], cost-minimization, CBAs), or broader measures of benefit and harm to individuals (eg, extended CEAs/CBAs), including measures of equity (eg, distributional CEAs). Although we are aware some studies comparing costs are labeled as CBAs, we recommend the use of this term for studies that include a monetary valuation of health outcomes. Although linked to economic evaluation, budget impact analyses and constrained optimization studies are beyond the scope of CHEERS guidance, because they require additional reporting that addresses population dynamics and feasibility constraints and are addressed in other reports.[58,59]

The primary audiences for the CHEERS 2022 statement are researchers reporting economic evaluations and peer reviewers and editors assessing them for publication. Although they are not intended to guide the conduct of economic evaluation, familiarity with reporting requirements will be useful for analysts when planning studies. CHEERS may be similarly useful for HTA bodies seeking guidance on reporting, because there is an increasing emphasis on transparency in decision making.[60] HTA and the use of economic evaluation are also becoming more commonplace globally.[3] In developing the guidelines, the TF considered issues that may be specific to regions with developing economies and healthcare systems, including examples of these by item, to ensure the reporting guidance will be useful in any social or political context.

CHEERS is relevant for any intervention intended to affect health and should also be widely applicable for both simple and

Table 1. CHEERS 2022 checklist

Section/topic	Item no.	Guidance for reporting	Reported in section
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	_____
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	_____
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	_____
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	_____
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	_____
Setting and location	6	Provide relevant contextual information that may influence findings.	_____
Comparators	7	Describe the interventions or strategies being compared and why chosen.	_____
Perspective	8	State the perspective(s) adopted by the study and why chosen.	_____
Time horizon	9	State the time horizon for the study and why appropriate.	_____
Discount rate	10	Report the discount rate(s) and reason chosen.	_____
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	_____
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	_____
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	_____
Measurement and valuation of resources and costs	14	Describe how costs were valued.	_____
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	_____
Rationale and description of model	16	If modeling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	_____
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	_____
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	_____
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	_____
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	_____
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	_____
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	_____
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure.	_____
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	_____

continued on next page

Table 1. Continued

Section/topic	Item no.	Guidance for reporting	Reported in section
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	_____
Discussion			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	_____
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	_____
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	_____

CHEERS indicates Consolidated Health Economic Evaluation Reporting Standards; no., number.

complex interventions, including programs of care involving researcher-driven or commercialized products (eg, drugs; macromolecules; cell-, gene-, and tissue-based therapies; vaccines; and medical devices), public health and social care interventions, processes of care (eg, e-health, care coordination, clinical decision rules, clinical pathways, information, and communication; medical and allied health services), and reorganization of care (eg, insurance redesign, alternative financing approaches, integrated care, scope of practice change, and workplace interventions).

CHEERS is also applicable to studies based on mathematical modeling or empirical research (eg, patient- or cluster-level human studies). Although CHEERS can be used for systematic reviews of economic evaluation, its use should be limited to assessing the quality of reporting of a study rather than the quality of its conduct. Given that there is no validated scoring system for the checklist, using it as a scoring tool could lead to misleading findings[37] and is strongly discouraged. If used to assess the quality of reporting in a systematic review, a qualitative assessment of completeness of reporting by item is a more appropriate approach. When applying the CHEERS statement, users may need to refer to additional reporting guidance (eg, for randomized controlled trials, patient and public involvement, modeling, health state preference measures), and these are referenced throughout the report.

How to Use CHEERS

The CHEERS 2022 statement (checklist and Explanation and Elaboration TF Report) replaces the 2013 CHEERS statement, which should no longer be used. The new CHEERS checklist contains 28 items with accompanying descriptions. Major changes are described in Box 1. Each section below describes a checklist item (Table 1) along with its description and an explanation of why it is important for interpreting a published economic evaluation. Empirical evidence to support the claim is provided, if available, as well as an illustrative example. All examples provided contain an open-access copyright to allow readers to further understand context. When examples make references to other works or article component (eg, figures), references and component labels within the examples have been relabeled to avoid confusion with references use within this report. Items and recommendations are subdivided into 7 main categories: (1) Title, (2) Abstract, (3) Introduction, (4) Methods, (5) Results, (6) Discussion, and (7) Other Relevant Information.

Those using the checklist should indicate the section of the article where relevant information can be found. We recommend using a section heading with a paragraph number because referring to line or page numbers becomes confusing as repagination or line number changes occur within or after the publication process. If an item does not apply to a particular economic evaluation (eg, items 11-13 for cost analyses or items 16 and 22 for nonmodeling studies), then checklist users are encouraged to report "Not Applicable." If information is otherwise not reported, checklist users are encouraged to write "Not Reported." Users should avoid the term "Not Conducted" because CHEERS is intended to guide and capture reporting.

As before, in developing the CHEERS statement, the TF recognizes that the amount of information required for adequate reporting will exceed conventional space limits of most journal

BOX 1. 2022 CHEERS - Major changes to the 2013, CHEERS Statement

- Items related to patients or service recipients, the general public, and community or stakeholder involvement and engagement added.
- Language broadened to make CHEERS more widely applicable to cost- benefit/benefit-cost analysis, as well as equity- or distributional cost-effectiveness.
- Item related to reporting and availability of a health economic analysis plan added.
- Item related to characterizing distributional effects added.
- Items distinguishing between model-based and study-based measures removed.
- Recommendation to report where publicly available models can be found added. Sharing of unlocked models with editors and reviewers encouraged.

CHEERS indicates Consolidated Health Economic Evaluation Reporting Standards.

reports. Therefore, in making our recommendations, we assume that authors and journals will make necessary information available to readers using online and supplementary appendices or other means.

To encourage dissemination and appropriate use of CHEERS, we would encourage authors to become familiar with and cite this open-access Explanation and Elaboration TF Report. In addition, we have also developed templates, an interactive form (https://ispor.org/cheers), and educational materials for authors and editors to facilitate its use. We encourage authors to visit the CHEERS[61] and EQUATOR[62] websites to discover what is available.

Checklist Items

Title

Item 1. Title: Identify the study as an economic evaluation and specify the interventions being compared.

Explanation. The title should enable economic evaluations to be easily identified through a literature search. There are at least 2.5 million research articles published annually and this volume continues to increase.[63] Identification of articles of interest is reliant on effective search strategies. Previous research has suggested current search approaches to identify economic evaluations fail to capture relevant studies.[64] Therefore, it is essential that economic evaluations are correctly indexed in electronic databases to help maximize sensitivity and precision of literature searches. Authors should use the term "economic evaluation" in the title and specify the interventions compared and the setting under investigation to ensure appropriate indexing and enhance discoverability of economic evaluations. Alternatively (or in addition), authors are encouraged to use specific terms to define the form of analysis (eg, "cost-effectiveness," "cost-utility," "cost-benefit," or "distributional cost-effectiveness analysis").

Example of Item 1: Title[65]

"Cost-effectiveness of a specialist smoking cessation package compared with standard smoking cessation services for people with severe mental illness in England: a trial-based economic evaluation from the SCIMITAR+ study"

Abstract

Item 2. Abstract: Provide a structured summary that highlights context, key methods, results, and alternative analyses.

Explanation. Journals and reporting guidelines recommend the use of structured abstracts when reporting original research or systematic reviews.[32,34] Structured abstracts contain headings that allow readers to quickly locate key information about the study. Journals may have guidance regarding the specific headings to be used and headings may also vary depending on the study and author preferences.

Abstracts are commonly used as a basis to screen articles for further review. Furthermore, some readers may only have access to the abstract, although this is less common with the increasing drive to open-access publications. The previous CHEERS TF Report highlighted evidence that the reporting quality of published abstracts of economic evaluations needed improvement because they commonly lacked critical information or were inaccurate.[4] An abstract should be sufficiently detailed to allow the reader to assess the relevance of the economic evaluation and to serve as an accurate summary of the study.

Authors should include a structured summary of the economic evaluation that includes the aim or objectives of the study; key methods, including study population and setting (including country), comparators, time horizon, inputs, perspective, currency year, and discount rate; results (mean values of costs and outcomes), including base case and key alternative analyses; and conclusions. Conclusions should indicate any potential impact on patients, the public, or application in policy or patient care and describe impact of relevant analyses of uncertainty. As a guide, we recommend a word limit of 300 words; nevertheless, we recognize journals may have their own limits that need to be observed and that on occasion there may be a need to exceed this limit for a particularly complex article.

Authors should additionally consider producing a plain language summary of their study, which would be helpful to nontechnical audiences, including patients, healthcare professionals, and the general public. Furthermore, we recommend authors check that the information in the abstract or plain language summary is consistent with that in the full text, that all information can be found in the body text, and that the conclusions are not different.

Example of Item 2: Abstract[66]

Introduction: Cannabinoid oils are being increasingly used to treat Dravet syndrome, yet the long-term costs and outcomes of this approach are unknown. Thus, we examined the cost effectiveness of cannabinoid oil as an adjunctive treatment (added to clobazam and valproate), compared with adjunctive stiripentol or with clobazam and valproate alone, for the treatment of Dravet syndrome in children.
Methods: We performed a probabilistic cost-utility analysis from the perspective of the Canadian public health care system, comparing cannabinoid oil and stiripentol (both on a background of clobazam and valproate) with clobazam and valproate alone. Costs and quality-adjusted life-years (QALYs) were estimated using a Markov model that followed a cohort of children aged from 5 to 18 years through model states related to seizure frequency. Model inputs were obtained from the literature. The cost effectiveness of adjunctive cannabinoid oil, adjunctive stiripentol, and clobazam/valproate alone was assessed through sequential analysis. The influence of perspective and other assumptions were explored in scenario analyses. All costs are expressed in 2019 Canadian dollars, and costs and QALYs were discounted at a rate of 1.5% per year.
Results: The incremental cost per QALY gained with the use of adjunctive cannabinoid oil, from the health care system perspective, was $32,399 compared with clobazam and valproate. Stiripentol was dominated by cannabinoid oil, producing fewer QALYs at higher costs. At a willingness-to-pay threshold of $50,000, cannabinoid oil was the optimal treatment in 76% of replications. From a societal perspective, cannabinoid oil dominated stiripentol and clobazam/valproate. The interpretation of the results was insensitive to model and input assumptions.
Conclusion: Compared with clobazam/valproate, adjunctive cannabinoid oil may be a cost-effective treatment for Dravet syndrome, if a decision maker is willing to pay at least $32,399 for each QALY gained. The opportunity costs of continuing to fund stiripentol, but not cannabinoid oil, should be considered.

Introduction

Item 3. Background and objectives: Give the context for the study, the study question and its practical relevance for decision making in policy or practice.

Explanation. Readers need to understand why the study was conducted and the specific policy or practice decision being addressed. Therefore, authors should provide an explicit statement of the motivation for the study, present the study question (ie, decision problem), explain its practical relevance for health policy or practice decisions, and describe its importance to patients and the general population.

Sometimes the motivation for a study may reflect the interests of researchers, but increasingly economic evaluations are being conducted to meet the needs of decision makers, such as determining whether a new treatment or intervention should be reimbursed. If the study was undertaken for a decision maker or to address a particular decision problem, this should be outlined. Otherwise, a description of the importance of the study question should be given.

It is not enough to state that "the purpose of the study was to assess the cost-effectiveness of treatment X." Correct specification of the study question or decision problem should be consistent with reporting items 5 to 8 and state the study population and subgroups, the setting and location, the study perspective, and the interventions or strategies being compared.

Example of Item 3: Background and objectives[67]

The Dutch national authorities responded to the recent mismatches by switching from the [trivalent influenza vaccine (TIV)] to the quadrivalent influenza vaccine (QIV) as of the 2019 to 2020 influenza season.[citation provided] QIV may provide better health outcomes compared to TIV because QIV contains both B-type strains in the vaccine, potentially avoiding future mismatches; however, QIV is also more expensive than TIV. The clinical and economic effects of replacing TIV with QIV for The Netherlands have so far only been captured by a straightforward static model, which estimated the cost-effectiveness of QIV if it had been implemented in The Netherlands during the last 8 influenza seasons.[citation provided] An integrated analysis designed to fully capture the complexity of the dynamics of infections in humans, including the indirect effects of herd protection on unvaccinated individuals, is yet to be realized. As these factors may considerably influence the cost-effectiveness of a national immunization program against influenza, this study aimed to assess the incremental price at which the switch from TIV to QIV is still cost-effective using a dynamic modeling approach.

Methods

Item 4. Health economic analysis plan: Indicate whether a health economic analysis plan was developed and where available.

Explanation. Statistical analysis plans are now routine in clinical trials and provide the reader with some reassurance that bias has not been introduced by selected reporting of results or analyses. Nevertheless, in contrast to statistical analysis plans, health economics analysis plans (HEAPs) are not very common in economic evaluations. A recent survey found that only approximately 30% of responding clinical trials units in the United Kingdom always use some form of HEAP and there was little consistency in the approach taken.[68] In addition, economic evaluations are not only conducted alongside clinical trials and may be based on alternative study designs or economic models. Nevertheless, there have been recent initiatives to improve the transparency of, and to build trust in, real-world secondary data studies for hypothesis testing.[69]

Currently, there is no standardized guidance on developing HEAPs, but a recent expert Delphi consensus survey identified 58 core items that were considered essential for inclusion within a HEAP.[70] Although this focused on economic evaluations conducted alongside randomized controlled trials, it should also be useful as a template for all types of economic evaluation (eg, model based, observational study based). Although the use of HEAPs is still in its infancy, authors should indicate whether a health economic analysis plan was developed and where it is available for readers to consult. Authors are encouraged to include available HEAPs as supplementary information or in an open-access repository to aid access.

Example of Item 4: Health economic analysis plan[71]

The economic analysis followed intention-to-treat (ITT) principles and a prospectively agreed analysis plan (see Appendix X).

Item 5. Study population: Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).

Explanation. Readers need information on the characteristics of the target population, plus any identifiable subgroups, to assess the relevance of the study to the population and potential subgroups of interest to them. The economic impact of any intervention can be quite different across subgroups, given that costs and consequences of interventions vary according to population characteristics. Understanding population features (such as age range, gender, sex, income level, and ethnic groups) and clinical characteristics (severity, subtypes of illness, histology, etc) that could affect the evaluation results will also aid in transferring (generalizing) results to local contexts, where characteristics may differ. In many instances, studies from which effectiveness estimates are taken will define baseline characteristics for an economic evaluation. Subgroups may relate to univariate risk factors (eg, presence or absence of a particular genotype or phenotype) or multivariate risk factors (eg, a continuum of cardiovascular risk as determined by a multivariable risk equation).

There is considerable evidence to suggest that subgroup analyses in clinical trials are often poorly conducted, reported, and interpreted.[72-77] Therefore, authors should report or provide a reference to factors that may support their inclusion and

interpretation of results, such as biological plausibility of hypotheses and prespecification of subgroup testing.[78]

Example of Item 5: Study population[79]

"Participants were men and women who presented at 40-80 years with total cholesterol concentrations of at least 3.5mmol/l (135mg/dl) and a medical history of coronary disease, cerebrovascular disease, other occlusive arterial disease, diabetes mellitus, or (if a man aged >= 65) treated hypertension … participants were divided into five similar sized groups of estimated five-year risk of a major vascular event, with average risks in the groups ranging from 12% to 42% (which correspond to risks of 4% to 12% for non-fatal myocardial infarction or coronary death)."

Item 6. Setting and location: Provide relevant contextual information that may influence findings.

Explanation. An economic evaluation addresses a question relevant to the place and setting in which resource allocation decisions are being contemplated. This includes the geographical location (country or countries) and the particular setting of healthcare (ie, primary, secondary, tertiary care, or community/public health interventions) and any other relevant sectors, such as payment schemes (health maintenances organization, national health insurance, or national health services), education, or legal systems.[57] A clear description of the location, setting, or other relevant aspects of the system in which the intervention is provided is needed so that readers can assess external validity, generalizability, and transferability of study results to their particular setting. Authors can subsequently interpret findings in light of system-specific factors in the "Discussion" section (see item 22).

Example of Item 6: Setting and location[80]

"The trial was conducted in 18 public primary health care centers in poor urban areas of Argentina (in Buenos Aires, Misiones, Tucuman, Corrientes, and Entre Ríos provinces). Cluster randomization was stratified by geographic region, and primary health care centers were randomly assigned to the control group or the intervention group."

Item 7. Comparators: Describe the interventions or strategies being compared and why chosen.

Explanation. Economic evaluations alongside studies compare only the interventions in the study concerned, whereas model-based evaluations allow a broader set of comparators to be assessed. Interventions and delivery of technologies may differ among countries or settings, making it important to describe the relevant characteristics of studied interventions. This includes intensity or frequency of treatment (for behavioral or nondrug interventions), drug dosage schedule, route, and duration of administration.

Particular consideration should be taken when reporting economic evaluations of complex interventions, which consist of multiple interacting components and may permit a certain degree of flexibility in the delivery of the intervention.[2] A detailed description of the elements in the intervention, including the complexity of the intervention and any variability in the manner of delivery, should be provided to allow a comprehensive understanding of how the intervention was performed. Pathway diagrams can be used, where appropriate, to depict the intervention. To guide the description of complex interventions, relevant checklists and guidelines can be referred to. For example, the Template for Intervention Description and Replication (TIDieR) checklist serves as a useful template to describe interventions[81] whereas Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: revised guideline (CReDECI 2) outlines specific recommendations on reporting complex interventions.[82]

Comparators may include "do nothing," "current practice," or "the most cost-effective alternative," but the underlying components or actions underlying these should still be described in detail. Authors should describe why particular comparators were chosen and should consider listing all potentially relevant comparators and explaining why a more common, lower priced, or more effective comparator was not considered.

Example of Item 7: Comparators[83]

"Patients randomized to the [cardiovascular risk reduction] intervention group received a medication therapy management review, laboratory assessment, individualized CV risk assessment and education, prescription recommendations, adaptation or de novo prescriptions, and monthly pharmacist follow-up visits (a minimum of every 3 to 4 weeks) for 3 months. The intervention was based on defined protocols from a clinical pathway (www.CKD pathway.ca; http://www.epicore.ualberta.ca/epirxisk) developed based on current Canadian guidelines. The usual care group did not receive the aforementioned interventions but received usual pharmacist and physician care."

Item 8. Study perspectives: State the perspectives adopted by the study and why chosen.

Explanation. The study perspective is the viewpoint from which costs and consequences associated with the comparators are evaluated. A study could be conducted from one or more stated perspectives, including a patient perspective, an institutional perspective (eg, hospital perspective), a healthcare payer's perspective (eg, sickness fund, Medicare in the United States), or a societal perspective. Most studies are conducted from a health system or payer perspective (eg, National Health Service in England or Medicare in the United States) or from a societal perspective.[84] The health system and payer's perspectives typically include direct medical care costs, including the cost of the intervention itself and follow-up treatment costs. A societal perspective will also estimate broader costs to society (eg, productivity losses resulting from poor health or premature death, informal care costs, or costs to other sectors such as the criminal justice system).[38]

Because these perspectives lack standard definitions and are often misspecified,[84] authors should describe the perspective (eg, healthcare system, societal) in terms of costs included and their associated components (eg, direct medical costs, direct nonmedical costs, and indirect/productivity costs) and how this fits the needs of the target audience and decision problem. Creating a structured table (called an "impact inventory") developed by the Second Panel may be helpful in conveying what costs and consequences were considered.[38] This will also facilitate reporting disaggregated impacts across these sectors and perspectives when reporting results, which is strongly encouraged (see item 23).[38] References to jurisdiction-specific guidelines or documents describing local

economic evaluation methods can also be provided, along with a reason for why these were chosen. Authors should also state why the perspective was chosen and, if applicable, state the decision makers for whom the study was conducted.

Example of Item 8: Study perspective(s)[85]

"A limited societal perspective was taken, in which health care costs and costs outside the health care sector (i.e., productivity losses related to MS, informal care, out-of-pocket or copayments for patients for equipment, aids and modifications, and community services, such as home help, transportation, or personal assistance) were included."

Item 9. Time horizon: State the time horizon for the study and why appropriate.

Explanation. The time horizon refers to the length of time over which costs and consequences of the interventions are being evaluated and reported. The results and interpretation of an economic evaluation, particularly in preventive medicine and treatment of chronic diseases, may be particularly sensitive to the choice of the time horizon.[86] An intervention with a large "up-front" cost that generates benefits over a period of years, for example, will become more cost-effective, the longer the time horizon considered.

Time horizons are typically long enough to capture the most important differences in costs and consequences and often longer than the length of follow-up in empirical studies. In these instances, it may be useful to report findings until the end of follow-up of a study and projected, longer-term costs and consequences. This can provide the reader with an understanding of the impact of extrapolation assumptions.

Example of Item 9: Time horizon[87]

"A 15-year time horizon was chosen for the base case of the analysis, beginning with the index procedures. A long-term time horizon (lifetime) was not considered appropriate due to the immaturity of utility data available for the analysis; extensive extrapolation over such a time horizon would be associated with considerable uncertainty. However, differences in HRQoL outcomes for patients treated with VBT and spinal fusion (eg due to improved range of motion), if present upon reaching skeletal maturity, are anticipated to persist into the long term. Therefore, it was important to choose a time horizon of sufficient length to capture plausible mid- to long-term differences in HRQoL outcomes. Additional time horizons (5, 10, and 20 years) were explored in scenario analyses."

Item 10. Discount rate: Report the discount rate and reason chosen.

Explanation. Healthcare interventions may result in short- or long-term impacts on cost and consequences. A discount rate reflects societal preferences for immediate impacts versus those that occur in the future. Discounting beyond the first year after an intervention allows analysts to provide present values by adjusting for time preferences, catastrophic risk, and the diminishing marginal utility of anticipated higher levels of future consumption. Reporting discount rates is important because the findings of an economic evaluation, specifically a more common situation in which costs or consequences of an intervention are not realized for several years, may be particularly sensitive to what discount rate is chosen.

Analysts will need to report the impact of findings when the discount rate is varied (item 23), which is of particular importance when outcomes occur far in the future.[88] Discount rates are not universal, so authors must say why particular rates were chosen. Typically, this involves citing local economic evaluation guidelines or treasury reports. Some jurisdictions recommend a common rate for discounting both costs and outcomes, whereas others prescribe differential rates. Although a discount rate for economic evaluations with short (1 year or less) time horizons may not be applied, analysts should report this as 0% for clarity.

Example of Item 10: Discount rate[89]

"In both cases discounting at a rate of 3.5% per year (for both healthcare costs and QALYs) was used. As an alternative scenario, we also evaluated the effects of applying a 1.5% discount rate to health impacts; this was in response to the CEMIPP report which highlighted that 3.5% discounting was not always appropriate given disparate delays from infection time to health effects, and..[as] …[t]his is the case for HPV, when there may be many years between vaccination, infection and the onset of life-threatening cancers. 1.5% was chosen"

Item 11. Selection of outcomes: Describe what outcomes were used as the measures of benefits and harms.

Explanation. Evaluation of the consequences of any set of comparators in health economic evaluation requires the selection of one or more outcome measures reflecting benefits and harms. Although these are typically health outcomes, they may also be one or more broader measures (eg, wellbeing, social care, recidivism, educational achievement) or any number of measures combined into a composite outcome (eg, quality-adjusted life-years [QALYs] or disability-adjusted life-years). Health outcomes often lack standard definitions (eg, severe exacerbation) and should be clearly defined. If a composite outcome measure (eg, QALYs, major adverse cardiovascular events) is used, the components of the composite measure and how they contribute to the overall effect should be made clear to the reader.

The choice of outcome typically depends on the type of analysis being performed and the perspective that is being adopted. For example, CEAs will typically focus on clinical outcomes (eg, life-years, cases avoided), where CUAs and some CBAs require additional consideration of preferences for these outcomes.

The rationale for choosing the outcome should be described. This typically involves describing the relevance of the outcome to patients, the public, key stakeholders (eg, carers, providers, or industry) and others affected. If a primary outcome is prespecified, authors should cite a protocol or clinical study publication from which it is derived and justify excluding any other outcomes that were prespecified. Authors are encouraged to describe the nature

of any patient, public, community, or stakeholder involvement and engagement in the choice of outcomes.

Example of Item 11: Selection of outcomes[90]

"An individual-based Markov model was constructed using guidance from a stakeholder advisory board (SAB), a patient Delphi panel, and published literature to evaluate direct-acting antivirals (DAAs) compared to no treatment…. beyond the traditional QALY health outcome, this study included two novel outcome measures developed from the HCV patient Delphi panel and reviewed by our SAB. Patients identified 'fear of harming others' as an important problem caused by having HCV in addition to the consideration of indirect costs such as 'financial issues' or 'impact on work or career.' This patient input was used to develop two measurable health outcomes in our model: infected life-years (ILYs) and workdays missed."

Item 12. Measurement of outcomes: Describe how outcomes used to capture benefits and harms were measured.

Explanation. The methods for measuring changes in outcomes should be described. If this is the first-time differences in clinical outcome measures are reported for the chosen comparators, authors should defer to existing reporting checklists for single study-based[32,91-94] or synthetic[34,95-99] approaches to estimation. Analysts should consult the EQUATOR Network[62] for specific information related to alternative study designs or outcome measures, if reported for the first time.

Preference-based outcomes that capture impacts on health (eg, QALYs or disability-adjusted life-years) or on patients and caregivers beyond health (eg, extending the QALY [e-QALY]s[100]) will additionally require reporting of the approach to obtaining preference measures and weights (item 13) and analytic considerations (item 17) for readers to understand how the underlying components (eg, preference weights and life-years) contribute to the overall measure and how the measure was constructed (eg, area under the curve approach).

Example of Item 12: Measurement of outcomes[101,102]

"We conducted a cost-effectiveness analysis (CEA) alongside the cluster-randomized, controlled, multicenter, prospective DeTaMAKS-trial ….Further details on the recruitment strategy of DCCs and the eligibility criteria of DCCs and participants are described in detail elsewhere…The trial's registration number is ISRCTN16412551. The effect of MAKS on cognitive abilities was operationalized by the Mini-Mental Status Examination (MMSE) [citation provided]. The effect on capabilities to perform ADLs was operationalized by the Erlangen Test of Activities of Daily Living in Persons with Mild Dementia and Mild Cognitive Impairment (ETAM) [citations provided]. MMSE and ETAM were both assessed at t0 and t1. Both tests have a range from 0 to 30 points with higher values indicating better performance."

"We previously published an agent-based model of C difficile transmission in a simulated general, 200-bed, tertiary, acute care adult hospital.[citation provided] Output from this model was used to evaluate the cost-effectiveness of infection control strategies in terms of 2 primary outcomes: the cost per quality-adjusted life-year (QALY) saved and cost per hospital-onset CDI (HO-CDI) averted… for additional modeling details, see the eAppendix in the Supplement."

Item 13. Valuation of outcomes: Describe the population and methods used to measure and value outcomes.

Explanation. Analyses based on preference-based outcome measures should describe how outcomes were measured and valued (eg, to estimate health state "utilities" [HSUs] or willingness to pay). If developed de novo, reporting guidance has been developed for direct approaches to monetary valuation for nonmarketed outcomes[103] (eg, stated preference surveys[104] [contingent valuation approaches,[105] conjoint analysis[106]/discrete choice experiments[107]]). Similarly, guidance is available for reporting of direct approaches to health state preference elicitation, including choice (eg, standard-gamble or time-trade-off methods) or scaling (eg, rating scales and ratio scales) methods.[108] An alternative approach is to develop HSUs through translating measures across quality-of-life instruments or patient-reported outcome measures (ie, mapping). In this case, the Mapping onto Preference-Based Measures Reporting Standards (MAPS) Statement should be used to guide reporting.[109]

Indirect approaches to obtaining preference measures may also be used. Reporting guidance is available to describe indirect approaches to consumer preferences (eg, hedonic wage models[110]). If multiattribute utility instruments are used to indirectly measure and value states of health (eg, EQ-5D-3L, SF-6D), the main characteristics should be described, including the name and version of the instrument, the format and frequency of administration of the instrument, the valuation method (eg, type of stated preference survey), the population from which valuations were obtained in terms of size and demographic characteristics, and the source of any (proxy) preference measurement and why this is appropriate. This is also applicable to instruments intended to measure broader impacts beyond health, such as capability, wellbeing, or social care (eg, Investigating Choice Experiments Capability Measure [ICECAP],[111] Adult Social Care Outcomes Toolkit [ASCOT][112]). A reference to the instrument, with details of its valuation approach, should be provided.[113]

Authors may also choose to obtain values from the literature. This could include identifying preference-based measures or monetized values for health states from studies using approaches as already described. If so, authors should report whether a systematic review was undertaken. Authors should be aware that some study designs (eg, cost-of-illness) do not apply preference-based measures or generate monetized values that reflect willingness to pay.[114] For systematic reviews of HSUs, recent guidance to aid reporting has been developed.[115] Authors are encouraged to fill out appropriate reporting checklists when citing sources of preference measures to guide readers, when completed checklists are lacking in original publications. Given the considerable detail required, authors are encouraged to use supplementary reports or appendixes to convey this information.

Example of Item 13: Valuation of outcomes[116,117]

"Under this approach, the health outcome in conventional cost-utility analyses, namely QALY, was monetised using individual WTP for an additional QALY gained. Based on a study that assessed WTP for the respondent's own additional QALY gained (WTPsel) in the UK[citation provided], we applied £23,000 to the discounted QALY gained."

"The main outcome measure for the cost-effectiveness analyses was QoL measured by the five-dimensional, three-level EuroQol (EQ-5D-3L).[citation provided] Dimensions assessed are mobility, self-care, usual activities, pain/discomfort and anxiety/depression which are scored on three levels, 'no problems', 'some problems' and 'extreme problems'. UK tariffs were used to transform scores into utilities which range from −0.59 (worse than dead) to 1 (full health).[citations provided] Utilities using Dutch tariffs range from −0.33 to 1.34.[citation provided] Quality-adjusted life years (QALYs) were calculated from utilities by using the area under the curve method."

Item 14. Measurement and valuation of resources and costs: Describe how costs were valued.

Explanation. Reporting of costs in health economic evaluation requires consideration of 2 related, but separate, processes: (1) the degree of disaggregation used in the identification and measurement of resource and cost components (eg, microcosting vs gross-costing) and (2) the method for the valuation of resource and cost components (eg, top-down vs bottom-up).[118] Approaches to cost estimation may vary widely because they require methodological choices and are likely to involve trade-offs or compromises between theoretical soundness and practical feasibility.[118]

Because of this, a key requirement is that authors are transparent about their chosen approach to the measurement and valuation of resources and costs and their data sources. The data sources for resource components could, for example, be derived from a single study, an existing database, routine sources, or the broader literature. Similarly, the prices (unit costs) attached to resource items might be derived from alternative sources for the purposes of a bottom-up, microcosting study, for example, national unit cost databases or institution-specific cost lists. Authors should be aware that microcosting studies may be poorly reported.[119]

If the economic evaluation adopts or cites published estimates using different methodological approaches for different sets of resource and cost components, then each should be described. It may also be relevant to report any adjustments made to cost estimates to approximate to opportunity costs. For example, if capital assets contribute to the cost calculus, authors should describe any adjustments that reflect potential returns on those assets. These issues are explored more fully, in the context of drug costs, in the ISPOR Good Research Practices for Measuring Drug Costs in Cost-Effectiveness Analysis TF Report.[120]

Example of Item 14: Measurement and valuation of resources and costs.[121]

"Resource assessments occurred at scheduled clinic visits. Use by patients of study and non-study drugs was recorded in the trial drug log. BP-related health service contacts were recorded during clinic visits using patient diaries as an aide memoire. At clinic visits, all health service resource use was recorded, together with attribution of resources to BP… Study drugs were prescribed at varying doses and durations. Using national Prescribing Cost Analysis (PCA) data, average costs per unit weight of therapeutic were determined and applied to patient drug use records: doxycycline £0.0015/mg and prednisolone £0.0221/mg. Use of topical steroids was costed similarly using PCA data. Costs of inpatient stays (in days) and outpatient visits were estimated using Hospital Episodes statistics (HES) and the National Schedule of Reference Costs (NSRC)"

Item 15. Currency, price date, and conversion: Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.

Explanation. It is important to report dates in the form of calendar years or financial years for estimated resource quantities or cost components and their associated prices (unit costs) because these assumptions can greatly affect the findings of the economic evaluation. Although prices for most resource items and cost components will be available for the same year for which overall costs are reported, some may only be available for previous years. In these cases, the method of price adjustment, for example, by applying a specific price index (eg, US Personal Health Care deflator), should be reported.

The currency used should be clearly reported, especially when >1 jurisdiction has a currency with the same name (eg, dollars, pesos). Depending on journal requirements, authors should consider using the convention described in International Organization for Standardization 4217 (eg, USD for US dollars, EUR for euros) to aid reporting. Some studies may include currency adjustments, specifically when prices of a resource item or cost component are not available in the country of interest or if analysts prefer to report findings in a widely used currency (eg, USD) or report results from several countries simultaneously.

If currency conversions are performed, the method used (eg, through purchasing power parities) should be reported. If the evaluation involves both price and currency adjustments, the stages followed to arrive at costs expressed in a target currency and price year and any accompanying algorithms should be reported. For example, the Campbell and Cochrane Economics Methods Group provides guidance and accompanying algorithms for adjusting costs to a specific target currency and price year using a gross domestic product deflator index values and purchasing power parity conversion rates produced by the International Monetary Fund and the Organisation for Economic Co-operation and Development.[122] The reporting of studies from different countries in a widely used currency, such as USD, may facilitate comparisons of the cost-effectiveness of different interventions but harbors caveats, outlined in the ISPOR Good Practices TF on Transferability of Economic Evaluations Across Jurisdictions.[123]

Example of Item 15: Currency, price date and conversion[124]

"We estimated the costs for the base-case and intervention scenarios in 2018 US dollars, adopting a South African health-care system perspective (table 1). Average costs reflect 2018 estimates for tuberculosis health-care and diagnostic services in Cape Town that were obtained through review of the published literature and the official price list of the National Health Laboratory Service, South Africa. Cost estimates from previous years were converted into US dollars (where applicable) and adjusted for inflation using an average annual South African gross domestic product deflator rate of 5.71%."

Item 16. Rationale and description of model: If modeling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.

Explanation. The article should describe the model structure used for analysis and explain why it is appropriate for use in the study. For consistency, analysts may want to use published guidance for describing model types.[125-127] This explanation might refer to the similarity of the model structure used for analysis to the model structure used in previous studies of the disease of interest where this is available.[126,128] Alternatively, if an innovative modeling approach is being used, this approach might be related to the outcomes needed for decision makers or how the chosen model structure better reflects disease natural history, current treatment practice, and efficacy and safety compared with previous models in the disease area. The use of an innovative approach might also be related to the extent

to which credible data are available to populate the model. In both cases, the model structure should be described in enough detail that an interested researcher could replicate it. In most cases, a figure illustrating the model structure and patient flows through the model is recommended.

Example of Item 16: Rationale and description of model[129]

"In our symptom-based care seeking model, we defined three TB-symptom levels—asymptomatic, nonspecific, classic—based on the corresponding probability of diagnostic evaluation for TB. We calculated monthly transition rates between these symptom levels based on three constraints: 1. Probability of progression is 2 times that of regression; 2. Lifetime probability of TB self-cure equals that of death in the absence of treatment (untreated case fatality ratio of 0.5); and 3. Mean duration of asymptomatic period is 9 months. These values (monthly transition rates between symptom levels and monthly probabilities of seeking care) were inputted into a decision tree Markov model which was constructed to reflect the diagnostic algorithm (CXR and Xpert) used for Active Case Finding (ACF) in the Zambia TB REACH program. 100,000 individuals defined by TB/HIV status and symptom level and modeled as having a one-time chance to attend ACF (86% for nonspecific and classic symptom). Those who did not access ACF were modeled as seeking routine care with a monthly probability based on symptom development (20% for nonspecific and 40% for classic symptom) throughout the duration of the analysis. Individuals with untreated TB at the end of each monthly cycle experienced a monthly probability of symptom level transition (progression or regression). More detailed model structure and clinical diagnostic algorithms are described in the supporting information S2 and S3 Tables in S1 File; S2 and S3 Figs in S1 File."

Item 17. Analytics and assumptions: Describe any methods for analyzing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.

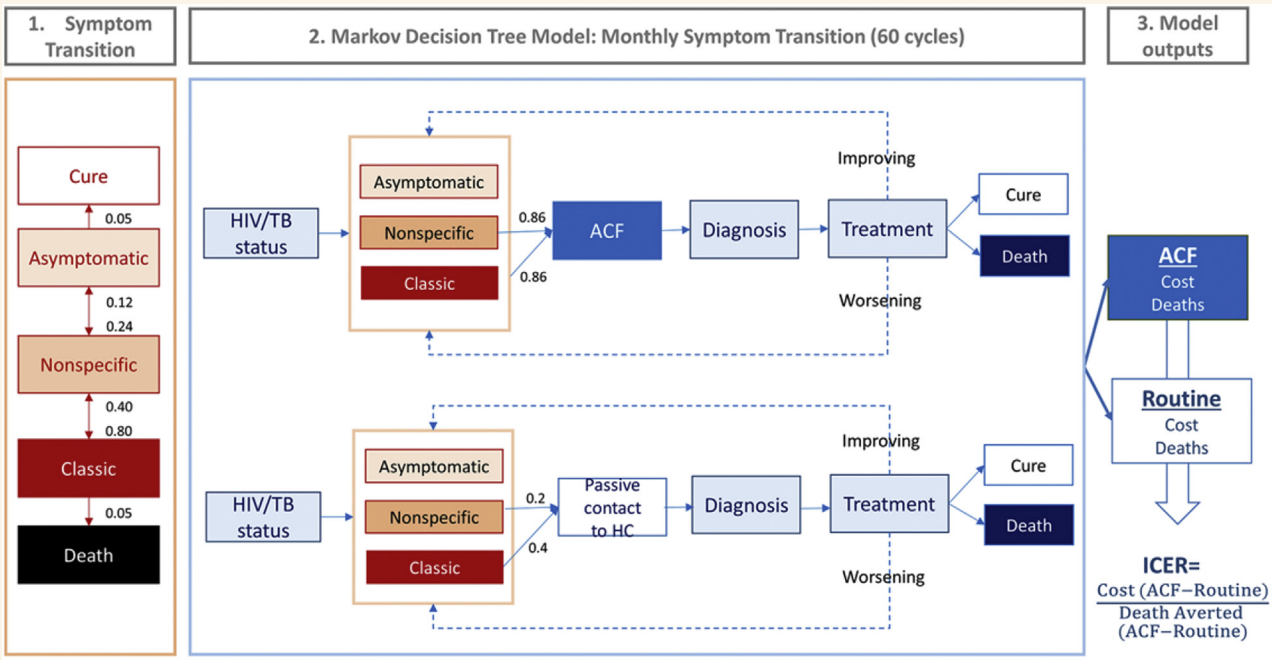
Explanation. Input values based on assumptions including structural assumptions in models make up a critical set of information needed to understand the report findings. The report should present a listing of all the assumptions and calculations needed for a reader with the necessary expertise to potentially replicate the analysis including programming and running the model.[128] There are also a variety of approaches to sharing models with peer reviewers or readers; this will be mandatory for journals with open data sharing policies. At a minimum, sharing of unlocked models with reviewers is encouraged regardless, as in most cases, a basic model description with calculations and assumptions are insufficient to allow a complete replication of findings that includes the use of additional macros, Visual Basic for Application code, and other hidden but important details.

Authors should provide the rationale for and the basis of assumptions (eg, specific data source/article, expert opinion, standard practice, or convenience). Assumptions may include information about the characteristics of the modeled population, disease natural history, and disease management patterns including choice of comparators and treatment pathways.[130]

Additional analytic methods may be required for study- or model-based analysis including approaches to transform or extrapolate data beyond observed values not addressed in items 11 to 15. This could include how preference-based outcomes are calculated (eg, area under the curve) or the durability of treatment efficacy beyond the time period observed in clinical trials.

Validation of assumptions, formulas, and modeling will require additional reporting that addresses what type of validation was undertaken and its approach. Given that the information needed to convey this may be extensive, citations to existing published reports or sharing of de novo information in appendices or open data repositories will likely be required. Reporting guidance for

Figure [X]. Model Structure



ACF indicates, Active Case Finding; HC, healthcare; HIV/TB; human immunodeficiency virus/tuberculosis; ICER, incremental cost-effectiveness ratio.

calibration and validation of modeling has been published to assist authors.[131-133]

Example of Item 17: Analytics and assumptions[134,135]

"A summary of … key assumptions around modelling approach [is] in Table 2; … [The model] is publicly available, accessed through the Open Research Exeter repository."
"We calibrated our [agent-based model] to capture the key characteristics of meningococcal epidemics under both strain replacement scenarios, including the age-distribution of meningococcal incidence (Figure [XA]), average carriage prevalence among different age groups (Figure [XB]), and weekly average incidence of meningococcal cases (Figure [XC]) between 2002 to mid-2015 (the full duration of the available time series)… We emphasize that our goal is not to fit to the timing of past epidemics but instead to calibrate the model against the periodicity of past epidemics in additional to calibration targets depicted in Figure [X]. Details of our calibration approach are described in the Appendix [X]"

Item 18. Characterizing heterogeneity: Describe any methods used for estimating how the results of the study vary for subgroups.

Explanation. The separation of heterogeneity from uncertainty is important for the interpretation of findings of any economic evaluation. Consideration should be given to how heterogeneity in a study's results could arise to appropriately explore and report the effect of different types of heterogeneity. This includes heterogeneity that results when treatment effects are homogeneous on the relative scale (eg, relative risk, odds ratios, or hazard ratios) but the baseline risks (prognosis) vary by characteristics of individuals and traditional subgroup differences when treatment effects differ and particular population characteristics are predictive of the treatment effect (effect modification). Authors should clearly describe their methods for investigating both potential types of heterogeneity. If assuming homogeneity across the population in their study, authors should justify this assumption.

Example of Item 18: Characterizing heterogeneity[136]

"Intention-to-treat comparisons were made for hospitalization and statin costs during the scheduled study treatment period. Previous analyses of [the Heart Protection Study] had indicated similar proportional reductions of ≈25% in the rate of [major vascular events] with allocation to 40 mg simvastatin daily in different categories of participant. Across the different subgroups studied, similar proportional reductions of ≈22% in UK hospitalization costs associated with vascular events, and similar absolute differences in the costs of statin treatment, were also observed between the study treatment groups. Consequently, it was hypothesized that the proportional reductions in US hospitalization costs associated with vascular events, and the absolute differences in US costs of statin treatment between the study treatment groups, would also be similar across different subcategories of participant. Hence, the absolute reduction in the US costs of vascular event hospitalizations in any particular subgroup was derived by applying the overall proportional reduction in vascular event costs observed among all participants to the vascular event costs observed in the placebo group for that particular subgroup. Absolute reductions in vascular deaths within subgroups were estimated similarly."

Item 19. Characterizing distributional effects: Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.

Explanation. Characterizing distributional effects may be important if decision makers are interested in the equity impacts of the interventions evaluated based on social variables such as socioeconomic status, ethnicity, and geographical location or disease categories such as disability and severity of illness.[137] Authors should describe any methods they applied to address distributional concerns through the use of population-specific parameters (eg, higher costs for rural settings, lower adherence for high-risk groups), differential weights applied to preference-based measures by distributional factors such as age,[138] or any adjustments to a cost-effectiveness threshold for special cases such as rare diseases or end-of-life treatment.[139]

The underpinning premise for characterizing distributional effects should be stated. For example, this might be driven by the requirements of methodological guidelines in the local jurisdiction or a desire by authors to advance egalitarian or other distributive notions of justice in society. Methods for assessing trade-offs between efficiency and equity concerns, such as the equity-efficiency impact plane, should be described.[137] If distributional concerns were not considered in the evaluation, then this should be explicitly stated.

Example of Item 19: Characterizing distributional effects[140]

"A series of scenario analyses was performed to explore the impact of altering the socioeconomic differences in model inputs on [distributional cost-effectiveness analysis] results, corresponding to the 4 questions raised in introduction. The intervention impacts estimated in each scenario analysis were compared with the base case estimates, which constitute the results when all of the socioeconomic differences in the model inputs mentioned previously are incorporated. We assume that the base case represents the best estimate of the intervention impacts. The base case results and the results of each scenario analysis are presented as scatter plots on the health equity impact plane. The differences from the base case reflect in which direction and to what extent each scenario affects how well each model estimates the intervention impact on the distribution of health."

Item 20. Characterizing uncertainty: Describe methods to characterize any sources of uncertainty in the analysis.

Explanation. Authors should report approaches to capturing uncertainty. Statistical uncertainty associated with economic evaluations undertaken with individual patient data (IPD) can be reflected by reporting confidence intervals or Bayesian credibility intervals of incremental costs and incremental effects. Because confidence or credible intervals can be problematic to estimate and misleading,[141] cost-effectiveness planes and cost-effectiveness acceptability curves may be more appropriate

presentational tools. These presentational devices are more consistent with decision making compared with an inferential approach to interpreting uncertainty. For model-based economic evaluations and hybrid analyses combining IPD analyses with models, parameter uncertainty may be represented for individual parameters in a deterministic sensitivity analysis or across all parameters simultaneously with probabilistic analysis. Where probabilistic analysis is used, the same presentational tools (cost-effectiveness planes/acceptability curves) can be used as for IPD analyses. For deterministic analyses, tornado diagrams are useful.

Approaches to capturing uncertainty that are not related to sampling, such as methodologic (eg, choice of discount rates, unit cost vectors, and study perspective) or structural (eg, duration of treatment, effectiveness over time, events included in analysis, model used) uncertainty, should also be described.

Example of Item 20: Characterizing uncertainty[136]

"Parameter uncertainty in the estimates of life years gained, hospitalization cost savings, and cost per life year gained was assessed by nonparametric bootstrapping of the event and cost equations used in the model.[citation provided]... The effects of changing selected analytic parameters on the cost-effectiveness estimates were assessed. First, the predicted life expectancy was adjusted for age- and gender-specific health-related quality of life derived from a representative sample of the US population in the Agency for Healthcare Research and Quality's Medical Expenditure Panel Survey. Second, an assessment was carried out for the impact on cost-effectiveness estimates of persistent use of statin therapy declining to 35% by the sixth year after initiation (i.e., persistence during each of the first 5 years of 80%, 70%, 60%, 50%, 40%, and 35% thereafter). Finally, the cost-effectiveness of lifetime use of generic 40 mg simvastatin at $0.20 per day was assessed. Further extrapolation was made (as in the UK setting [citation provided]) to 5 years beyond the eligible age limits for [the heart protection study (HPS)] (i.e., down to 35 years and up to 85 years) and to vascular risk down to a 5-year [major vascular event] risk of 5% (compared with the 12% risk in the lowest quintile of HPS)."

Item 21. Approach to engagement with patients and others affected by the study: Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (eg, clinicians or payers) in the design of the study.

Explanation. PPIE, wider community engagement, and stakeholder involvement aim to enhance the relevance, acceptability, and appropriateness of research, ultimately improving its quality.[142] Community engagement directly involves local populations in all aspects of decision making, implementation, and policy. It can strengthen local capacities, community structures, and local ownership to improve transparency, accountability, and optimal resource allocations across diverse settings. To understand the contribution PPIE or community engagement makes to research, we encourage reporting of the approach to stakeholder and PPIE when included in health economic evaluation.

Acknowledging that PPIE and community engagement in health economic evaluation is still in its infancy,[143,144] this item requires authors to report any approaches they use and is purposively broad. In addition to reporting the general approach to PPIE, authors may wish to report more specific details of PPIE using GRIPP2 guidance.[145] The involvement of stakeholders more traditionally used in developing economic evaluations (eg, clinicians, payers, industry) should be similarly mentioned.

Example of Item 21: Approach to engagement with patients and others affected by the study[146]

"We established a public reference group of individuals with an interest in vaccination and with a range of backgrounds who felt comfortable working in complex areas such as modelling. We used a series of 21 meetings or 'knowledge spaces' to create opportunities for deliberative dialogue about modelling in order to identify the potential areas where the public can contribute. Each meeting focused on a different topic or stage in the modelling process. Deliberative elements included presentations on concepts and methods to ensure the [Principal Investigator] Reference Group built up an understanding of the modelling process".

Results

Item 22. Study parameters: Report all analytic inputs (eg, values, ranges, references) including uncertainty or distributional assumptions.

Explanation. When models are used, sufficient information must be provided to allow interpretation by reviewers experienced with the same type of model, decision makers who must understand generalizability to their own decision context, and interested researchers who wish to replicate the analysis. Providing a table with all the input values and data sources used is critical to full reporting. Additional information on the study design of each source is also encouraged. A table with key parameters in the main body of the report with a supplementary table of the ranges and actual distributions including type of distribution and relevant moments used in the uncertainty analyses for all model parameters is a good approach (see Example). Given that some or many of these values will be transformed according to methods in items 9 to 17, Study Parameters are more appropriately reported in the "Results" section of a report.

Example of Item 22: Study parameters[134]

Input parameters	Value	Probability distribution[a]
Proportion of patients with pCR after neoadjuvant treatment, %		
HP	16.8	β (α = 18.00; β = 89.00)
THP	45.8	β (α = 49.00; β = 58.00)
DDAC/THP	56.5	β (α = 78.00; β = 60.00)
TCHP	52.5[b]	β (α = 115.00; β = 104.00)
Effect of adjuvant treatment		
Distant recurrence[c]		
3-y distant recurrence probability with H with residual disease (reference group), %	15.9	β (α = 118.00; β = 625.00)
RR by adjuvant treatment		
T-DM1 with residual disease	0.60	Log normal (μ = −0.51; σ = 0.09)
DDAC/THP followed by T-DM1 with residual disease	0.52[d]	Truncated normal (a = 0.18; b = 0.60)[e]
DDAC followed by T-DM1 with residual disease	0.40[d]	Truncated normal (a = 0.18; b = 0.60)[e]
H with pCR	0.18	Log normal (μ = −1.70; σ = 0.18)
Local recurrence[c]		
3-y locoregional recurrence probability for H with residual disease (reference group), %	4.6	β (α = 34.00; β = 709.00)
RR by adjuvant treatment		
All treatments with residual disease other than H	0.24[f]	Log normal (μ = −1.43; σ = 0.11)
H with pCR	0.24[g]	Log normal (μ = −1.43, σ = 0.11)
Subsequent distant recurrence after initial local recurrence		
10-y probability, %	18.9[h]	β (α = 13.00; β = 56.00)
Survival and mortality parameters		
Median survival, mo		
With distant recurrence	38	Normal (38.00; 4.08)
With acute myeloid leukemia	8	Normal (8.00; 2.00)
Mortality recurrence-free state	Background mortality, life table, age-dependent	NA
Annual risk of death due to CHF, %	12.7%	β (α = 69.93; β = 488.07)
Chemotherapy toxicity[c]		
CHF		
1-y probability in patients with non-AC chemotherapy (reference group), %	3.7	β (α = 100.32; β = 2647.72)
RR for AC chemotherapy	1.26	Log normal (μ = 0.23; σ = 0.08)
Acute myeloid leukemia		
1-y probability in patients with no chemotherapy (reference group), %	0.1%	β (α = 138.30; β = 197 505.60)
RR for non-AC chemotherapy	0.88	Log normal (μ = −0.13; σ = 0.35)
RR for AC chemotherapy	1.68	Log normal (μ = 0.52; σ = 0.28)
Costs, $[i]		
Neoadjuvant treatment regimen[j]		
HP	64 389	γ (α = 25.00; β = 2575.56)
THP	65 428	γ (α = 25.00; β = 2617.10)
DDAC/THP	106 787	γ (α = 25.00; β = 4271.49)
TCHP	153 257	γ (α = 25.00; β = 6130.28)
Adjuvant treatment regimen[j]		
H	108 995	γ (α = 25.00; β = 4359.78)
T-DM1	157 871	γ (α = 25.00; β = 6314.82)
DDAC/THP followed by T-DM1	264 658	γ (α = 25.00; β = 10586.32)
DDAC followed by T-DM1	199 230	γ (α = 25.00; β = 7969.21)
Adjuvant H after neoadjuvant TCHP	93 424	γ (α = 25.00; β = 3736.96)
Adjuvant T-DM1 after neoadjuvant TCHP	135 318	γ (α = 25.00; β = 5412.70)
Treatment cost of recurrence, $		
Locoregional recurrence		
First y	21 005[k]	γ (α = 25.00; β = 840.20)

continued

Input parameters	Value	Probability distribution[a]
After first y	2335[k]	γ (α = 25.00; β = 93.41)
Distant recurrence		
Annual cost of care	144 865[l]	γ (α = 25.00; β = 5794.62)
Chemotherapy toxic effects		
Initial CHF treatment	36 748	γ (α = 25.00; β = 1469.92)
Annual CHF care	7035	γ (α = 25.00; β = 281.40)
Lifetime treatment of acute myeloid leukemia	21 345	γ (α = 2530.10; β = 1/8.44)
Utilities of health states		
First y recurrence free	0.79	β (α = 87.73; β = 24.17)
Second y and after		
Without recurrence	0.83	β (α = 39.01; β = 8.33)
With local recurrence	0.72	β (α = 89.85; β = 34.60)
With distant recurrence	0.53	β (α = 4.61; β = 4.13)
With CHF	0.71	β (α = 72.38; β = 29.57)
With acute myeloid leukemia	0.26	β (α = 9.13; β = 25.98)
Last y with distant recurrence before death	0.16	β (α = 5.00; β = 26.26)

Abbreviations: CHF, congestive heart failure; DDAC, dose-dense anthracycline/cyclophosphamide; DDAC/THP, dose-dense anthracycline/cyclophosphamide followed by paclitaxel, trastuzumab, and pertuzumab; H, trastuzumab; HP, trastuzumab and pertuzumab; NA, not applicable; pCR, pathologic complete response; RR, relative risk; TCHP, docetaxel, carboplatin, trastuzumab, and pertuzumab; T-DM1, trastuzumab emtansine; THP, paclitaxel, trastuzumab, and pertuzumab triplet.

[a] Probability distributions of clinical and utility parameters were informed with summary statistics. For most cost parameters, no summary statistics were available, and we therefore assumed a 20% SE.

[b] This estimate was obtained using estimates for estrogen receptor–positive cancer and estrogen receptor–negative cancer and the proportion of patients with each type in the KATHERINE trial.

[c] We converted risks of recurrence, acute myeloid leukemia, and CHF to 1-year probabilities and used these in the model in the form of RRs.

[d] This is an assumption because of a lack of data for this setting. We assumed that the true value was between a 5-year probability of distant recurrence of 5% in patients with pCR receiving H (from Symmans et al[4]) for the proportion of patients who would have achieved pCR if treated with neoadjuvant DDAC/THP and a 3-year probability of distant recurrence for patients with residual disease receiving T-DM1 (from von Minckwitz et al[8]).

[e] A log-normal distribution was also examined for RR of distant recurrence for adjuvant DDAC/THP followed by T-DM1 with residual disease and RR of distant recurrence for adjuvant DDAC followed by T-DM1 with residual disease. We found that applying the log-normal distribution to these parameters did not alter the cost-effectiveness results of our study, and we assumed that the truncated normal distribution would better reflect assumptions of our study and characterize uncertainty in these parameters.

[f] There is no data on probability of local recurrence in patients with residual disease receiving DDAC/THP followed by T-DM1 or DDAC followed by T-DM1. Thus, we made a conservative assumption that it was equal to T-DM1 alone.

[g] Patients with pCR receiving H have a better prognosis than patients with residual disease receiving H. Thus, the local recurrence probability in the group H with pCR cannot be higher than the local recurrence probability in the group receiving H with residual disease. Gianni et al[5] reported higher local recurrence probabilities for patients with pCR because that study enrolled a higher-risk population at baseline than the KATHERINE trial. Consequently, we based the estimates of the local-recurrence probabilities for patients receiving H with pCR on the KATHERINE trial and assumed that these estimates were the same as estimates for the group receiving H with residual disease.

[h] The estimate was calculated using the number of patients who developed subsequent distant recurrence after an initial local recurrence during a 10-year period of the study by Wapnir et al.[34]

[i] All costs are expressed in 2020 US dollars. When necessary, we inflated unit costs to 2020 US dollars using the Consumer Price Index.

[j] We used drug-pricing data from McKesson Corporation to calculate the costs of each treatment regimen.

[k] A mean of local and regional recurrence provided by Schousboe et al[29] and inflated with Consumer Price Index from January 2008 to January 2020.

[l] The cost of distant-recurrence health state was estimated using the Flatiron Health Database for use of treatment regimens among patients with metastatic breast cancer and drug-pricing data from McKesson Corporation. We used utilization data for patients diagnosed after the Food and Drug Administration approval of T-DM1 (ie, March 2017 to July 2019).

Item 23. Summary of main results: Report the mean values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure.

Explanation. Authors should report the mean values for the main categories of estimated costs (including total costs) for each comparator group and the mean values for the main outcomes of interests (including outcome categories if applicable) for each comparator group. Both the discounted and undiscounted mean values for the main categories of costs and outcomes should be reported, to be transparent about how sensitive findings are to (the method and rate of) discounting.

Authors should also report the effect of underlying heterogeneity, such as reporting mean costs and effects by identifiable subgroups of the population of interest. Similarly, authors should strongly consider reporting disaggregated mean costs and consequences by perspective, to aid understanding of differential impacts, if applicable. When distributional assumptions are used to create weighted measures, both weighted and unweighted findings should be represented to aid interpretation.

Summary measures, such as incremental cost-effectiveness ratios, cost-benefit ratios, net health/monetary benefit outcomes can then additionally be reported. Reporting negative incremental cost-effectiveness ratios when an intervention is either dominant or dominated is not relevant for decision making and should be avoided. Estimates of net health benefit/net monetary benefit should be accompanied by the cost-effectiveness threshold to which they relate, and its source. A cost-effectiveness plane is a helpful aid to understanding the extent to which interventions are dominated or extendedly dominated.

Example of Item 23: Summary of main results[147]

Average undiscounted Life years and QALYs per patient for each allocation scheme

	Random allocation		Waiting time		2006 NKAS		Longevity matching		QALY maximizing	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Life y										
Transplant recipients (by age group)										
18–29	27.2	(24.7-29.7)	27.2	(24.0-30.3)	32.8	(30.3-35.3)	31.5	(29.3-33.7)	29.2	(27.3-31.2)
30–39	26.5	(24.6-28.4)	25.4	(23.5-27.3)	29.2	(27.7-30.8)	30.1	(28.6-31.7)	27.5	(26.2-28.8)
40–49	23.4	(22.3-24.6)	22.2	(21.0-23.3)	23.4	(22.4-24.5)	22.6	(21.6-23.6)	23.4	(22.5-24.4)
50–59	15.2	(14.5-15.9)	15.0	(14.3-15.7)	14.5	(13.8-15.2)	14.5	(13.7-15.2)	15.6	(14.7-16.6)
>60	11.2	(10.7-11.6)	11.4	(11.0-11.9)	10.7	(10.2-11.3)	11.0	(10.4-11.6)	13.2	(11.5-14.8)
Transplant recipients (all)	18.0	(17.5-18.5)	17.1	(16.7-17.6)	21.1	(20.5-21.7)	21.2	(20.7-21.8)	23.6	(23.0-24,2)
No transplant (all)	8.9	(8.8-9.1)	9.0	(8.9-9.1)	9.0	(8.9-9.1)	6.8	(6.7-6.9)	6.5	(6.4-6.6)
QALYs										
Transplant recipients (by age group)										
18–29	22.4	(20.4-24.5)	22.4	(19.8-24.9)	27.1	(25.0-29.2)	26.0	(24.1-27.8)	24.1	(22.5-25.7)
30–39	21.4	(19.9-22.9)	20.6	(19.1-22.2)	23.8	(22.5-25.1)	24.5	(23.2-25.8)	22.4	(21.3-23.5)
40–49	18.9	(18.0-19.9)	17.9	(17.0-18.8)	18.9	(18.0-19.8)	18.3	(17.5-19.1)	19.1	(18.3-19.9)
50–59	12.3	(11.7-12.9)	12.1	(11.6-12.7)	11.7	(11.1-12.3)	11.7	(11.1-12.3)	12.7	(12.0-13.5)
>60	9.0	(8.7-9.4)	9.2	(8.8-9.6)	8.7	(8.2-9.1)	8.9	(8.4-9.4)	10.7	(9.3-12.0)
Transplant recipients (all)	14.6	(14.2-15.0)	13.9	(13.5-14.2)	17.1	(16.6-17.6)	17.2	(16.8-17.7)	19.3	(18.8-19.8)
No transplant (all)	6.9	(6.8-7.0)	6.9	(6.9-7.0)	7.0	(6.9-7.1)	5.2	(5.1-5.3)	5.1	(5.0-5.1)

CI, confidence interval; NKAS, National Kidney Allocation Scheme; QALY, quality-adjusted life y.

[Discounted] cost-effectiveness results for transplant recipients, patients who did not receive a transplant and all patients combined

	Transplant recipients		No transplant		All patients				
	Absolute costs	Absolute QALYs	Absolute costs	Absolute QALYs	Absolute costs	Absolute QALYs	Incremental costs	Incremental QALYs	ICER
Longevity matching	£632	44 704	£841	20 961	£1473	65 665	–	–	–
QALY maximization	£681	48 045	£818	20 504	£1499	68 549	£25	2884	£8751
Random	£591	40 236	£1089	26 328	£1679	66 563	£181	–1986	Dominated
Waiting time	£584	39 496	£1099	26 572	£1684	66 068	£185	–2481	Dominated
2006 NKAS	£625	44 040	£1097	26 529	£1722	70 569	£224	2020	£110 741

ICER, incremental cost-effectiveness ratio; NKAS, National Kidney Allocation Scheme; QALY, quality-adjusted life y.

Item 24. Effect of uncertainty: Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.

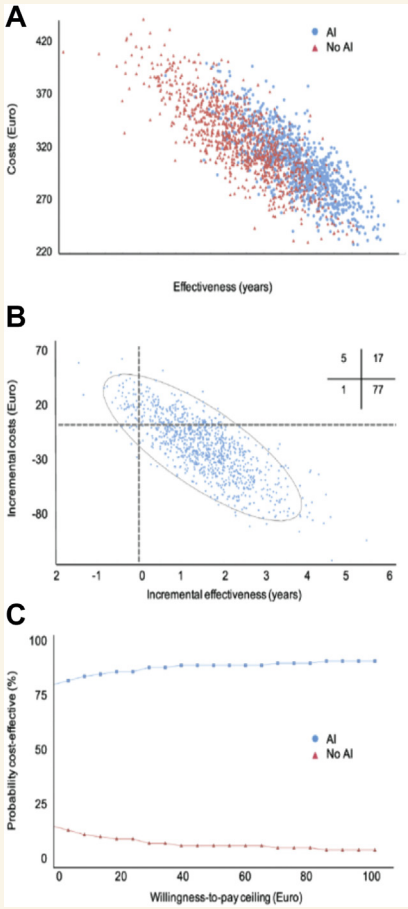
Explanation. Uncertainty should be described using appropriate uncertainty intervals for quantities. Authors should always report the impact of choice of discount rate and time horizon, at minimum, if included in the study. Authors are encouraged to use figures along with data where possible to depict the effect of uncertainty regarding structural or methodologic choices, such as extrapolation approaches. Tornado diagrams should be used if deterministic analyses are performed; cost-effectiveness plane scatter plots depicting distinguishable points for each intervention and accompanying cost-effectiveness acceptability curves should be used for probabilistic analysis, if appropriate.

Item 25. Effect of engagement with patients and others affected by the study: Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study.

Explanation. A key area of reporting is the difference, or the impact, patient, public, community, and stakeholder involvement has made to research because this builds the evidence base for practice.[148,149] When studies have involved patients, carer, payers, the public, or communities as active collaborators in the research process (as opposed to participants in a research study), we would encourage authors to report any difference this involvement made to the research. Differences may include differences in scope, methods, results, interpretation of results, or process of research. In addition to reporting the difference or impact of public or stakeholder involvement, authors may wish to report more detailed aspects of PPIE using GRIPP2 guidance.[145]

Example of Item 24: Effect of uncertainty[134]

Figure 2. Cost-effectiveness plane, incremental cost-effectiveness, and net-benefit analysis of the base case. (**A**) The costs and effectiveness of the 2 comparators are plotted for 1,000 sampled individuals in each group. (**B**) The incremental costs and effectiveness of artificial intelligence (AI) compared with no AI are plotted. Quadrants indicate comparative cost-effectiveness (e.g., upper right: higher costs at higher effectiveness; lower right: lower costs and higher effectiveness). Inserted cross-tabulation: Percentage of samples lying in different quadrants. (**C**) We plotted the probability of comparators being acceptable in terms of their cost-effectiveness depending on the willingness-to-pay threshold of a payer. The range of willingness to pay was expanded from 0 to 100 euro and did not considerably change beyond this threshold.



Example of Item 25: Effect of engagement with patients and others affected by the study[146]

[This] study identified the difference that public involvement can make to mathematical and economic modelling. At a macro level, we found the public contributed to reviewing context, reviewing relevance, assessing data and justifying model choice, troubleshooting, interpreting and reviewing outcomes and decision-making. At a micro level, we identified specific type of contribution according to each stage of the modelling process. Public contributors enhanced the validity of the model, potentially enhancing its relevance, utility and transparency through diverse inputs, enhancing the credibility, consistency and continuous development through scrutiny, in addition to contextualising the model within a wider societal view.

Discussion

Item 26. Study findings, limitations, generalizability, and current knowledge: Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.

Explanation. The discussion provides context to the results and aids the reader to interpret and critically review the study findings. Authors may wish to use subheadings to aid readability.[150] The discussion should summarize the key results and how these support the study conclusions. Authors should indicate the degree and main areas of uncertainty. Notable subgroup and distributional effects should be discussed together with any ethical and equity considerations, such as the use of sociodemographic characteristics or biomarkers to determine which subgroups should have access to treatment.[151,152] It is also important to relate the study findings to relevant decision-making frameworks or thresholds to demonstrate the relevance of the study to decision making for a relevant jurisdiction/setting.

Transparency and validation are essential for decision makers to have trust and confidence in economic data. A section on study limitations should include a discussion addressing the impact of assumptions and methodological choices that were made in the conduct of the study. Such assumptions and choices give rise to a number of areas of uncertainty. Any limitations arising from discrepancies in tests of model validity (or absence of validation) should also be discussed.[130,133]

It is important to discuss the potential impact of the research on patients, policy, or practice and highlight how the study advances knowledge. In this respect, the discussion section should relate the study findings back to the original decision question and explain how the results might affect the reader's understanding of the decision problem. The study findings should be discussed in the context of the current literature and possible explanations provided for differing results from previous studies. The generalizability (external validity) and potential transferability of the study findings to other settings

Example of Item 26: Study findings, limitations, generalizability, and current Knowledge[153]

[e.g., limitations]: "This analysis has important limitations. First, we assume homogenous population mixing. This assumption may over- or under-estimate the benefits of [polymerase chain reaction (PCR)] testing; however, we have calibrated our model to reflect observed data, using a transmission multiplier. When relevant, we selected values or made assumptions which would provide a conservative estimate of the benefits of testing (PCR sensitivity, test cost, transmission reduction after a negative test), and then varied these values widely in sensitivity analyses. Second, we do not address supply chain lapses which could impact the feasibility of implementing these strategies. Third, we exclude several factors that may result from expanded testing that would render these strategies even more cost-effective, including averting quality-of-life reductions due to [coronavirus disease 2019 (COVID)]-related morbidity or self-quarantine-related mental health issues, preventing school closure-related workforce gaps, increasing economic purchasing, and enabling economic activity to reopen due to reduced COVID incidence. We also assume that transmissions vary with a constant daily rate by disease state; emerging data suggest that infectivity may be highest early after acquisition of the virus. If true, testing strategies which diagnose people in early or asymptomatic stages of infection would be of higher value. Finally, we do not model contact tracing, which is likely to be a critical tool to respond to a patchwork of surging outbreaks over time."

should also be discussed. Finally, the discussion section should present future research directions. Questions related to the research problem that remain unanswered after the study or have become more focused as a result of the study should be presented.

Other relevant information

Item 27. Source of funding: Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis

Explanation. Funding relationships in economic evaluation have been shown to correlate with the direction of findings.[154-161] Authors should describe any relationship of the funders to other organizations or individuals with a financial or other interest in the work including nonmonetary sources of support. If no funding or nonmonetary support was received, authors should so state.

Example of Item 27: Source of Funding[162]

"This work was supported by the [National Institute for Health Research (NIHR)] School for Primary Care Research (grant reference 117a). [The author] was funded by NIHR Research Professorship (NIHR-RP-02-12-012). A trial steering committee provided independent supervision on behalf of the funder and sponsor (University of Bristol) and an independent data monitoring committee oversaw safety."

Item 28. Conflicts of interest: Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors (ICMJE) requirements.

Explanation. Authors should declare anything that readers might think is a competing interest, regardless of whether the authors themselves feel their impartiality is affected. Authors may be unaware of their bias, believe they are impartial, or believe that multiple COI cancel each other out and use this to justify keeping potential COIs concealed.[163-166] COI information may further help the reader interpret the credibility of the results. In the absence of a journal policy, we suggest that authors complete a standard COI form (eg, that of the ICMJE,[167] http://www.icmje.org/conflicts-of-interest/). At a minimum, authors should declare financial interests present within 36 months before publication and any other interests that could appear to have influenced the work.

Example of Item 28: Conflicts of Interest[162]

"All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Thompson reports that he has received funding from Alere Inc to conduct research on C-reactive protein point-of-care tests, has received funding from Roche Molecular Diagnostics for consultancy work."

Discussion

We hope this update of the CHEERS statement will be useful to those who need to identify, prepare, and interpret reports of health economic evaluations. Despite the promotion and increased number of available health economic evaluations and the availability of CHEERS in multiple languages since 2013, there is still some indication that CHEERS could be more widely and appropriately used. A convenience sample of 50 articles citing CHEERS revealed only 42% (95% confidence interval 28-56) made an appropriate use of CHEERS.[5] This is a similar rate to that observed in other major reporting guidelines (CONSORT, PRISMA, Animal Research: Reporting of In Vivo Experiments [ARRIVE]). The same study also found that the inappropriate use of CHEERS increased from its time of publication.

In creating this update, we also wanted to ensure the broadest possible application of CHEERS. Previous concerns raised about its lack of applicability in CBAs were understandable, given original CHEERS guidance leaning strongly toward proving direction for those conducting CEAs (including CUAs). This was driven, in part, by the small prevalence and impact of published CBAs at the time of the original CHEERS guidance. Nevertheless, it is clear that broader characterizations of the benefits of healthcare, in concert with the promotion and publication of other forms of economic evaluation, such as CBAs and distributional CEA, are becoming increasingly important. Health economic evaluation is also finding increasing application across a wider spectrum of health interventions. We hope the revised CHEERS statement addresses these concerns.

We are also aware that the final checklist reflects the perspectives of the TF members, PPIE advisors, Delphi Panel members, and peer reviewers involved. Although nominal group techniques such as the Delphi approach are intended to minimize the unnecessary influence of dominant experts in a group, we acknowledge the output of these processes is only as good as the experience and perspectives represented. Despite seeking a diversity of expertise, it is possible that more could be said for specific applications of CHEERS for interventions that have impacts beyond health (eg, educational, environmental, social care). We would encourage those who see opportunities to expand CHEERS 2022 items or to create additional reporting guidance that provides clarification in specific areas to provide feedback to, or work with, one or more members of the CHEERS TF to develop CHEERS extensions in these areas.

The updated guidance is also anticipating future developments in the conduct and reporting of published health economic evaluations. These include the use of health economic analysis plans, model sharing, and the increasing involvement of stakeholders in health research, including engagement with communities, patients, and the public. Although some on the Delphi Panel suggested these developments did not warrant their own reporting items, the TF ultimately felt addressing these developments through the creation of separate items could foster awareness of their use and development.

Given that there is an ever-increasing need for clarity of information to support healthcare decision making and attention to healthcare expenditure, we anticipate the role of published health economic evaluation to become even more important. Although we hope the CHEERS 2022 statement and accompanying resources will ultimately improve the quality of reporting (and decision making), the impact of the original CHEERS statement on reporting quality is still uncertain. A formal evaluation study is ongoing and results will be available in 2022.[168] In the meantime, we have focused our attention on strategies to increase the appropriate use of CHEERS, including creating a wider range of tools and resources for editors and authors, seeking endorsement across a larger group of journals, and increasing outreach efforts.

We also recognize researchers may also wish to translate CHEERS 2022 into other languages. In these cases, we would encourage appropriate methods[56,169] and collaboration with one or more TF members to ensure consistency with CHEERS. We encourage authors, peer reviewers, and editors to regularly consult the CHEERS 2022 webpage and to provide feedback on how it can be improved.

Conclusions

This Explanation and Elaboration Report is intended to aid users in appropriately applying the new CHEERS 2022 28-item checklist. The CHEERS 2022 statement is primarily intended for researchers reporting economic evaluations for peer-reviewed journals and the peer reviewers and editors assessing them for publication. Nevertheless, we anticipate familiarity with reporting requirements will be useful for analysts when planning studies. It may also be useful for HTA bodies seeking guidance on reporting, given that there is an increasing emphasis on transparency in decision making.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2021.10.008.

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Analysis and interpretation of data: Husereau, Drummond, Augustovski, Briggs, Carswell, Caulley, Chaiyakunapruk, de Bekker-Grob, Greenberg, Loder, Mauskopf, Mullins, Petrou, Pwu, Staniszewska
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Mr Husereau is a Task Force co-Chair and the submitting and corresponding author; Dr Drummond is a Task Force co-Chair. All other authors (Drs Augustovski, de Bekker-Grob, and Briggs, Mr Carswell, and Drs Caulley, Chaiyakunapruk, Greenberg, Loder, Mauskopf, Mullins, Petrou, Pwu, and Staniszewska—listed in alphabetical order by surname) and the cochairs conceived this article and designed the Delphi survey conducted to inform the guideline content. Mr Husereau conducted a literature review, administered the Delphi survey, and analyzed the data for both. Mr Husereau and Dr Drummond prepared materials for each meeting and led the drafting and editing of the article. Drs Augustovski, de Bekker-Grob, and Briggs, Mr Carswell, and Drs Caulley, Chaiyakunapruk, Greenberg, Loder, Mauskopf, Mullins, Petrou, Pwu, and Staniszewska drafted particular sections of the article. Drs Drummond and Staniszewska led the patient and public involvement and engagement (PPIE) advisory group. Mr Husereau and Dr Carswell led the Editors Advisory Group. All authors were involved in revising the article critically for important intellectual content. All authors approved the final version of the article. Mr Husereau is the guarantor of this work. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. Dr Moher served as scientific advisor and reviewed the initial proposal and attended initial meetings; all members of the PPIE (Ivett Jakab, Emma Kinloch, Eric Low, Jean Mossman, Declan Noone, Phil Posner, and Jo Watson) critically reviewed the initial checklist and suggested and provided review and advice on subsequent drafts of the checklist and Explanation and Elaboration Report. Members of the PPIE were invited to participate in the Delphi Panel exercise. All members of the PPIE and Delphi Panel were invited to review drafts of the checklist and accompanying report.

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