

GRADE Guidelines 30: The GRADE Approach to Assessing the Certainty of Evidence from Models – an Overview in the Context of Health Decision-making

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Abstract

Objectives:

To present the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) conceptual approach to the assessment of certainty of evidence from modelling studies (i.e. model outputs).

Study Design and Setting:

We performed expert consultations, held an international multi-disciplinary workshop, and further elaborated a conceptual approach for assessing the certainty of evidence from models within the context of systematic reviews, health technology assessments, and health care decisions. We assessed the content validity of the approach obtaining feedback from experts in a broad range of modelling and health care disciplines.

Results:

Workshop participants agreed, that the domains determining the certainty of evidence previously identified in the GRADE approach (risk of bias, indirectness, inconsistency, imprecision, reporting bias, magnitude of an effect, dose-response relation, and the direction of residual confounding) also apply in the context of assessing the certainty of evidence from models. The assessment itself will depend on the nature of model inputs and the model itself. We distinguished the assessment of the certainty of model outputs from a single model and across multiple models. We proposed a framework for selecting the best available evidence from models: 1) to develop de novo a model specific to the situation of interest, 2) to identify an existing model the outputs of which provide the highest certainty evidence for the situation of interest, that could be used either “off the shelf” or after adaptation, and 3) to use outputs from multiple models. We also present a summary of preferred terminology to facilitate communication among various modelling and health care disciplines.

Conclusions:

This conceptual GRADE approach provides a framework for using evidence from models in health decision making and the assessment of certainty of evidence from a model or models. The GRADE Working Group and the modelling community continue developing detailed methods and related guidance for the assessment of specific domains determining the certainty of evidence from models.

What is new

1. General concepts determining the certainty of evidence in the GRADE approach (risk of bias, indirectness, inconsistency, imprecision, reporting bias, magnitude of an effect, dose-response relation, and the direction of residual confounding) also apply in the context of assessing the certainty of evidence from models (model outputs).
2. Detailed assessment of the certainty of evidence from models differs for the assessment of outputs from a single model compared to the assessment of outputs across multiple models.
3. We propose a framework for selecting the best available evidence from models to inform health care decisions: to develop a model de novo, to identify an existing model the outputs of which provide the highest certainty evidence, or to use outputs from multiple models.
4. We suggest that the modelling and health care decision making communities collaborate further to clarify terminology used in the context of modelling and make it consistent across the disciplines to facilitate communication.

Introduction

When direct evidence to inform health decisions is not available or not feasible to **measure** (e.g. long-term effects of interventions or when studies in certain populations are perceived as unethical), modelling studies may be used to **predict** that “evidence” and inform decision-making.[1, 2] Health decision makers arguably also face many more questions than can be reasonably answered with studies that directly measure the outcomes. Formal modelling (as opposed to the back-of-the-envelope approaches), therefore, is increasingly being used to predict the disease dynamics and burden, the likelihood that an exposure represents a health hazard, the impact of interventions on health benefits and harms, or the economic efficiency of health interventions, among others [1]. Irrespective of the modelling discipline, decision makers need to know the best **estimates** of the modelled outcomes and how much **confidence** they may have in each estimate.[3] Knowing to what extent one can trust the outputs of a model is necessary when using them, frequently together with other information, to support health decisions [4].

Although a number of guidance documents on how to assess the trustworthiness of estimates obtained from different models in several health fields have been previously published [5-16], they are limited by combining aspects of methodological rigor together with completeness of reporting, and by making no clear distinction among various components affecting the trustworthiness of model outputs. Uncertainty about the outcomes estimated through modelling may result from the uncertainty about **model inputs** and from the uncertainty about a **model itself**. Thus, modellers and those using results from models should assess the credibility of both.[4] Authors have attempted to develop tools to assess model credibility, but many addressed only selected aspects, such as statistical reproducibility of data, the quality of reporting[17], or a combination of reporting with aspects of good modelling practices[7, 18-21]. Many tools also do not provide sufficiently detailed guidance on how to operationalize individual domains or criteria. There is therefore a need for further development of such tools in specific disciplines and their validation. Sufficiently detailed guidance for making and reporting these assessments is also necessary.

Models predict outcomes based on model inputs – previous observations, knowledge and assumptions about the situation being modelled. Thus, when developing new models or assessing whether or not an existing model has been optimally developed, one should specify *a priori* what are the most appropriate and relevant data sources to inform different parameters required for the model. These may be either single studies that provide the most direct information for the situation being modelled or a systematic review of multiple studies that identifies all relevant sources of data. The certainty of each of model inputs is determined by

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339 the risk of bias, directness and consistency of input data, precision of these estimates, and
340 other domains specified in the Grading of Recommendations Assessment, Development, and
341 Evaluation (GRADE) approach.[22-28]
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344 Various disciplines in health care and related areas that use modelling face similar challenges
345 when assessing the evidence generated using models and may benefit from shared solutions.
346 We present examples of selected models used in health-related disciplines in Table 1. Building
347 on the existing GRADE approach, we aim to refine and expand guidance how to assess the
348 certainty of model outputs. We formed a GRADE project group, comprised of individuals with
349 expertise in developing models and using model results in health-related disciplines, to create a
350 unified framework for assessing the certainty of model outputs to be used in the context of
351 systematic reviews [29], health technology assessments, health care guidelines, and other
352 health decision-making. In this article, we outline the proposed conceptual approach and clarify
353 key terminology (Table 2). The main target audience for this article includes researchers who
354 develop models and those who use models to inform health care-related decisions.
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360 What we mean by a model 361

362 Authors have used the term *model* to describe a variety of different concepts [2] and suggested
363 several broader or narrower definitions [6, 30], so even modellers in the relatively narrow
364 context of health sciences can differ in their views about what constitutes a model. Models vary
365 in their structure and degree of complexity. A very simple model might be an equation
366 estimating a variable not directly measured, such as the absolute effect of an intervention
367 estimated as the product of the intervention's relative effect and the assumed baseline risk in a
368 defined population (risk difference equals relative risk reduction multiplied by an assumed
369 baseline risk). On the other end of the spectrum there are elaborate mathematical models,
370 such as system dynamics models (e.g. infectious disease transmission), which may contain
371 dozens of sophisticated equations that require considerable computing power to solve.
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377 By their nature, such models only *resemble* the phenomena being modelled – i.e. specific parts
378 of the world that are interesting in the context of a particular decision – with necessary
379 approximations and simplifications, and to the extent that one actually knows and understands
380 the underlying mechanisms.[1] Given the complexity of the world, decision-makers often rely
381 on some sort of a model to answer health-related questions.
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385 In this article, we focus on quantitative mathematical models defined as “mathematical
386 framework representing variables and their interrelationships to describe observed phenomena
387 or predict future events”[30] used in health-related disciplines for decision-making (Table 1).
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395 These may be models of systems representing causal mechanisms (aka mechanistic models),
396 models predicting outcomes from input data (aka empirical models), and models combining
397 mechanistic with empirical approaches (aka hybrid models). We do not consider here statistical
398 models used to estimate the associations between measured variables (e.g. proportional
399 hazards models or models used for meta-analysis).
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402 403 The GRADE approach

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406 The GRADE working group was established in the year 2000 and continues as a community of
407 people with the aim to create a systematic, and transparent framework for assessing and
408 communicating the certainty of the available evidence used in making decisions in healthcare
409 and health-related disciplines.[31] The GRADE Working Group now includes over 600 active
410 members from 40 countries and serves as a think tank for advancing evidence-based decision-
411 making in multiple health-related disciplines (www.gradeworkinggroup.org). GRADE is widely
412 used internationally by over 100 organizations to address topics related to clinical medicine,
413 public health, coverage decisions, health policy, and environmental health.
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417 The GRADE framework uses concepts that are familiar to health scientists, grouping specific
418 items for evaluating the certainty of evidence in conceptually coherent domains. Specific
419 approaches to evaluate the concepts may differ depending on the nature of the body of
420 evidence (Table 2). GRADE domains include concepts such as risk of bias[28], directness of
421 information [24], precision of an estimate[23], consistency of estimates across studies[25], risk
422 of bias related to selective reporting[26], strength of the association, presence of a dose-
423 response gradient, and the presence of plausible residual confounding that can increase
424 confidence in estimated effects[27]. The general GRADE approach is applicable irrespective of
425 health discipline. It has been applied to rating the certainty of evidence for management
426 interventions, health care related tests and strategies [32, 33], prognostic information[34],
427 evidence from animal studies[35], use of resources and cost-effectiveness evaluations[36], and
428 values and preferences[37, 38]. While the GRADE Working Group has begun to address
429 certainty of modelled evidence in the context of test-treatment strategies[39], health care
430 resource use and costs[36], and environmental health[40], more detailed guidance is needed
431 for complex models such as those used in infectious diseases, health economics, public health,
432 and decision analysis.
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440 Methods

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451 On May 15 and 16, 2017, health scientists participated in a GRADE modelling project group
452 workshop in Hamilton, Ontario, Canada, to initiate a collaboration in developing common
453 principles for the application of the GRADE assessment of certainty of evidence to modelled
454 outputs. The National Toxicology Program of the Department of Health and Human Services in
455 the USA and the MacGRADE Center in the Department of Health Research Methods, Evidence,
456 and Impact at McMaster University sponsored the workshop which was co-organized by
457 MacGRADE Center and ICF International.
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462 Workshop participants were selected to ensure a broad representation of all modelling related
463 fields (Appendix). Participants had expertise in modelling in the context of clinical practice
464 guidelines, public health, environmental health, dose-response modelling, physiologically based
465 pharmacokinetic (PBPK) modelling, environmental chemistry, physical/chemical property
466 prediction, evidence integration, infectious disease, computational toxicology, exposure
467 modelling, prognostic modelling, diagnostic modelling, cost effectiveness modelling,
468 biostatistics, and health ethics.
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472 Leading up to the workshop, we held three webinars to introduce participants to the GRADE
473 approach. Several workshop participants (VM, KT, JB, AR, JW, JLB, HJS) collected and
474 summarized findings from literature and the survey of experts as background material that
475 provided a starting point for discussion. The materials included collected terminology
476 representing common concepts across multiple disciplines that relate to evaluating modelled
477 evidence, and a draft framework for evaluating modelled evidence. Participants addressed
478 specific tasks in small groups and large group discussion sessions and agreed on key principles
479 both during the workshop and through written documents.
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483 484 Results

485 486 Terminology

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489 Workshop participants agreed on the importance of clarifying terminology to facilitate
490 communication among modellers, researchers, and users of model outputs from different
491 disciplines. Modelling approaches evolved somewhat independently, resulting in different
492 terms being used to describe the same or very similar concepts or the same term being used to
493 describe different concepts. For instance, the concept of the extent to which one can
494 extrapolate from the available data to the context of interest has been referred to as
495 directness, applicability, generalizability, relevance, or external validity. The lack of
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standardized terminology leads to confusion and hinders effective communication and collaboration among modellers and users of models.

Overcoming these obstacles would require clarifying the definitions of concepts and agreeing on terminology across disciplines. Realizing that this involves changing established customary use of terms in several disciplines, workshop participants suggested accepting the use of alternative terminology while always being clear about the preferred terms to be used and the underlying concept that it refers to (Table 2). Experts attending a World Health Organization's consultation have very recently suggested a more extensive set of terms [41]. To facilitate future communication, participants of this workshop intend to further collaborate to build a comprehensive glossary of terminology related to modelling.

Outline of an approach to using model outputs for decision making

Workshop participants suggested an approach to incorporate model outputs in health-related decision making (Figure 1). In this article we only describe the general outline of the suggested approach – in subsequent articles we aim to discuss the details of the approach and provide more specific guidance how to apply it in different disciplines and contexts.

Researchers should start by designing a **conceptual ideal target model** that would best represent the actual phenomenon they are considering [13]. This target model would either guide the development of a new model or serve as a reference against which existing models could be compared. The ideal target model should reflect: 1) the relevant population (e.g., patients receiving some diagnostic procedure or exposed to some hazardous substance), 2) the exposures or health interventions being considered, 3) the outcomes of interest in that context, and 4) their relationships. [42]. Designing a priori a conceptual ideal target model will also reduce the risk of intentional or unintentional development of data-driven model, in which inputs and structure would be determined by what is feasible to develop given the available data and knowledge.

Participants identified 3 options in which users may incorporate model outputs in health decision-making (Figure 1):

1. Develop a model de novo designed specifically to answer the very question at hand.

Workshop participants agreed that in an ideal situation such an approach would almost always be the most appropriate for addressing the current problem of interest. Following this approach, however, requires suitable skills, ample resources, and time being available.

It also requires enough knowledge about the phenomenon being modelled to be able to tell

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563 whether or not the new model would have any advantage over already existing models
564 previously developed for the same or similar purpose.

- 566 **2. Search for an existing model describing the same or a very similar problem and use it “off-**
567 **the-shelf”** or adapt it appropriately in order to answer the current question. In practice
568 many researchers initially use this approach because of the above limitations of developing
569 a new model. However, it is often not possible to find an existing model that would be
570 directly relevant to the problem at hand and/or it is not feasible to adapt an existing model
571 when found. Any adaptation of a model requires availability of input data relevant for
572 current problem, appropriate expertise and resources, and access to the original model. The
573 latter is often not available (e.g. proprietary model or no longer maintained) or the
574 structure of the original model is not being transparent enough to allow adaptation (“black-
575 box”).
- 579 **3. Use the results from multiple existing models** found in the literature [43]. This approach
580 may be useful when a limited knowledge about the phenomenon being modelled makes it
581 impossible to decide which of the available models is more relevant, or when many
582 alternative models are relevant but use different input parameters. In such situations, one
583 may be compelled to rely on the results of several models, because an arbitrary selection of
584 the single, seemingly “best” model may provide incorrect estimates of outputs and lead to incorrect
585 decisions owing to “model selection bias”.

588 Identifying existing models that are similar to the ideal target model often requires performing
589 a scoping of the literature or a complete **systematic review** of potentially relevant models – a
590 structured process following a standardized set of methods with a goal to identify and assess all
591 available models that are accessible, transparently reported, and fulfil the pre-specified
592 eligibility criteria based on the conceptual ideal target model. Some prefer the term **systematic**
593 **survey** that differs from a systematic review in the initial intention to use the results: in
594 systematic reviews the initial intention is to combine the results across studies either
595 statistically through a meta-analysis or narratively summarizing their results when appropriate,
596 whereas in a systematic survey the initial intention is to examine the various ways that an
597 intervention or exposure has been modelled, to review the input evidence that has been used,
598 and ultimately to identify a single model that fits the conceptual ideal target model the best or
599 requires the least adaptation; only when such one model cannot be found, one may need to
600 use the results of multiple existing models.

606 If a systematic search revealed one or more models meeting the eligibility criteria, then
607 researchers would assess the certainty of outputs from each model. Depending on this
608 assessment, researchers may be able to use the results of a single most direct and lowest risk of
609 bias model “off-the-shelf” or proceed to adapt that model. If researchers failed to find an
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619 existing model that would be sufficiently direct and low risk of bias, then they would ideally
620 develop their own model *de novo*.
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622 623 *Assessing the certainty of outputs from a single model* 624

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626 When researchers develop their own model or when they identify a single model that is
627 considered sufficiently direct to the problem at hand, then they should assess the certainty of
628 its outputs (i.e. evidence generated from that model). Note, that if a model estimates multiple
629 outputs, researchers needs to assess the certainty of each output separately [23-28]. Workshop
630 participants agreed that all GRADE domains are applicable to assess the certainty of model
631 outputs, but further work is needed to identify examples and develop specific criteria to be
632 assessed, which may differ depending on the model being used and/or situation being
633 modelled.
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637 638 *Risk of bias in a single model* 639

640 The risk of bias of model outputs (i.e. model outputs being systematically overestimated or
641 underestimated) is determined by the credibility of a model itself and the certainty of evidence
642 for each of model inputs.
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645 The **credibility of a model**, also referred to as the quality of a model (Table 2) is influenced by
646 its conceptualization, structure, calibration, validation, and other factors. Determinants of
647 model credibility are likely to be specific to a modelling discipline (e.g., health economic models
648 have different determinants of their credibility, compared with PBPK models). There are some
649 discipline-specific guidelines or checklists developed for the assessment of credibility of a
650 model and other factors affecting the certainty of model outputs such as the framework to
651 assess adherence to good practice guidelines in decision-analytic modelling [18], the
652 questionnaire to assess relevance and credibility of modelling studies [18, 44, 45], good
653 research practices for modelling in health technology assessment [5, 6, 8, 9, 12-14], the
654 approaches to assessing uncertainty in read-across [46], and the quantitative structure-activity
655 relationships [47] in predictive toxicology. Workshop participants agreed that there is a need
656 for comprehensive tools developed specifically to assess credibility of various types of models
657 in different modelling disciplines.
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663 The **certainty of evidence in each of model inputs** is another critical determinant of the risk of
664 bias in a model. A model has several types of input data – bodies of evidence used to populate
665 a model (Table 2). When researchers develop their model *de novo*, in order to minimize the risk
666 of bias they need to specify those input parameters to which the model outputs are the most
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sensitive. For instance, in economic models these key parameters may include health effects, resource use, utility values, and baseline risks of outcomes. Model inputs should reflect the entire body of relevant evidence satisfying clear pre-specified criteria rather than an arbitrarily selected evidence that is based on convenience (“any available evidence”) or picked in any other non-systematic way (e.g., “first evidence found” – single studies that researchers happen to know about or are the first hits in a database search). The appropriate approach will depend on the type of data and may require performing a systematic review of evidence on each sensitive input variable [48-50]. Some inputs may have a very narrow inclusion criteria and therefore evidence from single epidemiological survey or population surveillance may provide all relevant data for the population of interest (e.g. baseline population incidence or prevalence).

The certainty of evidence for each input needs to be assessed following the established GRADE approach specific to that type of evidence (e.g. estimates of intervention effects or baseline risk of outcomes)[22, 32, 34, 37]. Following the logic of the GRADE approach, that the overall certainty of evidence cannot be higher than the lowest certainty for any body of evidence that is critical for a decision [51], we put forward that the overall rating of certainty of evidence across all model inputs should be limited by the **lowest certainty rating for any body of evidence (input data) to which the model output(s) have been found sensitive.**

Application of this approach requires a priori consideration of likely critical and/or important inputs when specifying the *conceptual ideal target model* and the examination of the results of *back-end* sensitivity analyses. In some cases, the above principle can extend to encompass decision uncertainty – the overall rating of certainty across model inputs for a single model should be tied to the certainty rating of the lowest rated body of evidence (input data) to which the decision is sensitive. For example, the latter extension is applicable when the outputs of a model-based economic evaluation include probabilities of an intervention (versus its comparator(s)) being cost-effective at a specified willingness-to-pay threshold.

Indirectness in a single model

By directness or relevance, we mean the extent to which model outputs directly represent the phenomenon being modelled. To evaluate the relevance of a model, one needs to compare it against the conceptual ideal target model. When there are concerns about the directness of the model or there is limited understanding of the system being modelled making it difficult to assess directness, then one may have lower confidence in model outputs.

Determining the directness of model outputs includes the assessment to what extent the modelled population, the assumed interventions and comparators, the time horizon, the analytic perspective, as well as the outcomes being modelled reflect those that are current interest. For instance, if the question is about the risk of birth defects in children of mothers chronically exposed to a certain substance, there may be concerns about the directness of the

evidence if the model assumed short-term exposure, the route of exposure was different, or the effects of exposure to a similar but not the same substance were measured.

Assessing indirectness in a single model requires evaluating 2 separate sources of indirectness:

1. indirectness of model inputs with respect to the model
2. indirectness of model outputs with respect to the decision problem at hand.

This conceptual distinction is important, because each type of indirectness needs to be assessed separately, even though to certain extent the latter may be determined by the former. Some authors also distinguish the “indirectness of the model structure with respect to decision problem at hand”, but we considered this part of risk of bias described above.

Using an existing model has an inherent limitation, that its inputs might have been direct for the decision problem addressed by its developers but are not direct with respect to the problem currently at hand. In this context, sensitivity analysis can help to assess to what extent model outputs are robust to the changes in input data or assumptions used in model development.

Inconsistency in a single model

Inconsistency refers to the difference in the results among two or more models. In the case of using a single model, this type of inconsistency becomes irrelevant. However, a single model may yield inconsistent outputs owing to an unexplained variability in the results of individual studies informing the best, pooled estimates of input variables. For instance, when developing a health economic model, a systematic review may yield several credible, but discrepant, utility estimates in the population of interest. If there is no plausible explanation for that difference in utility estimates, outputs of a model based on those inputs may also be inconsistent. Again, sensitivity analysis may help to make a judgment to what extent such inconsistency of model inputs would translate into a meaningful inconsistency in model outputs with respect to the decision problem at hand.

Imprecision in a single model

The overall certainty of model outputs may also be lower when the outputs are estimated imprecisely. For quantitative outputs one should examine not only the point estimate (e.g., average predicted event) but also the variability of that estimate (e.g., results of the probabilistic sensitivity analysis based in the distribution of the input parameters). It is essential that a report from a modelling study always includes information about output variability. Further guidance on how to assess imprecision in model outputs will need to take into account if the conclusions change according to that specific parameter. In some disciplines, for instance

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787 in environmental health, model inputs are frequently qualitative. Users of such models may
788 assess “adequacy” of the data, i.e. the degree of “richness” and quantity of data supporting
789 particular outputs of a model.
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791 792 *Risk of publication bias in the context of a single model*

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795 The risk of publication bias, also known as “reporting bias”, “non-reporting bias”, or “bias owing
796 to missing results”, as it is currently called in the Cochrane Handbook [52], is the likelihood that
797 relevant models have been constructed but were not published or otherwise made publicly
798 available. Risk of publication bias may not be relevant when assessing the certainty of outputs
799 of a single model constructed de novo. However, when one intends to reuse an existing model
800 but is aware or strongly suspects that similar models had been developed but are not available,
801 then one may be inclined to think that their outputs might have systematically differed from
802 the model that is available. In such a case, one may have lower confidence in the outputs of the
803 identified model if there is no reasonable explanation for the inability to obtain those other
804 models.
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809 810 *Domains that increase the certainty of outputs from a single model*

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812 The GRADE approach to rating the certainty of evidence recognized three situations when the
813 certainty of evidence can increase: large magnitude of an estimated effect, presence of a dose-
814 response gradient in an estimated effect, and an opposite direction of plausible residual
815 confounding.[27] Workshop participants agreed that presence of a **dose-response gradient** in
816 model outputs may be applicable in some modelling disciplines (e.g., environmental health).
817 Similarly, whether or not a **large magnitude of an effect** in model outputs increases the
818 certainty of the evidence may depend on the modelling discipline. The **effect of an opposite**
819 **direction of a plausible residual confounding** seems theoretically also applicable in assessing
820 the certainty of model outputs but an actual example of this phenomenon in modelling studies
821 has yet to be found.
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827 828 *Assessing the certainty of outputs across multiple models*

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830 Not infrequently, particularly in disciplines relying on mechanistic models, the current
831 knowledge about the real system being modelled is very limited precluding the ability to
832 determine which of the available existing models generates higher certainty outputs. Therefore,
833 it may be necessary to rely on the results across multiple models. Other examples include using
834 multiple models when no model was developed for the population directly of interest (e.g. the
835 European Breast Cancer Guideline for Screening and Diagnosis relied on a systematic review of
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843 modelling studies that compared different mammography screening intervals [53]) or when
844 multiple models of the same situation exist but vary in structure, complexity, and parameter
845 choices (e.g. HIV Modelling Consortium compared several different mathematical models
846 simulating the same antiretroviral therapy program and found that all models predicted that
847 the program has the potential to reduce new HIV infections in the population [54]).
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851 When researchers choose or are compelled to include outputs from several existing models,
852 they should assess the certainty of outputs across all included models. This assessment may be
853 more complex than for single models and single bodies of evidence. The feasibility of GRADE's
854 guidance to judge the certainty of evidence lies in the availability of accepted methods for
855 assessing most bodies of evidence from experimental to observational studies. However, the
856 methods for systematic reviews of modelling studies are less well-established, some stages of
857 the process are more complex, the number of highly skilled individuals with experience in such
858 systematic reviews is far lower, and there is larger variability in the results [55]. Additionally,
859 researchers must be careful to avoid "double counting" the same model as if it were multiple
860 models. For instance, the same model (i.e. same structure and assumptions) may have been
861 used in several modelling studies, in which investigators relied on different inputs. When facing
862 this scenario, researchers may need to decide which of the inputs are the most direct to their
863 particular question and include in only this model in the review.
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869 *Risk of bias across multiple models*

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872 The assessment of risk of bias across models involves an assessment of the risk of bias in each
873 individual model (see above discussion of risk of bias in single model) and subsequently making
874 a judgement about the overall risk of bias across all included models. Specific methods for
875 operationalizing this integration remain to be developed.
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878 *Indirectness across multiple models*

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881 As for the risk of bias, researchers need to assess indirectness of outputs initially for each of
882 included models and then integrate the judgements across models. Likewise, specific methods
883 for operationalizing this integration still remain to be developed. During this assessment
884 researchers may find some models too indirect to be informative for their current question and
885 decide to exclude them from further consideration. However, the criteria to determine which
886 models are too indirect should be developed a priori, before the search for the models is
887 performed and their results are known.
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Imprecision across multiple models

The overall certainty of model outputs may also be lower when model outputs are not estimated precisely. If researchers attempt a quantitative synthesis of outputs across models, they will report the range of estimates and variability of that estimates. When researchers choose to perform only a qualitative summary of the results across models, it is desirable that they report some estimate of variability in the outputs of individual models and an assessment of how severe the variability is (e.g. range of estimated effects).

Inconsistency of outputs across multiple models

The assessment of inconsistency should focus on unexplained differences across model outputs. If multiple existing models addressing the same issue produce considerably different outputs or reach contrasting conclusions, then careful comparison of the models may lead to a deeper understanding of the factors that drive outputs and conclusions. Ideally, the different modelling groups that developed relevant models would come together to explore the importance of differences in the type and structure of their models, and of the data used as model inputs.

Invariably there will be some differences among the estimates from different models. Researchers will need to assess whether or not these differences are important, i.e. whether they would lead to different conclusions. If the differences are important but can be explained by model structure, model inputs, the certainty of the evidence of the input parameters or other relevant reasons, one may present the evidence separately for the relevant subgroups. If differences are important, but cannot be clearly explained, the certainty of model outputs may be lower.

Risk of publication bias across multiple models

The assessment is similar to that of the risk of publication bias in the context of a single model.

Domains that increase the certainty of outputs across multiple models

All considerations are the same to those in the context of a single model.

Discussion

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955 The goal of the GRADE project group on modelling is to provide concepts and operationalization
956 of how to rate the certainty of evidence in model outputs. This article provides an overview of
957 the conclusions of the project group. This work is important because there is a growing need
958 and availability of modelled information resulting from a steadily increasing knowledge of the
959 complexity of the structure and interactions in our environment, and computational power to
960 construct and run models. Users of evidence obtained from modelling studies need to know
961 how much trust they may have in model outputs. There is a need to improve the methods of
962 constructing models and to develop methods for assessing the certainty in model outputs. In
963 this article we have attempted to clarify the most important concepts related to developing and
964 using model outputs to inform health-related decision-making. Our preliminary work identified
965 confusion about terminology, lack of clarity of what is a model, and need for methods to assess
966 certainty in model outputs as priorities to be addressed in order to improve the use of evidence
967 from modelling studies.
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974 In some situations, decision-makers might be better off developing a new model specifically
975 designed to answer their current question. However, we suggest that it is not always feasible to
976 develop a new model or that developing a new model might not be any better than using
977 already existing models, when the knowledge of the real life system to be modelled is limited
978 precluding the ability to choose one model that would be better than any other. Thus,
979 sometimes it may be necessary or more appropriate to use one or multiple existing models
980 depending on their availability, credibility, and relevance to the decision-making context. The
981 assessment of the certainty of model outputs will be conceptually similar when a new model is
982 constructed, or one existing model is used. The main difference between the latter two
983 approaches is the availability of information to perform a detailed assessment. That is,
984 information for one's own model may be easily accessible, but information required to assess
985 someone else's model will often be more difficult to obtain. Assessment of the certainty
986 evidence across models can build on existing GRADE domains but requires different
987 operationalization.
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993 Adoption of the GRADE approach by modelling disciplines and further development of methods
994 to assess the certainty of model outputs may be beneficial for health decision making, since it
995 builds on an existing, widely used framework that includes a systematic and transparent
996 evaluation process. Systematic approaches improve rigor of research, reducing the risk of error
997 and its potential consequences; transparency of the approach increases its trustworthiness.
998 There may be additional benefits related to other aspects of the broader GRADE approach, for
999 instance a potential to reduce unnecessary complexity and workload in modelling by careful
1000 consideration of the most direct evidence as model inputs. This may allow, for instance,
1001 optimization of the use of different streams of evidence as model inputs. Frequently, authors
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1011 introduce unnecessary complexity by considering multiple measures of the same outcome
1012 when focus could be on the most direct outcome measure.
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1015 The GRADE working group will continue developing methods and guidance for using model
1016 outputs in health-related decision-making. In subsequent articles we will provide more detailed
1017 guidance about choosing the “best” model when multiple models are found, using multiple
1018 models, integrating the certainty of evidence from various bodies of evidence with credibility of
1019 the model and arriving at the overall certainty in model outputs, how to assess the credibility of
1020 various types of models themselves, and further clarification of terminology. In the future we
1021 aim to develop and publish the detailed guidance for assessing certainty of evidence from
1022 models, the specific guidance for the use of modelling across health care-related disciplines
1023 (e.g. toxicology, environmental health or health economics), validation of the approach, and
1024 accompanying training materials and examples.
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Table 1. Examples of modelling methods in health-related disciplines (not comprehensive).

Decision analysis models	<p>Structured model representing health care pathways examining effects of an intervention on outcomes of interest.</p> <p>Types</p> <ul style="list-style-type: none"> ▪ Decision tree models ▪ State transition models <ul style="list-style-type: none"> ○ Markov cohort simulation ○ Individual based microsimulation (first-order Monte Carlo) ▪ Discrete event simulation ▪ Dynamic transmission models ▪ Agent based models <p>Examples</p> <ul style="list-style-type: none"> ▪ Estimation of long-term benefits and harms outcomes from complex intervention, e.g. minimum unit pricing of alcohol ▪ Cost effectiveness analysis of 18 FDG PET/CT for the diagnosis of lung cancer
Pharmacology and toxicology models	<p>Computational models developed to organize, analyse, simulate, visualize or predict toxicological and ecotoxicological effects of chemicals. In some cases, these models are used to estimate the toxicity of a substance even before it has been synthesized.</p> <p>Types</p> <ul style="list-style-type: none"> ▪ Structural alerts and rule-based models ▪ Read-Across ▪ Dose response and Time response ▪ Toxicokinetic (TK) and toxicodynamic(TD) ▪ Uncertainty factors ▪ Quantitative structure activity relationship (QSAR) ▪ Biomarker-based toxicity models <p>Examples</p> <ul style="list-style-type: none"> • Structural alerts for mutagenicity and skin sensitisation • Read-across for complex endpoints such as chronic toxicity • Pharmacokinetic (PK) models to calculate concentrations of substances in organs, following a variety of exposures QSAR models for carcinogenicity • TGx-DDI biomarker to detect DNA damage-inducing agents
Environmental models	<p>The EPA defined these models as: ‘A simplification of reality that is constructed to gain insights into select attributes of a physical, biological, economic, or social system.’ It involves the application of multidisciplinary knowledge to explain, explore and predict the Earth’s response to environmental change, and the interactions between human activities and natural processes.</p> <p>Classification (based on the CREM guidance document):</p> <ul style="list-style-type: none"> • Human activity models

	<ul style="list-style-type: none"> • Natural systems process • Emission models • Fate and transport models • Exposure models • Human health effects models • Ecological effects models • Economic impact models • Noneconomic impact models
	<p>Examples</p> <ul style="list-style-type: none"> • Land use regression models • IH SkinPerm [56] • ConsExpo [57] • other exposure models [58]
Other	<ul style="list-style-type: none"> • HopScore: An Electronic Outcomes-Based Emergency Triage System [59] • Computational general equilibrium (CGE) models [60]

Table 2. Selected commonly used and potentially confusing terms used in the context of modelling and the GRADE approach

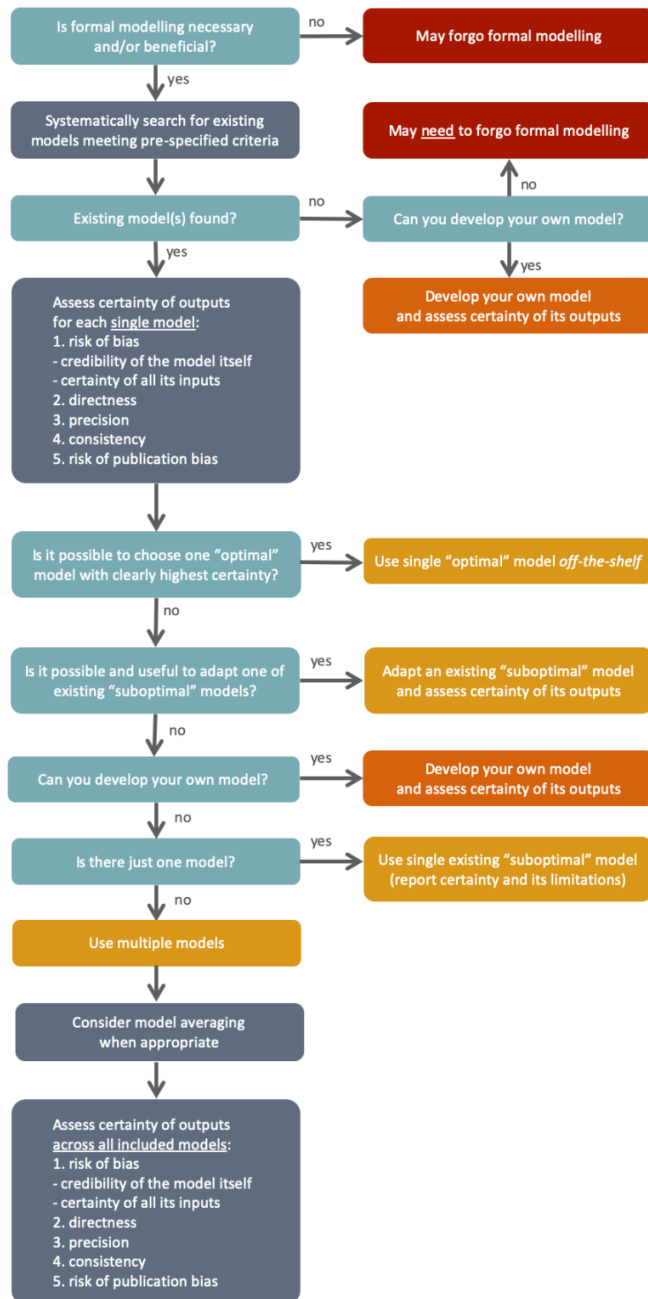
Term	General definition
Sources of evidence (may come from in vitro or in vivo experiment or a mathematical model)	
Streams of evidence	Parallel information about the same outcome that may have been obtained using different methods of estimating that outcome. For instance, evidence of the increased risk for developing lung cancer in humans after an exposure to certain chemical compound may come from several streams of evidence: 1) mechanistic evidence – models of physiological mechanisms, 2) studies in animals – observations and experiments in animals from different phyla, classes, orders, families, genera, and species (e.g., bacteria, nematodes, insects, fish, mice, rats), and 3) studies in humans.
Bodies of evidence	Information about multiple different aspects around a decision about the best course of action. For instance, in order to decide whether or not a given diagnostic test should be used in some people, one needs to integrate the bodies of evidence about: the accuracy of the test, the prevalence of the conditions being suspected, the natural history of these conditions, the effects of potential treatments, values and preferences of affected individuals, cost, feasibility, etc.
Quality	

(may refer to many concepts, thus alternative terms are preferred to reduce confusion)	
<p>Certainty of model outputs</p> <p>Alternative terms:</p> <ul style="list-style-type: none"> ▪ certainty of modelled evidence ▪ quality of evidence ▪ quality of model output ▪ strength of evidence ▪ confidence in model outputs 	<p>In the context of health decision-making, the certainty of evidence (term preferred over “quality” in order to avoid confusion with the risk of bias in an individual study) reflects the extent to which one’s confidence in an estimate of an effect is adequate to make a decision or a recommendation. Decisions are influenced not only by the best estimates of the expected desirable and undesirable consequences but also by one’s confidence in these estimates. In the context of evidence syntheses of separate bodies of evidence (e.g., systematic reviews), the certainty of evidence reflects the extent of confidence that an estimate of effect is correct. For instance, the attributable national risk of cardiovascular mortality resulting from exposure to air pollution measured in selected cities.</p> <p>The GRADE Working Group published several articles explaining the concept in detail.[22-28, 61] Note that the phrase “confidence in an estimate of an effect” does not refer to statistical confidence intervals. Certainty of evidence is always assessed for the whole body of evidence rather than on a single study level (single studies are assessed for risk of bias and indirectness).</p>
<p>Certainty of model inputs</p> <p>Alternative term:</p> <ul style="list-style-type: none"> ▪ quality of model inputs 	<p>Characteristics of data that are used to develop, train, or run the model, e.g., source of input values, their manipulation prior to input into a model, quality control, risk of bias in data, etc.</p>
<p>Credibility of a model</p> <p>Alternative terms:</p> <ul style="list-style-type: none"> ▪ quality of a model ▪ risk of bias in a model ▪ validity of a model 	<p>To avoid confusion and keep with terminology used by modelling community[7] we suggest using the term <i>credibility</i> rather than <i>quality</i> of a model. The concept refers to the characteristics of a model itself – its design or execution – that affect the risk that the results may overestimate or underestimate the true effect. Various factors influence the overall credibility of a model, such as its structure, the analysis and the validation of the assumptions made during modelling.</p>
<p>Quality of reporting</p>	<p>Refers to how comprehensively and clearly model inputs, a model itself, and model outputs have been documented and described such that they can be critically evaluated and used for decision-making. Quality of reporting and quality of a model are separate concepts: a model with a low quality of reporting is not necessarily a low-quality model and vice versa.</p>
<p>Directness</p>	

<p>Directness of a model</p> <p>Alternative terms:</p> <ul style="list-style-type: none"> ▪ relevance ▪ external validity ▪ applicability ▪ generalizability ▪ transferability ▪ translatability 	<p>By directness of a model we mean the extent to which the model represents the real-life situation being modelled which is dependent on how well the input data and the model structure reflect the scenario of interest.</p> <p>Directness is the term used in the GRADE approach, because each of the alternatives has been used usually in a narrower meaning.</p>
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* There may be either subtle or fundamental differences among some disciplines in how these terms are being used; for the purposes of this article, these terms are generalized rather than discipline specific.

Figure 1. The general approach to using modelled evidence and assessing its certainty in health-related disciplines.



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