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Methodological Guidelines and Publications of Benefit-risk Assessment for Health Technology Assessment: A Scoping Review

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Abstract

Objectives: To map the available methodological guidelines and documents for conducting and reporting benefit-risk assessment (BRA) during health technologies' lifecycle; and to identify methodological guidelines for BRA that could serve as the basis for the development of a BRA guideline for the context of health technology assessment (HTA) in Brazil.

Design: Scoping review.

Methods: Searches were conducted in three main sources up to March 2023: (1) electronic databases; (2) grey literature (48 HTA and regulatory organizations); and (3) manual search and contacting experts. We included methodological guidelines or publications presenting methods for conducting or reporting BRA of any type of health technologies in any context of the technology's lifecycle. Selection process and data charting were conducted by independent reviewers. We provided a structured narrative synthesis of the findings.

Results: From the 83 eligible documents, six were produced in the HTA context, 30 in the regulatory, and 35 involved guidance for BRA throughout the technology's lifecycle. We identified 129 methodological approaches for BRA in the documents. The most commonly referred to descriptive frameworks were the Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk, and Linked decisions (PrOACT-URL) and the Benefit Risk Action Team (BRAT). Multicriteria decision analysis was the most commonly cited quantitative framework. We also identified the most cited metric indices, estimation and utility survey techniques that could be used for BRA.

Conclusions: Methods for BRA in HTA are less established. The findings of this review, however, will support and the elaboration of the Brazilian methodological guideline on BRA for HTA.

Study registration: Open Science Framework (https://doi.org/10.17605/OSF.IO/69T3V).

Keywords: health technology assessment, benefit-risk assessment, benefit-risk evaluation, methodological guidelines, methodological guidance, scoping review.

Strengths and limitations of this study

- This is the first scoping review aiming at mapping methodological guidelines and publications on methods of benefit-risk assessment, especially in the context of health technology assessment (HTA).
- Our comprehensive search resulted in more than 12,000 retrieved references from electronic databases and 160 full-text documents from 48 HTA and regulatory organizations. We identified 129 methodological approaches for benefit-risk assessment, including frameworks, metric indices, estimation and utility survey techniques, in 83 eligible documents. Among the 83 eligible, only six methodological documents were produced in the context of HTA.
- The findings of this review will provide an important basis for future case studies and the elaboration of the Brazilian methodological guideline on BRA for HTA.

Introduction

Benefit-risk assessment (BRA), also referred to as risk-benefit or benefit-harm assessment, is an important component in decision-making throughout the lifecycle of a health technology, from its development, regulatory approval, postmarketing surveillance, decisions about incorporation and reimbursement in health technology assessment (HTA), decision-making in clinical practice, to its obsolescence.[1–3]

BRA of comparative technologies is usually carried out informally, without following a systematic and reproducible process,[3] which can lead to inappropriate or intransparent decisions. During the last two decades, efforts have been observed to apply more structured, objective and transparent approaches, aiming at better communication and decision-making.[1,3–5] For this purpose, several frameworks have been proposed to guide BRA.[1]

Structured approaches for BRA have been used, in particular for regulatory decisions and postmarketing surveillance. The European Medicines Agency (EMA) has been making recommendations on BRA structured methods for new drug applications since 2007.[6] The Pharmacoepidemiological Research on Outcomes of Therapeutics (PROTECT) initiative was established by a European Consortium aiming to support the monitoring of BRA of medicines in Europe and to provide recommendations to various stakeholders, particularly regulators.[7] With the same attention, in 2009 the Food and Drug Administration (FDA), in the United States of America (USA), initiated an effort to explore more systematic approaches for BRA as part of the drug review process and proposed its benefit-risk framework (FDA BRF).[8]

Concerning the HTA context, to the best of our knowledge, the efforts for using formal approaches for BRA are in a preliminary phase compared to the regulatory setting. In Brazil, the content of the HTA dossier submissions to the National HTA body, the *Comissão Nacional de Incorporação de Tecnologias* (CONITEC), should include the description of the

clinical evidence of the technology of interest (i.e., efficacy, effectiveness, accuracy and safety) compared to the technology already available in the public health system.[9] However, currently no recommendations regarding the scope, methods and reporting of BRA are provided by CONITEC.

This review represents the first phase in a larger project to improve the application of BRA in the context of the Brazilian HTA bodies. A partnership with *Rede Brasileira de Avaliação de Tecnologias em Saúde* (REBRATS), a strategic network to facilitate the elaboration of priority HTA studies for the Brazilian health system,[10] will provide methodological and training support to increase the use of BRA methods in the reports under deliberative decision-making processes. Furthermore, findings from this scoping review will inform the development of a methodological guideline on BRA for the CONITEC.

Therefore, the objectives of this scoping review were: (1) to map the available methodological guidelines and documents for conducting and reporting BRA during health technologies' lifecycle - within this objective, we pursue identifying the definitions of BRA, the approaches for conducting BRA and the visual tools for reporting BRA results that have been used; and (2) to identify methodological guidelines for BRA, which could be used as the basis for the development of a BRA guideline for the Brazilian HTA context.

Methods

Study design

This scoping review was based on the framework proposed by Arksey and O'Malley[11] and the updated guidelines by the Joanna Briggs Institute.[12,13] The review protocol is published in BMJ Open[14] and is registered in the Open Science Framework

(https://doi.org/10.17605/OSF.IO/69T3V). The reporting of this review follows the PRISMA Extension for Scoping Reviews (PRISMA-ScR) recommendations (Supplemental Table 1).[15]

Research question and eligibility criteria

Our research question was "What are the methods for BRA in the context of a health technology's lifecycle?". The relationship between our objectives, research question, and eligibility criteria is depicted in Supplemental Figure 1.

Our eligibility criteria followed the Population, Concept, and Context (PCC) mnemonic framework.[12,13] We included: (1) methodological documents concerning BRA involving any types of health technologies and populations (Population); (2) presenting methods for conducting or reporting BRA (Concept); (3) developed in any context of the health technology's lifecycle (Context). The types of publications included were full-text methodological guidelines, recommendations, standards, consensus, methodological reports, methodological reviews, methodological studies, research reports addressing specific methods for BRA, and reporting guidelines. We excluded editorials, comments, studies using qualitative methods, conference abstracts, studies reporting methods exclusively for either the assessment of benefit or risk/harm (i.e., not reporting BRA trade-off or balance), and publications focusing only on the description of a specific methodological approach that could be used for BRA but did not present the application for BRA.

Information sources and search strategy

We performed a comprehensive search on three main sources: (1) biomedical electronic databases (electronic databases); (2) websites of key HTA and drug regulatory organizations (grey literature); and (3) manual search and contacting experts in the field (manual search).

The search strategy in the: (1) Electronic databases (EMBASE via OVID and MEDLINE via PubMed) followed a three-step approach,[12,13] using indexed and free-text terms, validated filters,[16,17] and no language or publication date restrictions. The strategy was validated by an experienced research librarian and peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist.[18] These searches were completed in October 2022. The complete search strategy is presented in Supplemental Tables 2 and 3. (2) Grey literature consisted of searching the websites of 36 HTA bodies and global HTA networks, and twelve key regulatory authorities using free-text terms such as "benefits AND (risks OR harms) AND methods" or adaptations made accordingly, and no publication date restrictions. The search was performed using the language of origin of the evidence source, or when more than one language was available, preference was given to English, Spanish, and Portuguese. These searches were conducted from October 2022 to January 2023. The list of websites is presented in Supplemental Table 4. (3) Manual search consisted of hand-searching the reference lists of all relevant documents identified in the two previous sources, and contacting experts by email. We performed the manual searches and contacted the experts from February to March 2023.

Selection process

We conducted a pilot test for the selection process. All reviewers working in independent pairs screened the titles and abstracts of a random sample of 100 titles/abstracts,[13] using the pre-specified eligibility criteria. In case of disagreements higher than 15% within the pair, another random sample was screened. The pairs started screening the documents when 85% (or greater) agreement was achieved.

Three pairs of independent reviewers screened all references retrieved from the electronic database search by reading titles and abstracts. One pair of independent reviewers

screened the titles and abstracts identified from grey literature. The full-text of potentially eligible documents identified during the screening as well as those identified via manual search were retrieved and assessed by three pairs of reviewers according to the eligibility criteria. Any disagreements during the selection process were solved through a consensus within the team of reviewers, or by a third reviewer.

Charting the data, summarizing, and reporting the results

A charting form to guide the data extraction was developed using the classification of BRA methods and visual tools proposed by Mt-Isa et al.[3] and Hallgreen et al.[19] The definitions of benefit, risk/harm and BRA provided by the documents were grouped through analysis content.[20] The charting form was validated by the reviewers conducting the extraction from five eligible documents. Data extraction was performed by three pairs of independent reviewers. Any disagreements were solved through a consensus within the team of reviewers, or by a third reviewer.

We conducted a structured narrative synthesis and reported the results in evidence tables and figures along with descriptive statistics to identify common characteristics and map the evidence.

Patient and public involvement

Patients and/or the general public were not involved in the design, conduct, or reporting of this study. The findings of this review will provide an important basis for the elaboration of the Brazilian methodological guideline on BRA for HTA and we intend to collaborate with HTA experts, REBRATS and CONITEC to promote the use of BRA methods in the context of HTA.

Results

Figure 1 provides an overview of the selection process. Of 12,915 references retrieved from electronic databases, 11,761 were screened, the full-text of 66 were assessed, 34 were excluded (reasons are presented in Supplemental Table 5) and 32 publications were included.[1–3,5,19,21–47] Regarding grey literature, our search resulted in the identification of 160 documents. Among these, 25 were included.[6,8,48–70] Additionally, we retrieved 26 methodological documents through manual searches.[4,71–95] In total, our scoping review encompassed 83 documents or publications that met the eligibility criteria.

Characteristics of the included documents

Table 1 presents a condensed summary of the characteristics of the included documents. The majority were published by institutions in the USA, followed by the European Union or partnerships between European institutions. Accordingly, most of the documents originated within the regulatory framework of the USA and Europe, with seven from the EMA[6,48–53] and six from the FDA.[8,56–60] Figure 2 depicts the geographic area in which the documents were developed, highlighting the countries that produced documents for the HTA context.

Most of the documents were published during the years 2013-2017. The first document was published in 1998 by the Council for International Organizations of Medical Sciences (CIOMS) Working Group.[90] The first publication involving the HTA context was a review on multiple criteria decision analysis (MDCA) funded by the NICE Decision Support Unit (DSU), UK, published in 2011.[70] The two most recent documents within the HTA context, published in 2022, were the General Methods from the German Institute for Quality and Efficiency in Health Care (IQWiG),[65] and a Methodological Handbook for the

evaluations of clinical effectiveness, safety, and diagnostic validity of health technologies from a Spanish HTA body.[54]

More than 37% of the documents comprised literature reviews. Eighteen documents consisted of methodological reports (21.7%), informing and/or describing methods of BRA.[6,31,41,48–55,64,74,75,78,79,87,90] Thirteen (15.7%) were methodological guidelines providing recommendations for conducting BRA, mostly developed by regulatory agencies.[8,56–60,62,65–68,85,86] Furthermore, fourteen (16.8%) methodological papers have proposed new methods of BRA or their application, all of which were published in peer-reviewed journals.[24,25,30,33,47,61,63,69,73,77,81,84,94,95] We also identified six systematic reviews on BRA methods,[1,3,19,32,37,43] and one reporting guideline developed specifically for reporting of BRA of vaccines.[44]

Medicinal products [including the former (n=13),[4,6,24,28,36,38,48–53,80] pharmaceutical drugs (n=33),[2,3,5,21–23,31–35,37,39,40,42,45,58,61,66,71–73,75,77,78,81–83,85–87,89,90] vaccines (n=5),[43,44,88,94,95] or a combination of the previous with biologics and radiopharmaceuticals (n=6)][1,8,56,60,62,84] was the type of technology most addressed in the documents (n=57; 68.8%). Medical devices [including the former (n=6),[57,59,63,67,68,79] diagnostic tests (n=1),[25] or a combination of the previous with equipments (n=2)][46,47] were addressed in nine documents (10.8%). The remaining documents stated that the BRA methods could be applied to all types of technologies (general; n=17, 20.4%).[19,26,27,29,30,41,54,55,64,65,69,70,74,76,91–93]

Five of the documents produced for the HTA context were developed by HTA bodies.[54,55,65–67] One document was developed by an academic institution with the funding of an HTA body.[70] One document, although produced by a member of the International Network of Agencies for Health Technology Assessment (INAHTA), aimed to describe methods for BRA in systematic reviews.[41] Most of the documents, including all produced for the HTA context, were funded by institutions not involved in for-profit activities.

A possible conflict of interest, identified in about half of the documents, was present if the individuals involved in the document development received support or employment, any stocks or shares, and any consultation fees or other forms of remuneration from the industry.

Definitions of benefit, risk, and BRA

In total, 31 documents provided the definition of "benefits". We classified the definitions as "favorable effects" (n=11; 13.3%),[19,26,40,45,50,60,62,63,65,79,85] "positive results for an individual or a population, and the probability of achieving such results" (n=11; 13.3%),[5,6,32,39,48,49,68,78,90,91,93] "a potential effect that moves the condition of the patient from disease towards health" (n=6),[27,42,80,89,94,95] and "results that influence the overall benefit-risk balance in a clinically meaningful way and that provide evidence supporting the product approval" (n=3).[23,72,75]

Risks or harms were defined in 31 documents. Definitions that emerged were "unfavorable effects" (n=15; 18.1%),[26,27,40,45,50,60,63,65,75,79,80,85,91,94,95] "negative results for an individual or a population, and the probability that a negative event will happen" (n=10; 12.0%),[6,19,32,39,48,49,68,78,87,93] "a potential effect that moves the condition of the patient from health towards disease" (n=4),[42,62,89,90] and "results that influence the overall benefit-risk balance in a clinically meaningful way and that provide evidence not supporting the product approval" (n=2).[23,72]

BRA was defined in 28 documents, and most of them stated that BRA "involves balancing between benefit and risk, however, it does not specify whether the assessment is quantitative, qualitative or both" (n=20; 24.1%).[1,6,8,23,48–50,60,62,64–66,68,76,84–86,89,92,93] In contrast, other definitions emerged as "a quantitative or qualitative evaluation of medical product, incorporating explicit outcome weighting within a formal analysis taking both benefits and risks of the product into account" (n=5),[43,57,59,78,87] and "a quantitative evaluation of medical

product, incorporating explicit outcome weighting within a formal analysis taking both benefits and risks of the product into account" (n=3).[35,74,90]

Approaches for BRA

We identified 129 methodological approaches or elements of BRA, including frameworks, metric indices, estimation, and utility survey techniques. Figure 3 presents the approaches cited in at least five of the 83 eligible documents. In 14 (16.9%), only descriptive (i.e., qualitative) frameworks for BRA were reported,[8,22,24,26,57–59,67,71,81–83,85,86] 18 (21.7%) cited only quantitative frameworks,[25,27,30,37,44,46,47,61,64,69,70,77,80,84,89,92,94,95] and 58% reported both descriptive and quantitative frameworks. The descriptive frameworks most frequently cited in the documents were the Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk, and Linked decisions (PrOACT-URL),[1,3–5,19,22,26,28,32,34,36,38,40,42,43,45,50–52,68,71–75,78,79,87,91] and the Benefit Risk Action Team (BRAT) framework,[1–5,19,21,22,26,28,31,32,34,36,40,42,43,50,72–75,78,79,82,83,87,88,91] cited in 29 documents (34.9%) each. The descriptive frameworks most recommended were the PrOACT-URL[1,42,51,52,75,78,87] and the FDA BRF,[1,8,56–60] recommended in seven documents each (8.4%). Among the quantitative frameworks, MCDA was the most frequently cited (n=52; 62.7%)[1–6,19,21,23,28,29,31–34,36–43,45–52,56,64,65,68–70,72–79,87–89,91,92,94,95] and recommended (n=13; 15.7%).[38,39,42,47,50,52,69,73,74,77,78,87,95] Other frequent quantitative frameworks cited were Markov decision processes (MDP; n=18; 21.7%)[1,3,25,32,33,39,40,42–45,50–52,78,87,91,94] and decision trees (n=16; 19.3%).[1,3,25,29,32,40,42,43,46,47,50–52,75,78,87]

Metric indices were reported in 59 (71.1%) documents. The most cited threshold indices were the number needed to harm (NNH; n=38; 45.8%)[1–6,19,21,25,29,31,32,34,35,37,40–44,47–50,54,55,61,66,76–78,80,81,87,89,91–93] and the number needed to treat (NNT; n=37; 44.6%),[1–6,19,21,25,29,31,32,34,35,37,39–42,47–50,54,55,61,66,76–78,80,81,87,89,91–93] which were also recommended in four

documents.[2,66,78,87] The quality-adjusted life years (QALY) emerged as the most cited (n=37; 44.6%)[1–3,5,19,25,29,32,34,37,39–42,44,46–52,55,61,65,67,70,75,76,78–80,84,87,89–91] and recommended health index (n=3),[25,78,87] followed by the quality-adjusted time without symptoms and toxicity (Q-TWiST),[1,3,5,19,29,32,37,39–41,47,50,76,78,87,89,92] reported in 17 documents.[78,87] As for trade-off indices, the incremental net health benefit (INHB) was the index mostly cited (n=32; 38.6%)[1–3,5,19,21,25,29,32,34,37,40–43,46,47,49,50,55,61,64,67,68,76,78–80,87,89,91,95] and recommended (n=6; 7.2)%);[47,61,64,78,87,95] followed by the transparent uniform risk-benefit overview (TURBO)[1,3,6,29,32,41,42,48–50,76–78,80,87,90] and the benefit risk ratio (BRR),[2–5,19,32,37,40,43,44,78,84,87,90,92,95] each cited in 16 documents (19.3%).

Estimation techniques were reported in 41 documents. The probabilistic simulation method (PSM) was the most cited approach (n=32; 38.6%).[1,3–5,19,25,29,32,33,37,38,40–47,50–52,68–70,74–76,78,87,91,94] Indirect treatment comparison (ITC) and mixed treatment comparison (MTC) were cited 18 (21.7%)[1,3–5,32,33,40–42,47,54,55,64,65,67,74,78,87] and 17 (20.5%)[1,3–5,19,32,33,40–42,54,64–66,74,78,87] times, respectively. PSM,[38,78,87] and MTC,[1,78,87] were recommended in three documents.

Concerning utility survey assessment techniques, reported in 48 documents, the dominating approaches were the discrete choice experiment (DCE) and the conjoint analysis (CA), mentioned in 26 (31.3%)[1,3–5,19,30,32,34,40,41,44,46,47,61,63,65,67,70,74,76,78,79,87,93–95] and 22 (26.5%)[1,3,21,30,32,40–42,46,47,50–52,63,65,75,78,79,87,91,93,94] of the documents. DCE was recommended in three documents,[65,78,87] followed by swing weighting, recommended in two.[69,77]

Visual tools to present BRA results

Tools for visual representation of BRA results were used or cited in 75 documents. Summary tables were the most common tool, present in almost 60% of the documents. Tree diagrams and value trees were present in 34 (41%) documents, followed by bar charts

(33.7%), dot charts (33.7%), lines (31.3%), and area graphs (28.9%). "Non-conventional" visual tools that emerged were pictograms (n=5)[19,22,54,79,91] and suggestions for using interactive visual displays to enable active participation of the audience (n=4).[31,48,49,87] The complete list of visual tools to present the results of BRA is depicted in Table 2.

Methodological documents produced in the HTA context

Among the 83 eligible, six methodological documents (7.2%) were produced in the context of HTA,[54,55,65–67,70] although 35 (42.2%) explicitly stated that the BRA would be applicable throughout the lifecycle of the technology, which implies the context of HTA among others.

The guide for the elaboration of evaluation reports of medicines published by the *Agencia de Evaluación de Tecnologías Sanitarias de Andalucía* (AETSA), in Spain, suggests that the drug evaluation reports should present in the discussion section a comparison of the safety and efficacy results to obtain an overall assessment of the intervention,[66] but no structure, framework, or quantitative approach was recommended.

The EUnetHTA HTA Core Model for Rapid Relative Effectiveness, version 4.2 published in 2015, states that both relative benefits and harmful effects of a technology are essential in quantifying the net benefit of an intervention and are essential for being able to form a balanced view of the overall value of a technology.[55]

The methodological manual for the elaboration of evaluations of clinical effectiveness, safety, and diagnostic validity of health technologies published by the Colombian *Instituto de Evaluación Tecnologica en Salud* (IETS) provides overall guidance for conducting HTA reports. Concerning BRA, the manual states that effectiveness and safety outcomes should be included in the report, to allow the benefit-risk balance. However, although the conclusion of the HTA report must state whether the technologies of interest have less, similar, or greater

effectiveness and safety compared to their alternatives, the manual does not provide recommendations on how to evaluate the balance between them.[54]

In 2011, Thokala published a report about the applicability of MCDA for HTA. The author compared the MCDA process and the NICE technology appraisal process and described the general practical issues that might arise from using an MCDA approach in the HTA process.[70]

The General Methods, Version 6.1 of 2022, a comprehensive methodological guideline published by the German IQWiG states that each predefined patient-relevant outcome (both beneficial and harmful aspects) is initially assessed on an outcome-specific basis and then presented along with the respective certainty of the evidence for each outcome. Within the overall weighing of benefits and harms, these individual outcomes are then summarized into a global conclusion on the extent of added benefit. If needed, a joint combined measure of benefit-harm such as QALY can be used.[65]

The Australian Medical Services Advisory Committee (MSAC) guidelines suggest constructing an assessment framework or logic diagram to illustrate the necessary steps that link the use of a technology in the target population and the consequences on outcomes.[67] A guidance on formal BRA quantitative framework is not provided.[67]

Discussion

We have conducted a scoping review of available methodological guidelines and documents for conducting and reporting BRA during health technologies' lifecycle. We identified 129 approaches for conducting BRA and 37 visual tools for reporting BRA results. This is the first review stratifying the findings based on the HTA context. Confirming our previous perception about decision support in HTA, the efforts for using formal structured

approaches for BRA have been more modest in that context. Only six documents produced by HTA bodies were identified,[54,55,65–67,70] however, they do not provide detailed guidance on how to select the best approach and how to conduct BRA in the HTA context.

Mt-Isa et al. identified 49 approaches for BRA and classified them into four main categories which were followed in our review: frameworks, metrics, estimation techniques and utility survey techniques.[3] Frameworks, which can be subdivided into descriptive and quantitative, provide a structure that guides the assessment to support decision making.[3] They do not provide mathematical algorithms that result in automated decisions.[40] Descriptive frameworks provide qualitative instructions, while quantitative frameworks additionally can provide formal quantitative methods to assess the balance between benefits and risks or provide tools to evaluate long-term benefits and risks/harms.[3] Metrics are systems of measurement and can be subdivided into threshold indices (they handle either benefit or risk but not both), health indices (which include validated and standardized quality-of-life indicators) and trade-off indices (which integrate benefits and risks into a single metric representing the value of the trade-off for direct interpretation). Estimation techniques include generic statistical techniques, and they are applicable in combination with other methods. Utility survey techniques include methods to elicit and collect health utilities and value preferences and they also can be applied in combination with other methods.[3]

The assessed documents agree that some decisions are straightforward, but others need more objective criteria. In cases where a new technology increases benefits and decreases risks, or when the benefits clearly outweigh the risks, a formal quantitative BRA may not be essential. On the other hand, when the benefit-risk balance is not so clear and/or stakeholders preferences influence this balance, the additional use of quantitative BRA methods can be advantageous, if not crucial for decision making.[91] In all cases, at least a structured descriptive framework is recommended to transparently present the rationale to support

decision-making and ensure that key aspects of the assessment process are not overlooked.[87] As a second step, the explicit and quantitative assessment of benefit-risk balance may be added in situations where the trade-off is more difficult to judge.[96]

Strengths of our scoping review include a comprehensive search strategy resulting in more than 12,000 retrieved references from electronic databases and 160 full-text documents from 48 HTA and regulatory organizations. The selection and data charting processes were piloted to ensure concordance between the reviewers. Perhaps most importantly, this is the first scoping review aiming at mapping methodological guidelines on methods of BRA highlighting the findings for the HTA context.

As all systematic reviews, ours has several limitations. First, despite our comprehensive search, we may have missed eligible documents for BRA used by HTA and/or regulatory organizations not publicly available online or not searched by our group. Second, we included many documents produced by the same organizations. Therefore, although the documents were unique, they may present some overlapping and redundant content biasing our descriptive percentage results. Third, we identified the most cited BRA approaches, however, this does not mean that such approaches are the most used to support decision-making. Fourth, some of the methodological approaches might have been cited in the literature under different names and definitions, although they would fall into the same technical category. We have made efforts to collect the different spelling and wording approaches into the same technical nomenclature, however, we may have missed some specific approaches. Finally, appraising the features of the BRA approaches identified was beyond the scope of our review. This would require an extensive assessment from different health decision science perspectives and a full appraisal of all statistical and modeling methods. Such an assessment would result into a lenths report and be extremely laborious, precluding the timely conclusion of this review.

Although our goal was not to appraise the operational characteristics of each identified approach, we will test and explore the potential of at least the two most cited descriptive and quantitative frameworks in case studies in the context of HTA before making formal recommendations. We are aware that no best approach fits the multitude of populations, diseases, health technologies and their clinical applications, and therefore, our intention is not to prescribe or recommend any "one size fits all" BRA approach, but to highlight the uses, advantages, disadvantages, human resources training/skills and computational requirements to support the selection of the methodologies to be used in future BRA in HTA dossier submissions to the Brazilian CONITEC.

We will also face the challenge of making recommendations on the source of data to conduct BRA in the context of HTA, which might consider a broader spectrum of sources compared to BRA for regulatory marketing authorizations, as well as periodicity of BRA for monitoring technologies incorporated in the Brazilian public health system. These are topics not discussed in the documents identified in our review. Such aspects must be assessed and discussed in the future steps, and out intention is that the results and conclusions from this review will provide an important basis for these next steps towards a more explicit and transparent BRA in the context of HTA in Brazil.

Conclusions

Our review identified 129 methodological approaches for BRA, including descriptive and quantitative frameworks, metric indices, estimation and utility survey techniques, in 83 methodological guidelines and documents for conducting and reporting BRA in the different phases of the lifecycle of health technologies. Among the documents assessed, we identified only six methodological documents produced in the context of HTA. We will test and explore

the potential of the two most cited descriptive and quantitative frameworks in case studies in the context of HTA to evaluate their performance. The findings of this review will support these steps, and finally, inform the elaboration of the Brazilian methodological guideline on BRA for HTA.

Author contributions

BOA and PCS conceived the main idea behind this manuscript. EAS, BOA and PCS wrote the manuscript. EAS, BOA, FHAM, AFRB, NSF, FCG and PCS extracted data. EAS, SMD and PCS analysed, summarized and interpreted the findings. EAS, BJ, US and PCS critically revised the manuscript and made important intellectual contributions to its development. All authors read and approved the final version of the manuscript.

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Competing interests statement

The authors declare that they have no conflicts of interest.

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Ethical approval

This study does not involve human participants or animal subjects and therefore does not require ethics committee approval.

Data sharing statement

Not applicable. All data relevant to the study are included in the article or uploaded as supplementary information.

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94. Bollaerts K, Ledent E, de Smedt T, et al. ADVANCE system testing: Benefit-risk analysis of a marketed vaccine using multi-criteria decision analysis and individual-level state transition modelling. *Vaccine*. 2019;38 Suppl 2:B65-B75. doi:10.1016/j.vaccine.2019.09.034

95. Bollaerts K, De Smedt T, Donegan K, Titievsky L, Bauchau V. Benefit-Risk Monitoring of Vaccines Using an Interactive Dashboard: A Methodological Proposal from the ADVANCE Project. *Drug Saf*. 2018;41(8):775-786. doi:10.1007/s40264-018-0658-y

96. Hunink M, Weinstein M, Wittenberg E, et al. *Decision Making in Health and Medicine*. 2nd ed. Cambridge University Press; 2014.

Table 1. Characteristics of included documents

Characteristics	Context of decision					
	HTA (n=6)	Regulatory (n=30)	Postmarketing (n=7)	Throughout lifecycle (n=35)	Other* (n=5)	All (n=83)
Publication year						
2018-2023	3 (3.6%)	7 (8.4%)	3 (3.6%)	10 (12.1%)	2 (2.4%)	25 (30.1%)
2013-2017	2 (2.4%)	12 (14.4%)	3 (3.6%)	15 (18.0%)	1 (1.2%)	33 (39.8%)
2008-2012	1 (1.2%)	9 (10.8%)	1 (1.2%)	8 (9.6%)	2 (2.4%)	21 (25.3%)
2003-2007		1 (1.2%)		2 (2.4%)		3 (3.6%)
1998-2002		1 (1.2%)				1 (1.2%)
Publication type						
Literature review / case study	1 (1.2%)	11 (13.3%)	1 (1.2%)	17 (20.4%)	1 (1.2%)	31 (37.4%)
Methodological report	2 (2.4%)	10 (12.1%)		5 (6.0%)	1 (1.2%)	18 (21.8%)
Methodological guideline	3 (3.6%)	4 (4.8%)	3 (3.6%)	3 (3.6%)		13 (15.6%)
Methodological paper		4 (4.8%)	3 (3.6%)	6 (7.2%)	1 (1.2%)	14 (16.8%)
Systematic review		1 (1.2%)		4 (4.8%)	1 (1.2%)	6 (7.2%)
Reporting guidelines					1 (1.2%)	1 (1.2%)
Types of technologies						
Medicinal products	1 (1.2%)	20 (24.2%)	7 (8.4%)	27 (32.6%)	2 (2.4%)	57 (68.8%)
General	4 (4.8%)	4 (4.8%)		7 (8.4%)	2 (2.4%)	17 (20.4%)
Medical devices	1 (1.2%)	6 (7.2%)		1 (1.2%)	1 (1.2%)	9 (10.8%)
Main institution which developed the document						
Academic institution	1 (1.2%)	7 (8.4%)	1 (1.2%)	12 (14.4%)	4 (4.8%)	25 (30.2%)
Regulatory agency		12 (14.4%)	3 (3.6%)	3 (3.6%)		18 (21.7%)
Industry		7 (8.4%)	1 (1.2%)	11 (13.3%)		19 (22.9%)
HTA body	5 (6.0%)			1 (1.2%)	1 (1.2%)	7 (8.4%)
Public-private consortium		2 (2.4%)		6 (7.2%)		8 (9.6%)
Consulting firm		2 (2.4%)	2 (2.4%)	1 (1.2%)		5 (6.0%)
Professional society				1 (1.2%)		1 (1.2%)
Main institution which funded the document						
Regulatory agency		14 (16.8%)	1 (1.2%)	4 (4.8%)		19 (22.9%)
Government institution	2 (2.4%)	1 (1.2%)	2 (2.4%)	8 (9.6%)		13 (15.6%)
Industry		5 (6.0%)	2 (2.4%)	7 (8.4%)		14 (16.8%)
HTA body	4 (4.8%)			1 (1.2%)	2 (2.4%)	7 (8.4%)
Public-private consortium					2 (2.4%)	2 (2.4%)
Independent non-profit organization				1 (1.2%)		1 (1.2%)
Not reported		4 (4.8%)	2 (2.4%)	8 (9.6%)	1 (1.2%)	15 (18.0%)
No funding		6 (7.2%)		6 (7.2%)		12 (14.7%)

Characteristics	Context of decision					
	HTA (n=6)	Regulatory (n=30)	Postmarketing (n=7)	Throughout lifecycle (n=35)	Other* (n=5)	All (n=83)
Potential conflict of interest						
Yes		13 (15.6%)	4 (4.8%)	26 (31.5%)	2 (2.4%)	45 (54.3%)
No	2 (2.4%)	5 (6.0%)		4 (4.8%)	2 (2.4%)	13 (15.6%)
Not possible to identify/evaluate	4 (4.8%)	12 (14.5%)	3 (3.6%)	5 (6.0%)	1 (1.2%)	25 (30.1%)

HTA: health technology assessment.
*Other (n=5) stands for: Evidence synthesis (n=3), Clinical guideline development (n=1), Reporting guideline (n=1)
Numbers are presented as number of documents showing the characteristic (proportion of the total 83 documents).

Table 2. Types of identified visual tools to present results of BRA (total of publications n=83; publications that reported or presented visual tools n=74)

Types of visual tools*	Reported n (%)
Table	49 (59.0%)
Effects table	
Evidence table	
Tree diagram	34 (41.0%)
Value tree	
Bar chart	28 (33.7%)
Simple of grouped bar chart	
Tornado diagram	
Histogram	
Dot chart	28 (33.7%)
Forest plot	
Bubble chart	
Line graph	26 (31.3%)
Risk-benefit contour (RBC)	
Kaplan-Meier curve	
Area graph	24 (28.9%)
Risk-benefit plane (RBP) and risk-benefit acceptability threshold (RBAT)	
Distribution plot	
Probability of technical success (POTS) plot	
Scatter Plot	8 (9.6%)
Funnel plot	
Galbraith plot	
Matrix	6 (7.2%)
Pictogram	5 (6.0%)
Box plot	5 (6.0%)
Interactive visualization	4 (4.8%)
Transparent uniform risk–benefit overview (TURBO) diagram	4 (4.8%)
Risk scale/ladder	3 (3.6%)
Dashboard	3 (3.6%)
Network graph	3 (3.6%)
Pie chart	2 (2.4%)
Other[#]	6 (7.2%)

*More than one visual tool could be identified in each document.
[#]Other: presented in only one document [Cartoon/Symbol/Icon; Drugs facts box; Generic graphical display (no specific designation was given); Map; Sankey diagram; Traffic-light labelling].
Numbers are presented as number of documents showing the tool (proportion of the total 83 documents).

FIGURE LEGENDS

Figure 1. Overview of the selection process. HTA: health technology assessment.

Figure 2. Number of documents published per geographic area. Transcontinental: stands for ≥2 countries from different continents. Continent (Europe, North America): stands for ≥2 countries within the same continent.

Figure 3. BRA methodological approaches identified in the included documents and publications. Adapted from PROTECT. AE-NNT: Adverse event adjusted number needed to treat; AHP: Analytic hierarchy process; ASF: Ashby and Smith framework; Beckmann: Beckmann model (aka evidence based-model); BLRA: Benefit-less-risk analysis; BRAT: Benefit-risk action team; BRR: Benefit-risk ratio; CA: Conjoint analysis; CDS: Cross-design synthesis; CUI: Clinical utility index; CMR-CASS: CMR Health Canada, Australia's Therapeutic Goods Administration, SwissMedic and Singapore Health Science Authority; CPM: Confidence profile method; COBRA: Consortium on benefit-risk assessment; CV: Contingent valuation; DAG: Directed acyclic graphs; DALY: Disability-adjusted life years; DAM: Decision analytic model (specific designation was given to the model); DCE: Discrete choice experiment; DI: Desirability index; FDA BRF: FDA benefit-risk framework; GBR: Global benefit-risk; HALE: Health-adjusted life years; INHB: Incremental net health benefit; ITC: Indirect treatment comparison; KM: Kaplan-Meier; MAR: Maximum acceptable risk; MCDA: Multicriteria decision analysis; MCE: Minimum clinical efficacy; MDP: Markov decision process; MTC: Mixed treatment comparison; NCB: Net clinical benefit; NEAR: Net efficacy adjusted for risk; NNH: Number needed to harm; NNT: Number needed to treat; PBRER: Periodic benefit risk evaluation report; Principle of 3's: Principle of threes; PrOACT-URL: Problem, objectives, alternatives, consequences, trade-offs, uncertainty, risk, and linked decisions; PSM: Probabilistic simulation method; QALY: Quality-adjusted life years; Q-TWiST: Quality-adjusted time without

symptoms and toxicity; QFRBA: Quantitative framework for risk and benefit assessment; RBAT: Risk-benefit acceptability threshold; RBC: Risk-benefit contour; RBP: Risk-benefit plane; RV-MCE: Relative value-adjusted minimum clinical efficacy; RV-NNH: Relative value-adjusted number needed to (treat to) harm; RV-NNT: Relative value-adjusted number needed to treat; SABRE: Southeast Asia benefit-risk evaluation; SBRAM: Sarac's benefit-risk assessment; SG: Standard gamble; SMAA: Stochastic multicriteria acceptability analysis; SPM: Stated preference method; SW: Swing weighting; TTO: Time trade-off; TURBO: Transparent uniform risk benefit overview; UMBRA: Unified methodologies for benefit-risk assessment; UT-NNT: Utility-adjusted and time-adjusted number needed to treat.

*General: No specific designation was given to the descriptive framework.

#Other: approaches cited in <5 of the included documents (See Supplemental Table 6 for the complete list of approaches).

Numbers are presented as (number of documents citing the approach; proportion of the total 83 documents).

SUPPLEMENTARY MATERIAL

Supplemental Figure 1. Relationship between the objectives, research question, and eligibility criteria for the scoping review. BRA: benefit-risk assessment; HTA: health technology assessment.

Supplemental Table 1. PRISMA Extension for Scoping Reviews (PRISMA-ScR)

Supplemental Table 2. Electronic search strategy on EMBASE (OVID)

Supplemental Table 3. Electronic search strategy on MEDLINE (PubMed)

Supplemental Table 4. Sources of grey literature

Supplemental Table 5. Excluded publications and reasons

Supplemental Table 6. Methodological approaches for BRA cited in <5 of the included documents

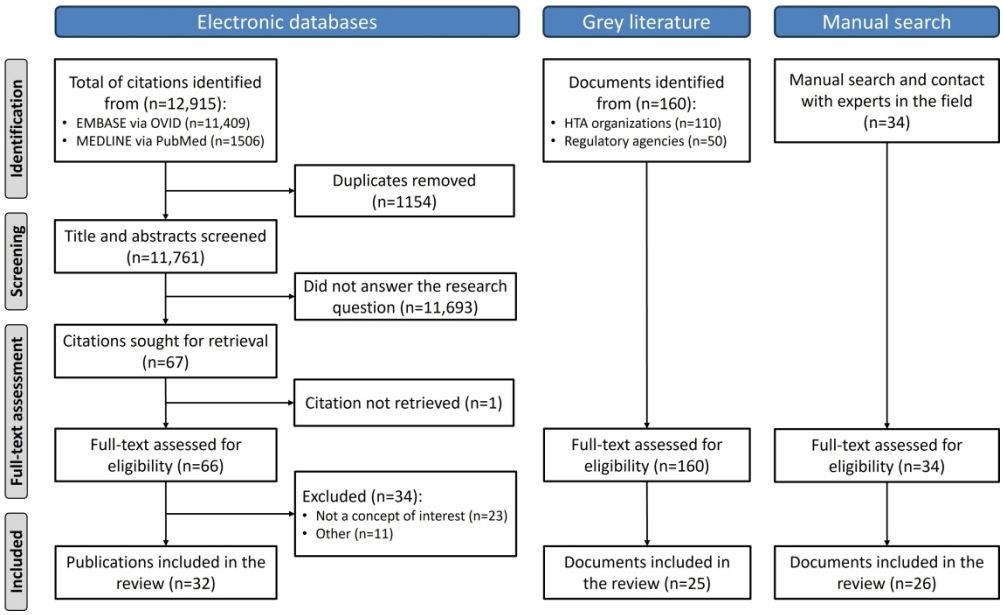


Figure 1. Overview of the selection process. HTA: health technology assessment.

356x217mm (300 x 300 DPI)

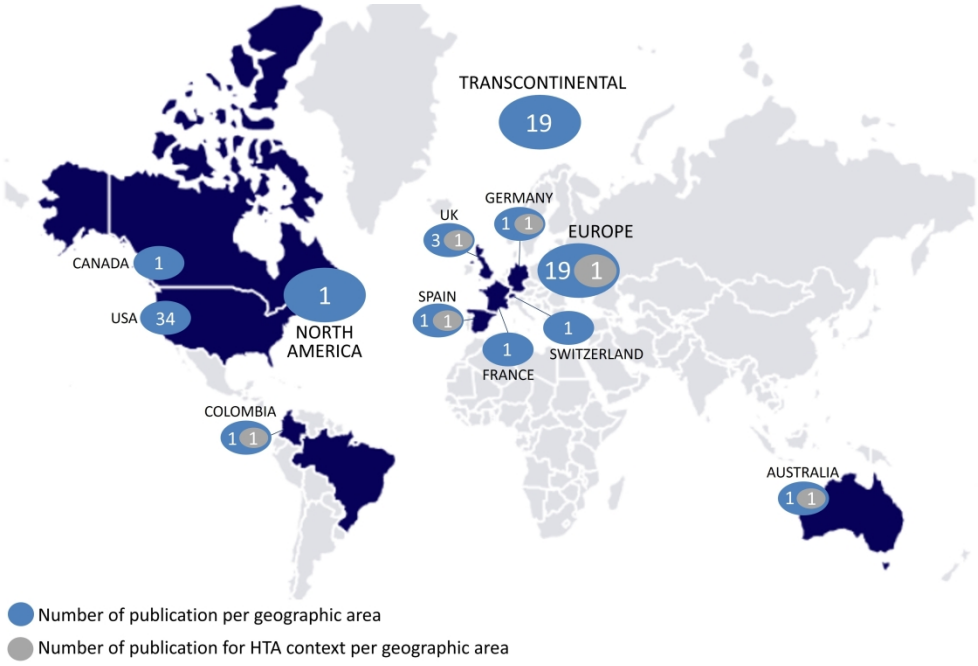


Figure 2. Number of documents published per geographic area. Transcontinental: stands for ≥2 countries from different continents. Continent (Europe, North America): stands for ≥2 countries within the same continent.

393x262mm (300 x 300 DPI)

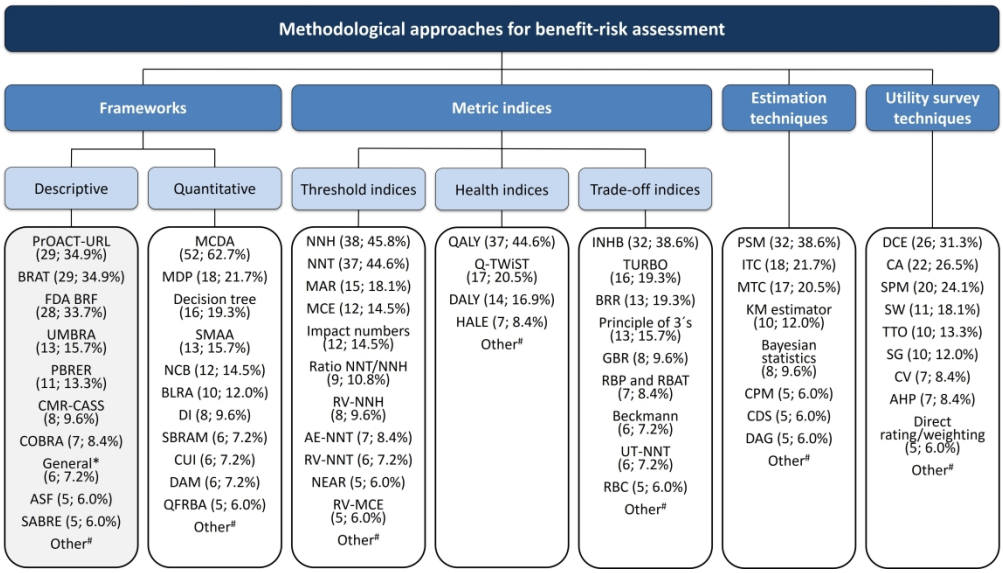


Figure 3. BRA methodological approaches identified in the included documents and publications. Adapted from PROTECT. AE-NNT: Adverse event adjusted number needed to treat; AHP: Analytic hierarchy process; ASF: Ashby and Smith framework; Beckmann: Beckmann model (aka evidence based-model); BLRA: Benefit-less-risk analysis; BRAT: Benefit-risk action team; BRR: Benefit-risk ratio; CA: Conjoint analysis; CDS: Cross-design synthesis; CUI: Clinical utility index; CMR-CASS: CMR Health Canada, Australia's Therapeutic Goods Administration, SwissMedic and Singapore Health Science Authority; CPM: Confidence profile method; COBRA: Consortium on benefit-risk assessment; CV: Contingent valuation; DAG: Directed acyclic graphs; DALY: Disability-adjusted life years; DAM: Decision analytic model (specific designation was given to the model); DCE: Discrete choice experiment; DI: Desirability index; FDA BRF: FDA benefit-risk framework; GBR: Global benefit-risk; HALE: Health-adjusted life years; INHB: Incremental net health benefit; ITC: Indirect treatment comparison; KM: Kaplan-Meier; MAR: Maximum acceptable risk; MCDA: Multicriteria decision analysis; MCE: Minimum clinical efficacy; MDP: Markov decision process; MTC: Mixed treatment comparison; NCB: Net clinical benefit; NEAR: Net efficacy adjusted for risk; NNH: Number needed to harm; NNT: Number needed to treat; PBRER: Periodic benefit risk evaluation report; Principle of 3's: Principle of threes; PrOACT-URL: Problem, objectives, alternatives, consequences, trade-offs, uncertainty, risk, and linked decisions; PSM: Probabilistic simulation method; QALY: Quality-adjusted life years; Q-TWiST: Quality-adjusted time without symptoms and toxicity; QFRBA: Quantitative framework for risk and benefit assessment; RBAT: Risk-benefit acceptability threshold; RBC: Risk-benefit contour; RBP: Risk-benefit plane; RV-MCE: Relative value-adjusted minimum clinical efficacy; RV-NNH: Relative value-adjusted number needed to (treat to) harm; RV-NNT: Relative value-adjusted number needed to treat; SABRE: Southeast Asia benefit-risk evaluation; SBRAM: Sarac's benefit-risk assessment; SG: Standard gamble; SMAA: Stochastic multicriteria acceptability analysis; SPM: Stated preference method; SW: Swing weighting; TTO: Time trade-off; TURBO: Transparent uniform risk benefit overview; UMBRA: Unified methodologies for benefit-risk assessment; UT-NNT: Utility-adjusted and time-adjusted number needed to treat.

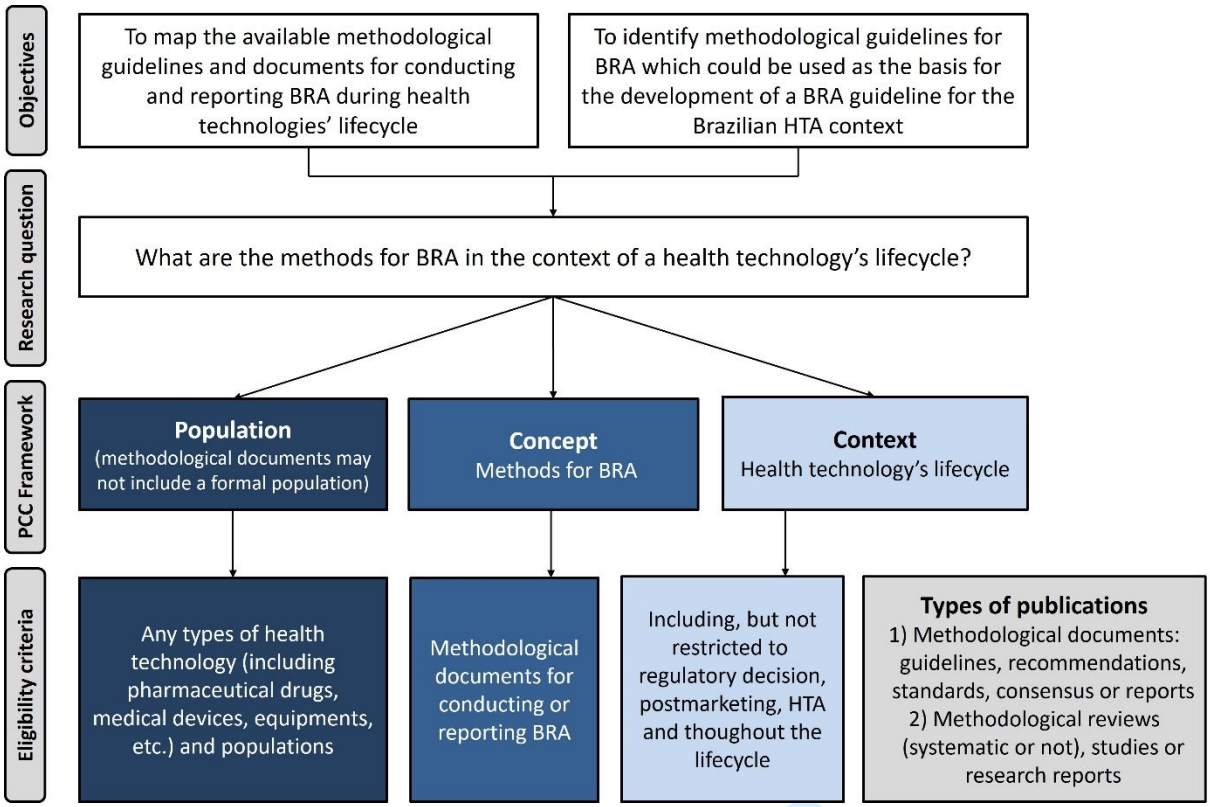
*General: No specific designation was given to the descriptive framework.

#Other: approaches cited in <5 of the included documents (See Supplemental Table 6 for the complete list of approaches).

Numbers are presented as (number of documents citing the approach; proportion of the total 83 documents).

453x256mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL



Supplemental Figure 1. Relationship between the objectives, research question, and eligibility criteria for the scoping review. BRA: benefit-risk assessment; HTA: health technology assessment.

Supplemental Table 1. PRISMA Extension for Scoping Reviews (PRISMA-ScR)

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	6,7
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	8
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	8
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	9 and Supplementary material
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	9 and Supplementary material
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	9,10
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	published protocol (doi:10.1136/bmjopen-2023-075333)
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	10
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	11, Figure 2 and Supplementary material
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	11,12
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	13-17
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	13-17
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	17-18
Limitations	20	Discuss the limitations of the scoping review process.	18-19
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	20-21
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	21

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Supplemental Table 2. Electronic search strategy on EMBASE (OVID)

Line	Searches	Results
1	risk benefit analysis/	61035
2	(risk adj1 benefit).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	78214
3	(benefit adj1 harm).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	746
4	maximum acceptable risk.mp.	114
5	numbers needed to treat/	1715
6	number* needed to treat.mp.	9158
7	number* needed to harm.mp.	1500
8	time without symptoms.mp.	215
9	minimum cinical efficacy.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	0
10	multicriteria decision analysis/	698
11	or/1-10 **[Concept 1: Benefit-risk assessment]**	89136
12	(method* or appraisal or framework or model).ti,ab.	13405124
13	11 and 12 **[Concept 1 and Concept 2: Methods]**	31415
14	guidance.ti,ab.	208292
15	guideline.ti,ab.	115535
16	review.pt.	2966321
17	(systematic review or meta-analysis).pt.	0
18	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	565454
19	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	354133
20	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	16897
21	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	51129
22	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	45458
23	(handsearch* or hand search*).ti,ab,kf.	13083
24	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	44220
25	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	18609
26	(meta regression* or metaregression*).ti,ab,kf	16328
27	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	674328
28	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	407265
29	(cochrane or (health adj2 technology assessment) or evidence report).jw.	29425
30	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	24270
31	(outcomes research or relative effectiveness).ti,ab,kf.	15531
32	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	7039
33	(meta-analysis or systematic review).mp	636752
34	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	407
35	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	256

Line	Searches	Results
36	umbrella review*.ti,ab,kf.	1228
37	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	27
38	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	18
39	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	22
40	or/14-39 **[Concept 3: type of studies]**	3802406
41	13 and 40 **[Concept 1/2 AND Concept 3]**	**11409**

Date of search: October 24, 2022

Supplemental Table 3. Electronic search strategy on MEDLINE (PubMed)

Line	Searches	Results
1	(("benefit-risk" OR "benefit risk" OR "benefit-harm" OR "benefit harm" OR "harm-benefit" OR "harm benefit" OR "risk-benefit" OR "risk benefit" OR "risk-benefit" OR "risk benefit" OR "benefit-risk"	16,526
2	"Transparent uniform risk benefit overview"	3
3	"Stated preference method and maximum acceptable risk"	43
4	"Relative value adjusted number needed To treat"	144
5	"Risk–benefit plane"	3
6	"Risk–benefit Contour"	996
7	"time without symptoms and toxicity" AND TWiST	140
8	"Quality-adjusted time without symptoms and toxicity"	172
9	"Quantitative framework for risk and benefit assessment"	225
10	"Probabilistic simulation methods"	4,802
11	"minimum target event risk for treatment"	229
12	"NNT/NNH ratio"	15
13	"Number needed to treat" AND "number needed to treat to harm"	765
14	"threshold NNT"	4
15	"Net clinical benefit"	652
16	"Minimum clinical efficacy"	3
17	"Multicriteria decision analysis"	336
18	"Incremental net health benefit"	39
19	"Gail/National Cancer Institute"	3
20	"Boers' 3x3 table"	1
21	"Benefit-less-risk analysis"	3
22	OR/1-21 **[Concept 1: Benefit-risk assessment]**	24,674
23	"method*"[Title]	537,649
24	"Appraisal"[Title/Abstract]	42,055
25	"Framework"[Title/Abstract]	340,239
26	"Model"[Title/Abstract]	2,569,154
27	OR/23-36 **[Concept 2: Methods]**	3,342,355
28	"Guidance"[Title/Abstract]	149,210
29	"Guidelines"[Title/Abstract]	401,771
30	"Review"[Publication Type]	3,078,354
31	("systematic"[Filter] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR ("systematic"[Filter] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta analy*"[Text Word] OR "metanaly*"[Text Word] OR "metaanaly*"[Text Word] OR "met analy*"[Text Word] OR "integrative research"[Title/Abstract] OR "integrative review*"[Title/Abstract] OR "integrative overview*"[Title/Abstract] OR "research integration*"[Title/Abstract] OR "research overview*"[Title/Abstract] OR "collaborative review*"[Title/Abstract] OR "collaborative overview*"[Title/Abstract] OR "systematic review"[Publication Type] OR "systematic reviews as topic"[MeSH Terms] OR "systematic review*"[Title/Abstract] OR "technology assessment*"[Title/Abstract] OR "technology overview*"[Title/Abstract] OR "technology appraisal*"[Title/Abstract] OR "technology assessment, biomedical"[MeSH Terms] OR "HTA"[Title/Abstract] OR "HTAs"[Title/Abstract] OR "comparative efficacy"[Title/Abstract] OR "comparative effectiveness"[Title/Abstract] OR "outcomes research"[Title/Abstract] OR "indirect comparison*"[Title/Abstract] OR "Bayesian comparison"[Title/Abstract] OR (("indirect treatment"[Title/Abstract] OR "mixed-treatment"[Title/Abstract]) AND "comparison*"[Title/Abstract]) OR "embase*"[Title/Abstract] OR "cinahl*"[Title/Abstract] OR "systematic overview*"[Title/Abstract] OR "methodological overview*"[Title/Abstract] OR "methodologic overview*"[Title/Abstract] OR "methodological review*"[Title/Abstract] OR "methodologic review*"[Title/Abstract] OR "quantitative review*"[Title/Abstract] OR "quantitative overview*"[Title/Abstract] OR "quantitative	599,287

Line	Searches	Results
	synthes*"[Title/Abstract] OR "pooled analy*"[Title/Abstract] OR "Cochrane"[Title/Abstract] OR "Medline"[Title/Abstract] OR "Pubmed"[Title/Abstract] OR "Medlars"[Title/Abstract] OR "handsearch*"[Title/Abstract] OR "hand search*"[Title/Abstract] OR "meta regression*"[Title/Abstract] OR "metaregression*"[Title/Abstract] OR "data synthes*"[Title/Abstract] OR "data extraction"[Title/Abstract] OR "data abstraction*"[Title/Abstract] OR "mantel haenszel"[Title/Abstract] OR "peto"[Title/Abstract] OR "der-simonian"[Title/Abstract] OR "dersimonian"[Title/Abstract] OR "fixed effect*"[Title/Abstract] OR "multiple treatment comparison"[Title/Abstract] OR "mixed treatment meta analys*"[Title/Abstract] OR "umbrella review*"[Title/Abstract] OR ("multiple paramet*"[Title/Abstract] AND "evidence synthesis"[Title/Abstract]) OR ("multi paramet*"[Title/Abstract] AND "evidence synthesis"[Title/Abstract]) OR ("multiparameter*"[Title/Abstract] AND "evidence synthesis"[Title/Abstract]) OR "Cochrane Database Syst Rev"[Journal] OR "health technology assessment winchester england"[Journal] OR "evid rep technol assess full rep"[Journal] OR "evid rep technol assess summ"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "health technol assess rockv"[Journal] OR "Health Technol Assess Rep"[Journal]))	
32	OR/28-31 **[Concept 3: types of studies]**	3,784,327
33	#22 AND #27 AND #32 **[Concept 1 AND Concept 2 AND Concept 3]**	**1506**

Date of search: October 25, 2022

Supplemental Table 4. Sources of grey literature

#	ORGANIZATION	ABBREVIATION	COUNTRY
Health Technology Assessment (HTA) bodies and global HTA networks			
1	Adelaide Health Technology Assessment	AHTA	Australia
2	Agencia de Evaluación de Tecnologías Sanitarias de Andalucia	AETSA	Spain
3	Agency for Healthcare Research and Quality	AHRQ	United States
4	Association of Austrian Social Insurance Institutions	HVB	Austria
5	Austrian Institute for Health Technology Assessment	AIHTA	Austria
6	Canadian Agency for Drugs and Technologies in Health	CADTH	Canada
7	Centro Nacional de Excelencia Tecnológica en Salud	CENETEC	Mexico
8	Comissão Nacional de Incorporação de Tecnologias no SUS	CONITEC	Brazil
9	Dental and Pharmaceutical Benefits Agency	TLV	Sweden
10	European Network for Health Technology Assessment	EUnetHTA	Europa
11	Finnish Coordinating Center for Health Technology Assessment	FINCCHTA	Finland
12	Gemeinsamer Bundesausschuss	G-BA	Germany
13	Haute Autorité de Santé	HAS	France
14	Health Insurance Review and Assessment Agency	HIRA	South Korea
15	Health Technology Assessment International	HTAi	International
16	Healthcare Improvement Scotland	HIS	United Kingdom
17	Institute for Clinical and Economic Reviews	ICER	United States
18	Institute for Clinical Effectiveness and Health Policy	IECS	Argentine
19	Institute for Quality and Efficiency in Health Care	IQWiG	Germany
20	Instituto de Evaluación Tecnológica en Salud	IETS	Columbia
21	International Network of Agencies for Health Technology Assessment	INAHTA	International
22	Italian National Agency for Regional Healthcare Services	AGENAS	Italy
23	National Centre for Pharmacoeconomics	NCPE	Ireland
24	National Health Care Institute (Zorginstituut Nederland)	ZIN	Netherlands
25	National HTA Program for Medical Devices	PNHTADM	Italy
26	National Institute for Health and Care Excellence	NICE	United Kingdom
27	National Institute for Health and Disability Insurance	NIHDI	Belgium
28	National Institute for Health Technology Assessment	NIHTA	Taiwan
29	Network of HTA research agencies in Asia and Pacific regions	HTAsiaLink	Asia
30	Professional Society for Health Economics and Outcomes Research	ISPOR	International

#	ORGANIZATION	ABBREVIATION	COUNTRY
31	Red Española de Agencias de Evaluación de Tecnologías Sanitarias y Prestaciones del Sistema Nacional de Salud	REDETS	Spain
32	Rede de Avaliação de Tecnologia em Saúde das Américas	RedETSA	Latin America
33	Scottish Medicines Consortium	SMC	United Kingdom
34	Social & Health Services and Labour Market	DEFACTUM	Denmark
35	Swedish Agency for Health Technology Assessment and Assessment of Social Services	SBU	Sweden
36	Unidad Coordinadora de Evaluación y Ejecución de Tecnologías Sanitarias	UCEETS	El Salvador
Regulatory Agencies			
1	Agence Nationale de Sécurité du Médicament et des Produits de Santé	ANSM	France
2	Agência Nacional de Vigilância Sanitária	ANVISA	Brazil
3	Danish Medicines Agency	DMA	Denmark
4	European Medicines Agency	EMA	Europe
5	Health Canada/Santé Canadá	HC	Canada
6	Medical Products Agency	MPA	Sweden
7	Medicines and Healthcare products Regulatory Agency	MHRA	United Kingdom
8	Pharmaceuticals and Medical Devices Agency	PMAJ	Japan
9	Swiss Agency for Therapeutic Products	SATP	Switzerland
10	The Central Drugs Standard Control Organization	CDSCO	India
11	Therapeutic Goods Administration	TGA	Australia
12	U.S. Food and Drug Administration	FDA	United States

Supplemental Table 5. Excluded publications and reasons

#	Author	Reference	Reason
1	Angelis et al.	Value Health. 2020; 23(8):1040–1048. doi: 10.1016/j.jval.2020.04.1828	Other (It was not a concept of interest because it assessed methods exclusively for the harm or benefit outcomes, not the BRA balance)
2	Baltussen et al.	Value Health. 2019; 22(11):1283–1288. doi: 10.1016/j.jval.2019.06.014	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
3	Boada et al.	PLoS One. 2008;3(10):e3580. doi: 10.1371/journal.pone.0003580	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
4	Bouvy et al.	Patient. 2020 Apr;13(2):145-149. doi: 10.1007/s40271-019-00408-4	Other: paper addressed preferences methods but not as methods of BRA or in the BRA context
5	Chachoua et al.	Front Med. 2020 Oct 26;7:543046. doi: 10.3389/fmed.2020.543046	Other: paper addressed preferences methods but not as methods of BRA or in the BRA context
6	Chan et al.	Pharm Res 39, 1761–1777 (2022). doi: 10.1007/s11095-022-03201-5	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
7	Cruccu et al.	Pain Practice. 2007;7(3):230–233. doi: 10.1111/j.1533-2500.2007.00131.x	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
8	EL Masri et al.	Patient Prefer Adherence. 2022;16:2609-2637. doi: 10.2147/PPA.S375062	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
9	Frazão et al.	BMC Med Inform Decis Mak. 2018;18(1):90. doi: 10.1186/s12911-018-0663-1	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
10	Garrison et al.	Health Affairs. 2007;26(3):684–695. doi: 10.1377/hlthaff.26.3.684	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
11	Garrison et al.	Pharmacoeconomics. 2010;28(10):855-65. doi: 10.2165/11538640-000000000-00000	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
12	Hart et al.	Bundesgesundheitsblatt Gesundheitsforsch.Gesundheitsschutz. 2005;48:204–214. doi: 10.1007/s00103-004-0977-2	Other: paper addressed preferences methods but not as methods of BRA or in the BRA context
13	Khan et al.	Med Decis Making. 2022;42(2):262-274. doi: 10.1177/0272989X211019040	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
14	Lackey et al.	Ther Innov Regul Sci. 2021;55(1):170-179. doi: 10.1007/s43441-020-00203-6	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
15	Liberti et al.	Pharm Med. 2011;25(3):139-146. doi: 10.1007/BF03256855	Other: Opinion paper
16	Luteijin et al.	Food Chem Toxicol. 2012;50(1):26-32. doi: 10.1016/j.fct.2011.06.008	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
17	Maloney et al.	Int J Technol Assess Health Care. 2019;35(5):384-392. doi: 10.1017/S026646231900062X	Other: Methodological research using qualitative methods
18	Miller et al.	Value Health. 2017;20(2):296-298. doi: 10.1016/j.jval.2016.11.010	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA

#	Author	Reference	Reason
19	Moore et al.	Cureus. 2021;13(7):e16528. doi: 10.7759/cureus.16528	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
20	Norton et al.	Ther Innov Regul Sci. 2011;45:741–747. doi: 10.1177/009286151104500510	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
21	Ouellet et al.	Expert Opin Drug Saf. 2010 Mar;9(2):289-300. doi: 10.1517/14740330903499265.	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
22	Pane et al.	Pharmacoepidemiol Drug Saf. 2019;28(9):1155-1165. doi: 10.1002/pds.4859	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
23	Pignatti et al.	Mol Oncol. 2015;9(5):1034-41. doi: 10.1016/j.molonc.2014.10.003	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
24	Puhan et al.	BMC Med. 2015;13:250. doi: 10.1186/s12916-015-0493-2	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
25	Radawski et al.	Pharmacoepidemiol Drug Saf. 2020;29(12):1532-1539. doi: 10.1002/pds.5167	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
26	Rajczi et al.	J Law Med Ethics. 2004;32(2):338-48. doi: 10.1111/j.1748-720x.2004.tb00480.x	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
27	Rid et al.	Kennedy Inst Ethics J. 2011;21(2):141-79. doi: 10.1353/ken.2011.0007	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
28	Smith et al.	Ther Innov Regul Sci. 2021;55(2):415-425. doi: 10.1007/s43441-020-00230-3	Other: Qualitative research
29	Tervonen et al.	Med Decis Making. 2015;35(7):859-71. doi: 10.1177/0272989X15587005	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
30	van der Zanden et al.	Clin Pharmacol Ther. 2021;110(4):952-965. doi: 10.1002/cpt.2336	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
31	Vass et al.	Pharmacoeconomics. 2017;35(9):859-866. doi: 10.1007/s40273-017-0518-0	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
32	Waddingham et al.	Biom J. 2016 Jan;58(1):28-42. doi: 10.1002/bimj.201300254	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
33	Walker et al.	Clin Pharmacol Ther. 2011;89(2):179-82. doi: 10.1038/clpt.2010.290	Other: Discussions or lessons learned of a workshop conference
34	Wen et al.	Value Health. 2014;17(5):619-28. doi: 10.1016/j.jval.2014.04.008	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA

Supplemental Table 6. Methodological approaches for BRA cited in <5 of the included documents

Approach	N of documents	% (from total of 83)
Descriptive frameworks		
Boers´ 3x3 table	4	4.8%
Outcome measures in rheumatology (OMERACT) 3x3	3	3.6%
Medical Device Innovation Consortium (MDIC) framework	3	3.6%
Benefit-risk analysis for foods (BRAFO)	2	2.4%
Benefit-Risk Assessment Framework Into the Common Technical Document for marketing authorization applications	2	2.4%
Centre for Innovation in Regulatory Science (CIRS) 7-step framework	2	2.4%
Benefit-risk assessment in new and old drugs (BRAIN)	1	1.2%
Benefit-risk assessment. communication. and evaluation (BRACE)	1	1.2%
Core structured benefit-risk assessment (cSBRA)	1	1.2%
Framework for BRA the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction or have endocrine-disrupting properties	1	1.2%
Quantitative frameworks		
Gail/National Cancer	4	4.8%
System dynamics	3	3.6%
Bayesian beliefs networks (BBN)	3	3.6%
Discrete event simulation (DES)	3	3.6%
Dynamic model	3	3.6%
Weighted net clinical benefit (wNCB)	3	3.6%
Benefit-risk assessment model (BRAM)	2	2.4%
Influence/relevance diagram	2	2.4%
Joint modeling framework for benefit-risk evaluation	2	2.4%
Bayesian decision analysis (BDA) method	1	1.2%
Bayesian Markov model	1	1.2%
Benefit-risk utility function and its corresponding ROC curve	1	1.2%
Hierarchical Bayesian Benefit-Risk (HBBR) Modeling	1	1.2%
ICER Value Assessment Framework (ICER Evidence Rating Matrix)	1	1.2%
Prospective BRA monitoring framework	1	1.2%
Statistical framework for periodic BRA	1	1.2%
Evidence-based benefit and risk model	1	1.2%
Threshold indices		
Minimal acceptable benefit (MAB)	3	3.6%
Ratio number needed to harm per number needed to treat (NNH/NNT)	3	3.6%
Threshold number needed to treat (NNTt)	3	3.6%
Number needed to vaccinate (NNV)	2	2.4%
Minimum target event risk for treatment (MERT)	2	2.4%
Probability of technical success (POTS)	1	1.2%
Minimally important difference (MID)	1	1.2%
Margin of Exposure (MoE)	1	1.2%
Margin of Safety (MoS)	1	1.2%
Number needed to treat for benefit (NNT-B)	1	1.2%
Unmitigated failure (NNHu)	1	1.2%
Unqualified success [treatment success without treatment induced side effects (NNTu)]	1	1.2%
Number needed to diagnose (NND)	1	1.2%
Number needed to misdiagnose (NNM)	1	1.2%
Number needed to screen (NNS)	1	1.2%
Number needed to benefit (NNB)	1	1.2%
Health indices		
Drug-attributed loss of quality-adjusted life year (DALQALY)	1	1.2%
Validated health-related quality of life measures	1	1.2%
Trade-off indices		

Approach	N of documents	% (from total of 83)
Incremental benefit-risk ratio (IBRR)	4	4.8%
Incremental net health benefit with relative-value-adjusted life year (INHB-RVALY)	2	2.4%
Incremental net health benefit with quality-adjusted life-year (INHB-QALY)	2	2.4%
Incremental net health benefit with maximum acceptable risk (INHB-MAR)	1	1.2%
Exposure-adjusted incidence rate (EAIR)	1	1.2%
Utility survey techniques		
Best-worst scaling exercise	4	4.8%
Threshold technique	4	4.8%
Ranking exercise	4	4.8%
Direct elicitation method	2	2.4%
Deliberative dialogue	2	2.4%
Direct assessment questions	2	2.4%
Outranking method	2	2.4%
Point allocation	2	2.4%
Indirect elicitation methods [Short Form–36 Health Survey (SF-36), Euro Quality-of-Life five-dimensions (EQ-5D), Health Utility Index]	2	2.4%
Delphi technique	1	1.2%
Graded pairs	1	1.2%
Index of Well-Being	1	1.2%
Nominal group	1	1.2%
Visual Analogue Scale (VAS)	1	1.2%
Utility survey technique	1	1.2%

BRA: benefit-risk assessment; ROC: receiver operating characteristic.

BMJ Open

Methodological Guidelines and Publications of Benefit-risk Assessment for Health Technology Assessment: A Scoping Review

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Complete List of Authors:	Suzumura, Erica; Universidade de Sao Paulo, Departamento de Medicina Preventiva; UMIT TIROL Private Universitat fur Gesundheitswissenschaften und -technologie GmbH, Department of Public Health, Health Services Research and Health Technology Assessment DE OLIVEIRA ASCEF, BRUNA; Universidade de Sao Paulo, Departamento de Medicina Preventiva Maia, Fernando; Universidade de Sao Paulo, Departamento de Medicina Preventiva Bortoluzzi, Aline ; Universidade de Sao Paulo, Departamento de Medicina Preventiva Domingues, Sidney; Universidade de Sao Paulo, Departamento de Medicina Preventiva Farias, Natalia ; Universidade de Sao Paulo, Departamento de Medicina Preventiva Gabriel, Franciele; Universidade de São Paulo, Ciências Farmacêuticas Jahn, Beate ; UMIT TIROL Private Universitat fur Gesundheitswissenschaften und -technologie GmbH, Public Health, Health Services Research and Health Technology Assessment Siebert, Uwe; UMIT TIROL Private Universitat fur Gesundheitswissenschaften und -technologie GmbH, Public Health, Health Services Research and Health Technology Assessment; Harvard University T H Chan School of Public Health, Departments of Epidemiology and Health Policy & Management De Soarez, Patricia Coelho; Universidade de Sao Paulo, Departamento de Medicina Preventiva
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Health policy, Health services research, Research methods
Keywords:	PUBLIC HEALTH, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, STATISTICS & RESEARCH METHODS

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Methodological Guidelines and Publications of Benefit-risk Assessment for Health Technology Assessment: A Scoping Review

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Abstract

Objectives: To map the available methodological guidelines and documents for conducting and reporting benefit-risk assessment (BRA) during health technologies' lifecycle; and to identify methodological guidelines for BRA that could serve as the basis for the development of a BRA guideline for the context of health technology assessment (HTA) in Brazil.

Design: Scoping review.

Methods: Searches were conducted in three main sources up to March 2023: (1) electronic databases; (2) grey literature (48 HTA and regulatory organizations); and (3) manual search and contacting experts. We included methodological guidelines or publications presenting methods for conducting or reporting BRA of any type of health technologies in any context of the technology's lifecycle. Selection process and data charting were conducted by independent reviewers. We provided a structured narrative synthesis of the findings.

Results: From the 83 eligible documents, six were produced in the HTA context, 30 in the regulatory, and 35 involved guidance for BRA throughout the technology's lifecycle. We identified 129 methodological approaches for BRA in the documents. The most commonly referred to descriptive frameworks were the Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk, and Linked decisions (PrOACT-URL) and the Benefit Risk Action Team (BRAT). Multicriteria decision analysis was the most commonly cited quantitative framework. We also identified the most cited metric indices, estimation and utility survey techniques that could be used for BRA.

Conclusions: Methods for BRA in HTA are less established. The findings of this review, however, will support and the elaboration of the Brazilian methodological guideline on BRA for HTA.

Study registration: Open Science Framework (https://doi.org/10.17605/OSF.IO/69T3V).

Keywords: health technology assessment, benefit-risk assessment, benefit-risk evaluation, methodological guidelines, methodological guidance, scoping review.

Strengths and limitations of this study

- This is the first scoping review aiming at mapping methodological guidelines and publications on methods of benefit-risk assessment, especially in the context of health technology assessment (HTA).
- We used the framework proposed by Arksey and O'Malley and the refinements made by the Joanna Briggs Institute.
- We performed an electronic search on the main databases as well as manual searches on a vast source of grey literature, including 38 HTA bodies and networks, and 12 regulatory agencies' websites.
- Despite our attempt to conduct a comprehensive search, we may have missed documents reporting methodological recommendations or guidelines for benefit–risk assessment methods used in practice which were not publicly available online.
- The extraction of data may have been impacted by the great variety and inconsistent classification of benefit-risk assessment frameworks and methods, and data synthesis may have been impacted by some overlapping and redundant content from documents produced by the same organizations.

Introduction

Benefit-risk assessment (BRA), also referred to as risk-benefit or benefit-harm assessment, is an important component in decision-making throughout the lifecycle of a health technology, from its development, regulatory approval, postmarketing surveillance, decisions about incorporation and reimbursement in health technology assessment (HTA), decision-making in clinical practice, to its obsolescence.[1–3]

BRA of comparative technologies is usually carried out informally, without following a systematic and reproducible process,[3] which can lead to inappropriate or intransparent decisions. During the last two decades, efforts have been observed to apply more structured, objective and transparent approaches, aiming at better communication and decision-making.[1,3–5] For this purpose, several frameworks have been proposed to guide BRA.[1]

Structured approaches for BRA have been used, in particular for regulatory decisions and postmarketing surveillance. The European Medicines Agency (EMA) has been making recommendations on BRA structured methods for new drug applications since 2007.[6] The Pharmacoepidemiological Research on Outcomes of Therapeutics (PROTECT) initiative was established by a European Consortium aiming to support the monitoring of BRA of medicines in Europe and to provide recommendations to various stakeholders, particularly regulators.[7] With the same attention, in 2009 the Food and Drug Administration (FDA), in the United States of America (USA), initiated an effort to explore more systematic approaches for BRA as part of the drug review process and proposed its benefit-risk framework (FDA BRF).[8]

Concerning the HTA context, to the best of our knowledge, the efforts for using formal approaches for BRA are in a preliminary phase compared to the regulatory setting. In Brazil, the content of the HTA dossier submissions to the National HTA body, the *Comissão Nacional de Incorporação de Tecnologias* (CONITEC), should include the description of the

clinical evidence of the technology of interest (i.e., efficacy, effectiveness, accuracy and safety) compared to the technology already available in the public health system.[9] However, currently no recommendations regarding the scope, methods and reporting of BRA are provided by CONITEC.

This review represents the first phase in a larger project to improve the application of BRA in the context of the Brazilian HTA bodies. A partnership with *Rede Brasileira de Avaliação de Tecnologias em Saúde* (REBRATS), a strategic network to facilitate the elaboration of priority HTA studies for the Brazilian health system,[10] will provide methodological and training support to increase the use of BRA methods in the reports under deliberative decision-making processes. Furthermore, findings from this scoping review will inform the development of a methodological guideline on BRA for the CONITEC.

Therefore, the objectives of this scoping review were: (1) to map the available methodological guidelines and documents for conducting and reporting BRA during health technologies' lifecycle - within this objective, we pursue identifying the definitions of BRA, the approaches for conducting BRA and the visual tools for reporting BRA results that have been used; and (2) to identify methodological guidelines for BRA, which could be used as the basis for the development of a BRA guideline for the Brazilian HTA context.

Methods

Study design

This scoping review was based on the framework proposed by Arksey and O'Malley[11] and the updated guidelines by the Joanna Briggs Institute.[12,13] The review protocol is published in BMJ Open[14] and is registered in the Open Science Framework

(https://doi.org/10.17605/OSF.IO/69T3V). The reporting of this review follows the PRISMA Extension for Scoping Reviews (PRISMA-ScR) recommendations (Supplemental Table 1).[15]

Research question and eligibility criteria

Our research question was "What are the methods for BRA in the context of a health technology's lifecycle?". The relationship between our objectives, research question, and eligibility criteria is depicted in Figure 1.

Our eligibility criteria followed the Population, Concept, and Context (PCC) mnemonic framework.[12,13] We included: (1) methodological documents concerning BRA involving any types of health technologies and populations (Population); (2) presenting methods for conducting or reporting BRA (Concept); (3) developed in any context of the health technology's lifecycle (Context). The types of publications included were full-text methodological guidelines, recommendations, standards, consensus, methodological reports, methodological reviews, methodological studies, research reports addressing specific methods for BRA, and reporting guidelines. We excluded editorials, comments, studies using qualitative methods, conference abstracts, studies reporting methods exclusively for either the assessment of benefit or risk/harm (i.e., not reporting BRA trade-off or balance), and publications focusing only on the description of a specific methodological approach that could be used for BRA but did not present the application for BRA.

In case an eligible document stated methods for BRA balance and, in addition, other metric indices for quantifying either benefits or harms that fall into the categorization proposed by Mt-Isa et al.[3] which was followed for data charting (see section "Charting the data, summarizing, and reporting the results"), such indices were also reported in our review.

Information sources and search strategy

We performed a comprehensive search on three main sources: (1) biomedical electronic databases (electronic databases); (2) websites of key HTA and drug regulatory organizations (grey literature); and (3) manual search and contacting experts in the field (manual search).

The search strategy in the: (1) Electronic databases (EMBASE via OVID and MEDLINE via PubMed) followed a three-step approach,[12,13] using indexed and free-text terms, validated filters,[16,17] and no language or publication date restrictions. The strategy was validated by an experienced research librarian and peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist.[18] These searches were completed in October 2022. The complete search strategy is presented in Supplemental Tables 2 and 3. (2) Grey literature consisted of searching the websites of 36 HTA bodies and global HTA networks, and twelve key regulatory authorities using free-text terms such as "benefits AND (risks OR harms) AND methods" or adaptations made accordingly, and no publication date restrictions. The search was performed using the language of origin of the evidence source, or when more than one language was available, preference was given to English, Spanish, and Portuguese. These searches were conducted from October 2022 to January 2023. The list of websites is presented in Supplemental Table 4. (3) Manual search consisted of hand-searching the reference lists of all relevant documents identified in the two previous sources, and contacting experts by email. We performed the manual searches and contacted the experts from February to March 2023.

Selection process

We conducted a pilot test for the selection process. All reviewers working in independent pairs screened the titles and abstracts of a random sample of 100 titles/abstracts,[13] using the pre-specified eligibility criteria. In case of disagreements higher

than 15% within the pair, another random sample was screened. The pairs started screening the documents when 85% (or greater) agreement was achieved.

Three pairs of independent reviewers screened all references retrieved from the electronic database search by reading titles and abstracts. One pair of independent reviewers screened the titles and abstracts identified from grey literature. The full-text of potentially eligible documents identified during the screening as well as those identified via manual search were retrieved and assessed by three pairs of reviewers according to the eligibility criteria. Any disagreements during the selection process were solved through a consensus within the team of reviewers, or by a third reviewer.

Charting the data, summarizing, and reporting the results

A charting form to guide the data extraction was developed using the classification of BRA methods and visual tools proposed by Mt-Isa et al.[3] and Hallgreen et al.[19] The definitions of benefit, risk/harm and BRA provided by the documents were grouped through analysis content.[20] The charting form was validated by the reviewers conducting the extraction from five eligible documents. Data extraction was performed by three pairs of independent reviewers. Any disagreements were solved through a consensus within the team of reviewers, or by a third reviewer.

We conducted a structured narrative synthesis and reported the results in evidence tables and figures along with descriptive statistics to identify common characteristics and map the evidence.

Patient and public involvement

Although is important to have the involvement of patients and the general public in the HTA decision making processes, such stakeholders are usually not involved in

methodological reviews as the present one. Therefore, patients and/or the general public were not involved in the design, conduct, or reporting of this study. The findings of this review will provide an important basis for the elaboration of the Brazilian methodological guideline on BRA for HTA and we intend to collaborate with HTA experts, REBRATS and CONITEC to promote the use of BRA methods in the context of HTA.

Results

Figure 2 provides an overview of the selection process. Of 12,915 references retrieved from electronic databases, 11,761 were screened, the full-text of 66 were assessed, 34 were excluded (reasons are presented in Supplemental Table 5) and 32 publications were included.[1–3,5,19,21–47] Regarding grey literature, our search resulted in the identification of 160 documents. Among these, 25 were included.[6,8,48–70] Additionally, we retrieved 26 methodological documents through manual searches.[4,71–95] In total, our scoping review encompassed 83 documents or publications that met the eligibility criteria.

Characteristics of the included documents

Table 1 presents a condensed summary of the characteristics of the included documents. The majority were published by institutions in the USA, followed by the European Union or partnerships between European institutions. Accordingly, most of the documents originated within the regulatory framework of the USA and Europe, with seven from the EMA[6,48–53] and six from the FDA.[8,56–60] Figure 3 depicts the geographic area in which the documents were developed, highlighting the countries that produced documents for the HTA context.

Most of the documents were published during the years 2013-2017. The first document was published in 1998 by the Council for International Organizations of Medical Sciences (CIOMS) Working Group.[90] The first publication involving the HTA context was a review on multiple criteria decision analysis (MDCA) funded by the NICE Decision Support Unit (DSU), UK, published in 2011.[70] The two most recent documents within the HTA context, published in 2022, were the General Methods from the German Institute for Quality and Efficiency in Health Care (IQWiG),[65] and a Methodological Handbook for the evaluations of clinical effectiveness, safety, and diagnostic validity of health technologies from a Spanish HTA body.[54]

More than 37% of the documents comprised literature reviews. Eighteen documents consisted of methodological reports (21.7%), informing and/or describing methods of BRA.[6,31,41,48–55,64,74,75,78,79,87,90] Thirteen (15.7%) were methodological guidelines providing recommendations for conducting BRA, mostly developed by regulatory agencies.[8,56–60,62,65–68,85,86] Furthermore, fourteen (16.8%) methodological papers have proposed new methods of BRA or their application, all of which were published in peer-reviewed journals.[24,25,30,33,47,61,63,69,73,77,81,84,94,95] We also identified six systematic reviews on BRA methods,[1,3,19,32,37,43] and one reporting guideline developed specifically for reporting of BRA of vaccines.[44]

Medicinal products [including the former (n=13),[4,6,24,28,36,38,48–53,80] pharmaceutical drugs (n=33),[2,3,5,21–23,31–35,37,39,40,42,45,58,61,66,71–73,75,77,78,81–83,85–87,89,90] vaccines (n=5),[43,44,88,94,95] or a combination of the previous with biologics and radiopharmaceuticals (n=6)][1,8,56,60,62,84] was the type of technology most addressed in the documents (n=57; 68.8%). Medical devices [including the former (n=6),[57,59,63,67,68,79] diagnostic tests (n=1),[25] or a combination of the previous with equipments (n=2)][46,47] were addressed in nine documents (10.8%). The

remaining documents stated that the BRA methods could be applied to all types of technologies (general; n=17, 20.4%).[19,26,27,29,30,41,54,55,64,65,69,70,74,76,91–93]

Five of the documents produced for the HTA context were developed by HTA bodies.[54,55,65–67] One document was developed by an academic institution with the funding of an HTA body.[70] One document, although produced by a member of the International Network of Agencies for Health Technology Assessment (INAHTA), aimed to describe methods for BRA in systematic reviews.[41] Most of the documents, including all produced for the HTA context, were funded by institutions not involved in for-profit activities.

A possible conflict of interest, identified in about half of the documents, was present if the individuals involved in the document development received support or employment, any stocks or shares, and any consultation fees or other forms of remuneration from the industry.

Definitions of benefit, risk, and BRA

In total, 31 documents provided the definition of "benefits". We classified the definitions as "favorable effects" (n=11; 13.3%),[19,26,40,45,50,60,62,63,65,79,85] "positive results for an individual or a population, and the probability of achieving such results" (n=11; 13.3%),[5,6,32,39,48,49,68,78,90,91,93] "a potential effect that moves the condition of the patient from disease towards health" (n=6),[27,42,80,89,94,95] and "results that influence the overall benefit-risk balance in a clinically meaningful way and that provide evidence supporting the product approval" (n=3).[23,72,75]

Risks or harms were defined in 31 documents. Definitions that emerged were "unfavorable effects" (n=15; 18.1%),[26,27,40,45,50,60,63,65,75,79,80,85,91,94,95] "negative results for an individual or a population, and the probability that a negative event will happen" (n=10; 12.0%),[6,19,32,39,48,49,68,78,87,93] "a potential effect that moves the condition of the patient from health towards disease" (n=4),[42,62,89,90] and "results that influence the overall benefit-risk

balance in a clinically meaningful way and that provide evidence not supporting the product approval" (n=2).[23,72]

BRA was defined in 28 documents, and most of them stated that BRA "involves balancing between benefit and risk, however, it does not specify whether the assessment is quantitative, qualitative or both" (n=20; 24.1%).[1,6,8,23,48–50,60,62,64–66,68,76,84–86,89,92,93] In contrast, other definitions emerged as "a quantitative or qualitative evaluation of medical product, incorporating explicit outcome weighting within a formal analysis taking both benefits and risks of the product into account" (n=5),[43,57,59,78,87] and "a quantitative evaluation of medical product, incorporating explicit outcome weighting within a formal analysis taking both benefits and risks of the product into account" (n=3).[35,74,90]

Approaches for BRA

We identified 129 methodological approaches or elements of BRA, including frameworks, metric indices, estimation, and utility survey techniques. Figure 4 presents the approaches cited in at least five of the 83 eligible documents (See Supplemental Table 6 for the complete list of approaches). In 14 (16.9%), only descriptive (i.e., qualitative) frameworks for BRA were reported,[8,22,24,26,57–59,67,71,81–83,85,86] 18 (21.7%) cited only quantitative frameworks,[25,27,30,37,44,46,47,61,64,69,70,77,80,84,89,92,94,95] and 58% reported both descriptive and quantitative frameworks. The descriptive frameworks most frequently cited in the documents were the Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk, and Linked decisions (PrOACT-URL),[1,3–5,19,22,26,28,32,34,36,38,40,42,43,45,50–52,68,71–75,78,79,87,91] and the Benefit Risk Action Team (BRAT) framework,[1–5,19,21,22,26,28,31,32,34,36,40,42,43,50,72–75,78,79,82,83,87,88,91] cited in 29 documents (34.9%) each. The descriptive frameworks most recommended were the PrOACT-URL[1,42,51,52,75,78,87] and the FDA BRF,[1,8,56–60] recommended in seven documents each (8.4%). Among the quantitative frameworks, MCDA was the most

frequently cited (n=52; 62.7%)[1–6,19,21,23,28,29,31–34,36–43,45–52,56,64,65,68–70,72–79,87–89,91,92,94,95] and recommended (n=13; 15.7%).[38,39,42,47,50,52,69,73,74,77,78,87,95] Other frequent quantitative frameworks cited were Markov decision processes (MDP; n=18; 21.7%)[1,3,25,32,33,39,40,42–45,50–52,78,87,91,94] and decision trees (n=16; 19.3%).[1,3,25,29,32,40,42,43,46,47,50–52,75,78,87]

Metric indices were reported in 59 (71.1%) documents. The most cited threshold indices were the number needed to harm (NNH; n=38; 45.8%)[1–6,19,21,25,29,31,32,34,35,37,40–44,47–50,54,55,61,66,76–78,80,81,87,89,91–93] and the number needed to treat (NNT; n=37; 44.6%),[1–6,19,21,25,29,31,32,34,35,37,39–42,47–50,54,55,61,66,76–78,80,81,87,89,91–93] which were also recommended in four documents.[2,66,78,87] The quality-adjusted life years (QALY) emerged as the most cited (n=37; 44.6%)[1–3,5,19,25,29,32,34,37,39–42,44,46–52,55,61,65,67,70,75,76,78–80,84,87,89–91] and recommended health index (n=3),[25,78,87] followed by the quality-adjusted time without symptoms and toxicity (Q-TWiST),[1,3,5,19,29,32,37,39–41,47,50,76,78,87,89,92] reported in 17 documents.[78,87] As for trade-off indices, the incremental net health benefit (INHB) was the index mostly cited (n=32; 38.6%)[1–3,5,19,21,25,29,32,34,37,40–43,46,47,49,50,55,61,64,67,68,76,78–80,87,89,91,95] and recommended (n=6; 7.2)%);[47,61,64,78,87,95] followed by the transparent uniform risk-benefit overview (TURBO)[1,3,6,29,32,41,42,48–50,76–78,80,87,90] and the benefit risk ratio (BRR),[2–5,19,32,37,40,43,44,78,84,87,90,92,95] each cited in 16 documents (19.3%).

Estimation techniques were reported in 41 documents. The probabilistic simulation method (PSM) was the most cited approach (n=32; 38.6%).[1,3–5,19,25,29,32,33,37,38,40–47,50–52,68–70,74–76,78,87,91,94] Indirect treatment comparison (ITC) and mixed treatment comparison (MTC) were cited 18 (21.7%)[1,3–5,32,33,40–42,47,54,55,64,65,67,74,78,87] and 17 (20.5%)[1,3–5,19,32,33,40–42,54,64–66,74,78,87] times, respectively. PSM,[38,78,87] and MTC,[1,78,87] were recommended in three documents.

Concerning utility survey assessment techniques, reported in 48 documents, the dominating approaches were the discrete choice experiment (DCE) and the conjoint analysis

(CA), mentioned in 26 (31.3%)[1,3–5,19,30,32,34,40,41,44,46,47,61,63,65,67,70,74,76,78,79,87,93–95] and 22 (26.5%)[1,3,21,30,32,40–42,46,47,50–52,63,65,75,78,79,87,91,93,94] of the documents. DCE was recommended in three documents,[65,78,87] followed by swing weighting, recommended in two.[69,77]

Visual tools to present BRA results

Tools for visual representation of BRA results were used or cited in 75 documents. Summary tables were the most common tool, present in almost 60% of the documents. Tree diagrams and value trees were present in 34 (41%) documents, followed by bar charts (33.7%), dot charts (33.7%), lines (31.3%), and area graphs (28.9%). "Non-conventional" visual tools that emerged were pictograms (n=5)[19,22,54,79,91] and suggestions for using interactive visual displays to enable active participation of the audience (n=4).[31,48,49,87] The complete list of visual tools to present the results of BRA is depicted in Table 2.

Methodological documents produced in the HTA context

Among the 83 eligible, six methodological documents (7.2%) were produced in the context of HTA,[54,55,65–67,70] although 35 (42.2%) explicitly stated that the BRA would be applicable throughout the lifecycle of the technology, which implies the context of HTA among others.

The guide for the elaboration of evaluation reports of medicines published by the *Agencia de Evaluación de Tecnologías Sanitarias de Andalucía* (AETSA), in Spain, suggests that the drug evaluation reports should present in the discussion section a comparison of the safety and efficacy results to obtain an overall assessment of the intervention,[66] but no structure, framework, or quantitative approach was recommended.

The EUnetHTA HTA Core Model for Rapid Relative Effectiveness, version 4.2 published in 2015, states that both relative benefits and harmful effects of a technology are

essential in quantifying the net benefit of an intervention and are essential for being able to form a balanced view of the overall value of a technology.[55]

The methodological manual for the elaboration of evaluations of clinical effectiveness, safety, and diagnostic validity of health technologies published by the Colombian *Instituto de Evaluación Tecnologica en Salud* (IETS) provides overall guidance for conducting HTA reports. Concerning BRA, the manual states that effectiveness and safety outcomes should be included in the report, to allow the benefit-risk balance. However, although the conclusion of the HTA report must state whether the technologies of interest have less, similar, or greater effectiveness and safety compared to their alternatives, the manual does not provide recommendations on how to evaluate the balance between them.[54]

In 2011, Thokala published a report about the applicability of MCDA for HTA. The author compared the MCDA process and the NICE technology appraisal process and described the general practical issues that might arise from using an MCDA approach in the HTA process.[70]

The General Methods, Version 6.1 of 2022, a comprehensive methodological guideline published by the German IQWiG states that each predefined patient-relevant outcome (both beneficial and harmful aspects) is initially assessed on an outcome-specific basis and then presented along with the respective certainty of the evidence for each outcome. Within the overall weighing of benefits and harms, these individual outcomes are then summarized into a global conclusion on the extent of added benefit. If needed, a joint combined measure of benefit-harm such as QALY can be used.[65]

The Australian Medical Services Advisory Committee (MSAC) guidelines suggest constructing an assessment framework or logic diagram to illustrate the necessary steps that link the use of a technology in the target population and the consequences on outcomes.[67] A guidance on formal BRA quantitative framework is not provided.[67]

Discussion

We have conducted a scoping review of available methodological guidelines and documents for conducting and reporting BRA during health technologies' lifecycle. We identified 129 approaches for conducting BRA and 37 visual tools for reporting BRA results. This is the first review stratifying the findings based on the HTA context. Confirming our previous perception about decision support in HTA, the efforts for using formal structured approaches for BRA have been more modest in that context. Only six documents produced by HTA bodies were identified,[54,55,65–67,70] however, they do not provide detailed guidance on how to select the best approach and how to conduct BRA in the HTA context.

Mt-Isa et al. identified 49 approaches for BRA and classified them into four main categories which were followed in our review: frameworks, metrics, estimation techniques and utility survey techniques.[3] Frameworks, which can be subdivided into descriptive and quantitative, provide a structure that guides the assessment to support decision making.[3] They do not provide mathematical algorithms that result in automated decisions.[40] Descriptive frameworks provide qualitative instructions, while quantitative frameworks additionally can provide formal quantitative methods to assess the balance between benefits and risks or provide tools to evaluate long-term benefits and risks/harms.[3] Metrics are systems of measurement and can be subdivided into threshold indices (they handle either benefit or risk but not both), health indices (which include validated and standardized quality-of-life indicators) and trade-off indices (which integrate benefits and risks into a single metric representing the value of the trade-off for direct interpretation). Estimation techniques include generic statistical techniques, and they are applicable in combination with other methods. Utility survey techniques include methods to elicit and collect health utilities and value preferences and they also can be applied in combination with other methods.[3]

The assessed documents agree that some decisions are straightforward, but others need more objective criteria. In cases where a new technology increases benefits and decreases risks, or when the benefits clearly outweigh the risks, a formal quantitative BRA may not be essential. On the other hand, when the benefit-risk balance is not so clear and/or stakeholders preferences influence this balance, the additional use of quantitative BRA methods can be advantageous, if not crucial for decision making.[91] In all cases, at least a structured descriptive framework is recommended to transparently present the rationale to support decision-making and ensure that key aspects of the assessment process are not overlooked.[87] As a second step, the explicit and quantitative assessment of benefit-risk balance may be added in situations where the trade-off is more difficult to judge.[96]

Strengths of our scoping review include a comprehensive search strategy resulting in more than 12,000 retrieved references from electronic databases and 160 full-text documents from 48 HTA and regulatory organizations. The selection and data charting processes were piloted to ensure concordance between the reviewers. Perhaps most importantly, this is the first scoping review aiming at mapping methodological guidelines on methods of BRA highlighting the findings for the HTA context.

As all scoping reviews, ours has several limitations. First, despite our comprehensive search, we may have missed eligible documents for BRA used by HTA and/or regulatory organizations not publicly available online or not searched by our group. Second, we included many documents produced by the same organizations. Therefore, although the documents were unique, they may present some overlapping and redundant content biasing our descriptive percentage results. Third, we identified the most cited BRA approaches, however, this does not mean that such approaches are the most used to support decision-making. Fourth, some of the methodological approaches might have been cited in the literature under different names and definitions, although they would fall into the same technical category.

We have made efforts to collect the different spelling and wording approaches into the same technical nomenclature, however, we may have missed some specific approaches. Finally, appraising the features of the BRA approaches identified was beyond the scope of our review. This would require an extensive assessment from different health decision science perspectives and a full appraisal of all statistical and modeling methods. Such an assessment would result into a lenths report and be extremely laborious, precluding the timely conclusion of this review.

Although our goal was not to appraise the operational characteristics of each identified approach, we will test and explore the potential of at least the two most cited descriptive and quantitative frameworks in case studies in the context of HTA before making formal recommendations. We are aware that no best approach fits the multitude of populations, diseases, health technologies and their clinical applications, and therefore, our intention is not to prescribe or recommend any "one size fits all" BRA approach, but to highlight the uses, advantages, disadvantages, human resources training/skills and computational requirements to support the selection of the methodologies to be used in future BRA in HTA dossier submissions to the Brazilian CONITEC.

We will also face the challenge of making recommendations on the source of data to conduct BRA in the context of HTA, which might consider a broader spectrum of sources compared to BRA for regulatory marketing authorizations, as well as periodicity of BRA for monitoring technologies incorporated in the Brazilian public health system. In addition, the election of the method to be applied for BRA also have to consider the need for rapid evaluation, especially in case of a public health crisis.[97] These are topics not discussed in the documents identified in our review. Such aspects must be assessed and discussed in the future steps, and our intention is that the results and conclusions from this review will provide an

important basis for these next steps towards a more explicit and transparent BRA in the context of HTA in Brazil.

Conclusions

Our review identified 129 methodological approaches for BRA, including descriptive and quantitative frameworks, metric indices, estimation and utility survey techniques, in 83 methodological guidelines and documents for conducting and reporting BRA in the different phases of the lifecycle of health technologies. Among the documents assessed, we identified only six methodological documents produced in the context of HTA. We will test and explore the potential of the two most cited descriptive and quantitative frameworks in case studies in the context of HTA to evaluate their performance. The findings of this review will support these steps, and finally, inform the elaboration of the Brazilian methodological guideline on BRA for HTA.

Author contributions

BOA and PCS conceived the main idea behind this manuscript. EAS, BOA and PCS wrote the manuscript. EAS, BOA, FHAM, AFRB, NSF, FCG and PCS extracted data. EAS, SMD and PCS analysed, summarized and interpreted the findings. EAS, BJ, US and PCS critically revised the manuscript and made important intellectual contributions to its development. All authors read and approved the final version of the manuscript.

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Competing interests statement

The authors declare that they have no conflicts of interest.

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Ethical approval

This study does not involve human participants or animal subjects and therefore does not require ethics committee approval.

Data sharing statement

Not applicable. All data relevant to the study are included in the article or uploaded as supplementary information.

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6

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Table 1. Characteristics of included documents

Characteristics	Context of decision					
	HTA (n=6)	Regulatory (n=30)	Postmarketing (n=7)	Throughout lifecycle (n=35)	Other* (n=5)	All (n=83)
Publication year						
2018-2023	3 (3.6%)	7 (8.4%)	3 (3.6%)	10 (12.1%)	2 (2.4%)	25 (30.1%)
2013-2017	2 (2.4%)	12 (14.4%)	3 (3.6%)	15 (18.0%)	1 (1.2%)	33 (39.8%)
2008-2012	1 (1.2%)	9 (10.8%)	1 (1.2%)	8 (9.6%)	2 (2.4%)	21 (25.3%)
2003-2007		1 (1.2%)		2 (2.4%)		3 (3.6%)
1998-2002		1 (1.2%)				1 (1.2%)
Publication type						
Literature review / case study	1 (1.2%)	11 (13.3%)	1 (1.2%)	17 (20.4%)	1 (1.2%)	31 (37.4%)
Methodological report	2 (2.4%)	10 (12.1%)		5 (6.0%)	1 (1.2%)	18 (21.8%)
Methodological guideline	3 (3.6%)	4 (4.8%)	3 (3.6%)	3 (3.6%)		13 (15.6%)
Methodological paper		4 (4.8%)	3 (3.6%)	6 (7.2%)	1 (1.2%)	14 (16.8%)
Systematic review		1 (1.2%)		4 (4.8%)	1 (1.2%)	6 (7.2%)
Reporting guidelines					1 (1.2%)	1 (1.2%)
Types of technologies						
Medicinal products	1 (1.2%)	20 (24.2%)	7 (8.4%)	27 (32.6%)	2 (2.4%)	57 (68.8%)
General	4 (4.8%)	4 (4.8%)		7 (8.4%)	2 (2.4%)	17 (20.4%)
Medical devices	1 (1.2%)	6 (7.2%)		1 (1.2%)	1 (1.2%)	9 (10.8%)
Main institution which developed the document						
Academic institution	1 (1.2%)	7 (8.4%)	1 (1.2%)	12 (14.4%)	4 (4.8%)	25 (30.2%)
Regulatory agency		12 (14.4%)	3 (3.6%)	3 (3.6%)		18 (21.7%)
Industry		7 (8.4%)	1 (1.2%)	11 (13.3%)		19 (22.9%)
HTA body	5 (6.0%)			1 (1.2%)	1 (1.2%)	7 (8.4%)
Public-private consortium		2 (2.4%)		6 (7.2%)		8 (9.6%)
Consulting firm		2 (2.4%)	2 (2.4%)	1 (1.2%)		5 (6.0%)
Professional society				1 (1.2%)		1 (1.2%)
Main institution which funded the document						
Regulatory agency		14 (16.8%)	1 (1.2%)	4 (4.8%)		19 (22.9%)
Government institution	2 (2.4%)	1 (1.2%)	2 (2.4%)	8 (9.6%)		13 (15.6%)
Industry		5 (6.0%)	2 (2.4%)	7 (8.4%)		14 (16.8%)
HTA body	4 (4.8%)			1 (1.2%)	2 (2.4%)	7 (8.4%)
Public-private consortium					2 (2.4%)	2 (2.4%)
Independent non-profit organization				1 (1.2%)		1 (1.2%)
Not reported		4 (4.8%)	2 (2.4%)	8 (9.6%)	1 (1.2%)	15 (18.0%)
No funding		6 (7.2%)		6 (7.2%)		12 (14.7%)

Characteristics	Context of decision					
	HTA (n=6)	Regulatory (n=30)	Postmarketing (n=7)	Throughout lifecycle (n=35)	Other* (n=5)	All (n=83)
Potential conflict of interest						
Yes		13 (15.6%)	4 (4.8%)	26 (31.5%)	2 (2.4%)	45 (54.3%)
No	2 (2.4%)	5 (6.0%)		4 (4.8%)	2 (2.4%)	13 (15.6%)
Not possible to identify/evaluate	4 (4.8%)	12 (14.5%)	3 (3.6%)	5 (6.0%)	1 (1.2%)	25 (30.1%)

HTA: health technology assessment.
*Other (n=5) stands for: Evidence synthesis (n=3), Clinical guideline development (n=1), Reporting guideline (n=1)
Numbers are presented as number of documents showing the characteristic (proportion of the total 83 documents).

Table 2. Types of identified visual tools to present results of BRA (total of publications n=83; publications that reported or presented visual tools n=74)

Types of visual tools*	Reported n (%)
Table	49 (59.0%)
Effects table	
Evidence table	
Tree diagram	34 (41.0%)
Value tree	
Bar chart	28 (33.7%)
Simple of grouped bar chart	
Tornado diagram	
Histogram	
Dot chart	28 (33.7%)
Forest plot	
Bubble chart	
Line graph	26 (31.3%)
Risk-benefit contour (RBC)	
Kaplan-Meier curve	
Area graph	24 (28.9%)
Risk-benefit plane (RBP) and risk-benefit acceptability threshold (RBAT)	
Distribution plot	
Probability of technical success (POTS) plot	
Scatter Plot	8 (9.6%)
Funnel plot	
Galbraith plot	
Matrix	6 (7.2%)
Pictogram	5 (6.0%)
Box plot	5 (6.0%)
Interactive visualization	4 (4.8%)
Transparent uniform risk–benefit overview (TURBO) diagram	4 (4.8%)
Risk scale/ladder	3 (3.6%)
Dashboard	3 (3.6%)
Network graph	3 (3.6%)
Pie chart	2 (2.4%)
Other[#]	6 (7.2%)

*More than one visual tool could be identified in each document.
[#]Other: presented in only one document [Cartoon/Symbol/Icon; Drugs facts box; Generic graphical display (no specific designation was given); Map; Sankey diagram; Traffic-light labelling].
Numbers are presented as number of documents showing the tool (proportion of the total 83 documents).

FIGURE LEGENDS

Figure 1. Relationship between the objectives, research question, and eligibility criteria for the scoping review. BRA: benefit-risk assessment; HTA: health technology assessment.

Figure 2. Overview of the selection process. HTA: health technology assessment.

Figure 3. Number of documents published per geographic area. Transcontinental: stands for ≥2 countries from different continents. Continent (Europe, North America): stands for ≥2 countries within the same continent.

Figure 4. BRA methodological approaches identified in the included documents and publications. Adapted from PROTECT. AE-NNT: Adverse event adjusted number needed to treat; AHP: Analytic hierarchy process; ASF: Ashby and Smith framework; Beckmann: Beckmann model (aka evidence based-model); BLRA: Benefit-less-risk analysis; BRAT: Benefit-risk action team; BRR: Benefit-risk ratio; CA: Conjoint analysis; CDS: Cross-design synthesis; CUI: Clinical utility index; CMR-CASS: CMR Health Canada, Australia's Therapeutic Goods Administration, SwissMedic and Singapore Health Science Authority; CPM: Confidence profile method; COBRA: Consortium on benefit-risk assessment; CV: Contingent valuation; DAG: Directed acyclic graphs; DALY: Disability-adjusted life years; DAM: Decision analytic model (specific designation was given to the model); DCE: Discrete choice experiment; DI: Desirability index; FDA BRF: FDA benefit-risk framework; GBR: Global benefit-risk; HALE: Health-adjusted life years; INHB: Incremental net health benefit; ITC: Indirect treatment comparison; KM: Kaplan-Meier; MAR: Maximum acceptable risk; MCDA: Multicriteria decision analysis; MCE: Minimum clinical efficacy; MDP: Markov decision process; MTC: Mixed treatment comparison; NCB: Net clinical benefit; NEAR: Net efficacy adjusted for risk; NNH: Number needed to harm; NNT: Number needed to treat; PBRER: Periodic benefit risk evaluation report; Principle of 3's: Principle of threes; PrOACT-URL: Problem, objectives,

alternatives, consequences, trade-offs, uncertainty, risk, and linked decisions; PSM: Probabilistic simulation method; QALY: Quality-adjusted life years; Q-TWiST: Quality-adjusted time without symptoms and toxicity; QFRBA: Quantitative framework for risk and benefit assessment; RBAT: Risk-benefit acceptability threshold; RBC: Risk-benefit contour; RBP: Risk-benefit plane; RV-MCE: Relative value-adjusted minimum clinical efficacy; RV-NNH: Relative value-adjusted number needed to (treat to) harm; RV-NNT: Relative value-adjusted number needed to treat; SABRE: Southeast Asia benefit-risk evaluation; SBRAM: Sarac's benefit-risk assessment; SG: Standard gamble; SMAA: Stochastic multicriteria acceptability analysis; SPM: Stated preference method; SW: Swing weighting; TTO: Time trade-off; TURBO: Transparent uniform risk benefit overview; UMBRA: Unified methodologies for benefit-risk assessment; UT-NNT: Utility-adjusted and time-adjusted number needed to treat.

*General: No specific designation was given to the descriptive framework.

#Other: approaches cited in <5 of the included documents (See Supplemental Table 6 for the complete list of approaches).

Numbers are presented as (number of documents citing the approach; proportion of the total 83 documents).

SUPPLEMENTARY MATERIAL

Supplemental Table 1. PRISMA Extension for Scoping Reviews (PRISMA-ScR)

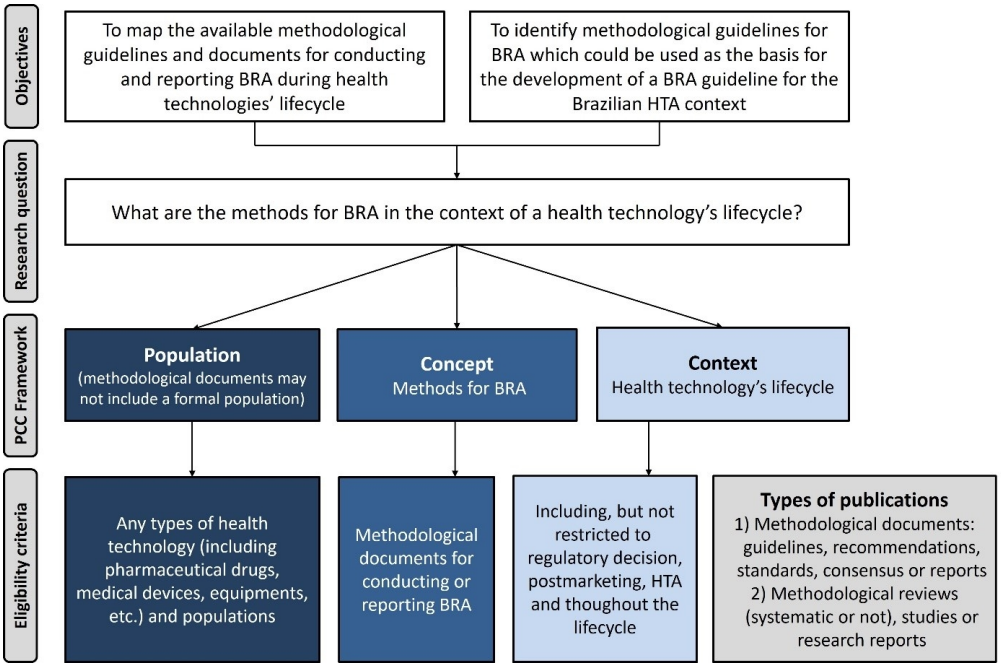
Supplemental Table 2. Electronic search strategy on EMBASE (OVID)

Supplemental Table 3. Electronic search strategy on MEDLINE (PubMed)

Supplemental Table 4. Sources of grey literature

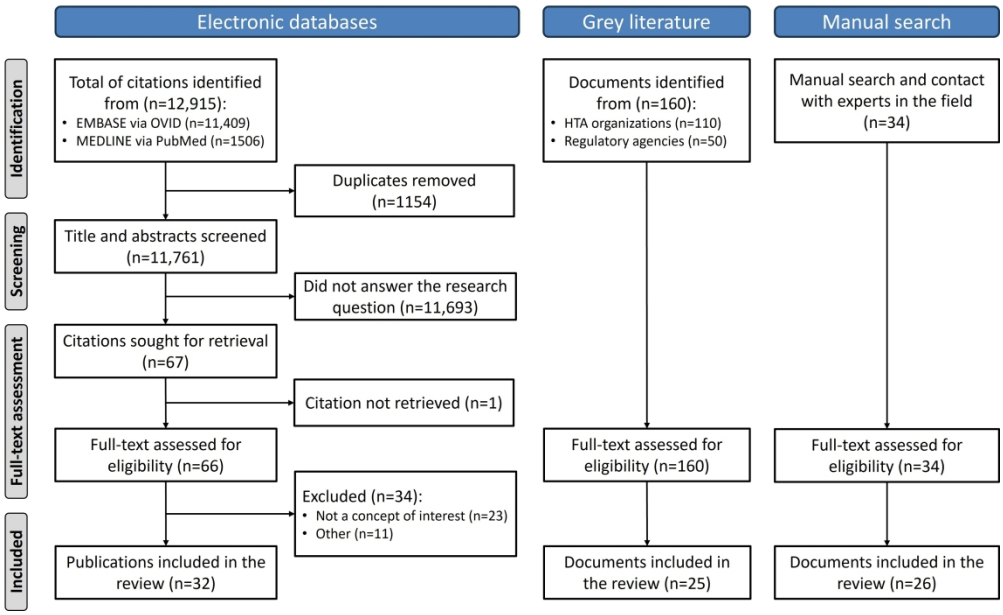
Supplemental Table 5. Excluded publications and reasons

Supplemental Table 6. Methodological approaches for BRA cited in <5 of the included documents



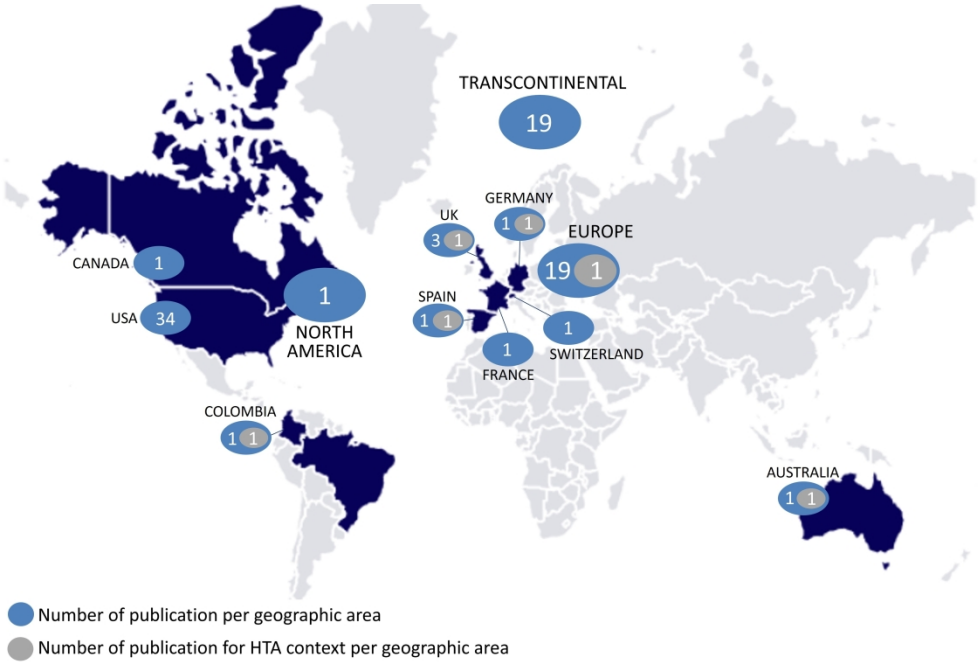
Relationship between the objectives, research question, and eligibility criteria for the scoping review. BRA: benefit-risk assessment; HTA: health technology assessment.

160x105mm (220 x 220 DPI)



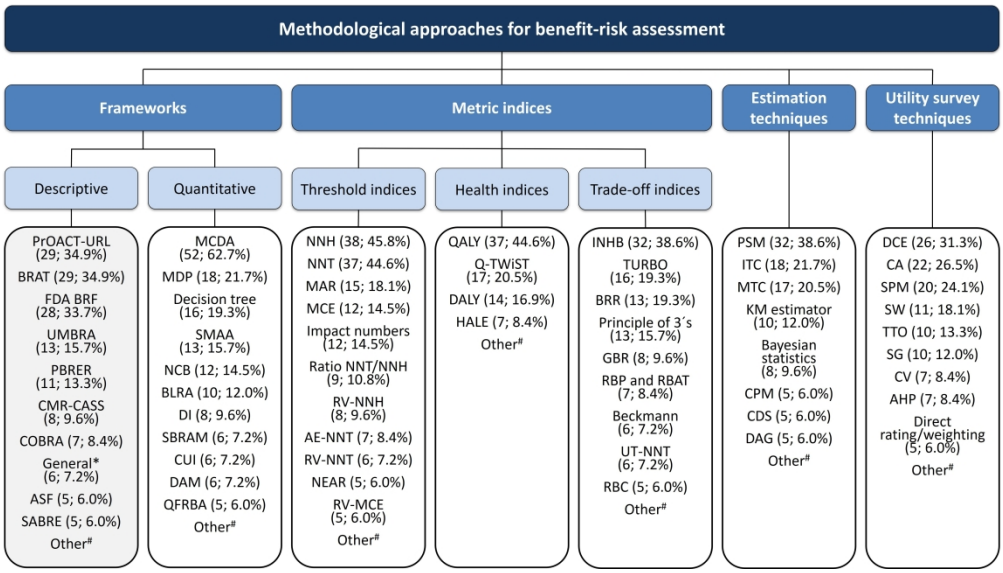
Overview of the selection process. HTA: health technology assessment.

356x217mm (300 x 300 DPI)



Number of documents published per geographic area. Transcontinental: stands for ≥2 countries from different continents. Continent (Europe, North America): stands for ≥2 countries within the same continent.

393x262mm (300 x 300 DPI)



BRA methodological approaches identified in the included documents and publications. Adapted from PROTECT. AE-NNT: Adverse event adjusted number needed to treat; AHP: Analytic hierarchy process; ASF: Ashby and Smith framework; Beckmann: Beckmann model (aka evidence based-model); BLRA: Benefit-less-risk analysis; BRAT: Benefit-risk action team; BRR: Benefit-risk ratio; CA: Conjoint analysis; CDS: Cross-design synthesis; CUI: Clinical utility index; CMR-CASS: CMR Health Canada, Australia's Therapeutic Goods Administration, SwissMedic and Singapore Health Science Authority; CPM: Confidence profile method; COBRA: Consortium on benefit-risk assessment; CV: Contingent valuation; DAG: Directed acyclic graphs; DALY: Disability-adjusted life years; DAM: Decision analytic model (specific designation was given to the model); DCE: Discrete choice experiment; DI: Desirability index; FDA BRF: FDA benefit-risk framework; GBR: Global benefit-risk; HALE: Health-adjusted life years; INHB: Incremental net health benefit; ITC: Indirect treatment comparison; KM: Kaplan-Meier; MAR: Maximum acceptable risk; MCDA: Multicriteria decision analysis; MCE: Minimum clinical efficacy; MDP: Markov decision process; MTC: Mixed treatment comparison; NCB: Net clinical benefit; NEAR: Net efficacy adjusted for risk; NNH: Number needed to harm; NNT: Number needed to treat; PBRER: Periodic benefit risk evaluation report; Principle of 3's: Principle of threes; PrOACT-URL: Problem, objectives, alternatives, consequences, trade-offs, uncertainty, risk, and linked decisions; PSM: Probabilistic simulation method; QALY: Quality-adjusted life years; Q-TWiST: Quality-adjusted time without symptoms and toxicity; QFRBA: Quantitative framework for risk and benefit assessment; RBAT: Risk-benefit acceptability threshold; RBC: Risk-benefit contour; RBP: Risk-benefit plane; RV-MCE: Relative value-adjusted minimum clinical efficacy; RV-NNH: Relative value-adjusted number needed to (treat to) harm; RV-NNT: Relative value-adjusted number needed to treat; SABRE: Southeast Asia benefit-risk evaluation; SBRAM: Sarac's benefit-risk assessment; SG: Standard gamble; SMAA: Stochastic multicriteria acceptability analysis; SPM: Stated preference method; SW: Swing weighting; TTO: Time trade-off; TURBO: Transparent uniform risk benefit overview; UMBRA: Unified methodologies for benefit-risk assessment; UT-NNT: Utility-adjusted and time-adjusted number needed to treat.
*General: No specific designation was given to the descriptive framework.
#Other: approaches cited in <5 of the included documents (See Supplemental Table 6 for the complete list of approaches).
Numbers are presented as (number of documents citing the approach; proportion of the total 83 documents).

453x256mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

Supplemental Table 1. PRISMA Extension for Scoping Reviews (PRISMA-ScR)

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	6,7
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	8
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	8
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	9 and Supplementary material
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	9 and Supplementary material
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	9,10
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	published protocol (doi:10.1136/bmjopen-2023-075333)

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	10
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	11, Figure 2 and Supplementary material
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	11,12
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	13-17
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	13-17
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	17-18
Limitations	20	Discuss the limitations of the scoping review process.	18-19
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	20-21
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	21

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Supplemental Table 2. Electronic search strategy on EMBASE (OVID)

Line	Searches	Results
1	risk benefit analysis/	61035
2	(risk adj1 benefit).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	78214
3	(benefit adj1 harm).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	746
4	maximum acceptable risk.mp.	114
5	numbers needed to treat/	1715
6	number* needed to treat.mp.	9158
7	number* needed to harm.mp.	1500
8	time without symptoms.mp.	215
9	minimum clinical efficacy.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	0
10	multicriteria decision analysis/	698
11	or/1-10 **[Concept 1: Benefit-risk assessment]**	89136
12	(method* or appraisal or framework or model).ti,ab.	13405124
13	11 and 12 **[Concept 1 and Concept 2: Methods]**	31415
14	guidance.ti,ab.	208292
15	guideline.ti,ab.	115535
16	review.pt.	2966321
17	(systematic review or meta-analysis).pt.	0
18	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	565454
19	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	354133
20	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	16897
21	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	51129
22	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	45458
23	(handsearch* or hand search*).ti,ab,kf.	13083
24	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	44220
25	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	18609
26	(meta regression* or metaregression*).ti,ab,kf	16328
27	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	674328
28	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	407265
29	(cochrane or (health adj2 technology assessment) or evidence report).jw.	29425
30	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	24270
31	(outcomes research or relative effectiveness).ti,ab,kf.	15531
32	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	7039
33	(meta-analysis or systematic review).mp	636752
34	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	407
35	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	256

Line	Searches	Results
36	umbrella review*.ti,ab,kf.	1228
37	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	27
38	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	18
39	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	22
40	or/14-39 **[Concept 3: type of studies]**	3802406
41	13 and 40 **[Concept 1/2 AND Concept 3]**	**11409**

Date of search: October 24, 2022

Supplemental Table 3. Electronic search strategy on MEDLINE (PubMed)

Line	Searches	Results
1	"benefit-risk" OR "benefit risk" OR "benefit-harm" OR "benefit harm" OR "harm-benefit" OR "harm benefit" OR "risk-benefit" OR "risk benefit" OR "risk-benefit" OR "risk benefit" OR "benefit-risk"	16,526
2	"Transparent uniform risk benefit overview"	3
3	"Stated preference method and maximum acceptable risk"	43
4	"Relative value adjusted number needed To treat"	144
5	"Risk–benefit plane"	3
6	"Risk–benefit Contour"	996
7	"time without symptoms and toxicity" AND TWiST	140
8	"Quality-adjusted time without symptoms and toxicity"	172
9	"Quantitative framework for risk and benefit assessment"	225
10	"Probabilistic simulation methods"	4,802
11	"minimum target event risk for treatment"	229
12	"NNT/NNH ratio"	15
13	"Number needed to treat" AND "number needed to treat to harm"	765
14	"threshold NNT"	4
15	"Net clinical benefit"	652
16	"Minimum clinical efficacy"	3
17	"Multicriteria decision analysis"	336
18	"Incremental net health benefit"	39
19	"Gail/National Cancer Institute"	3
20	"Boers' 3x3 table"	1
21	"Benefit-less-risk analysis"	3
22	OR/1-21 **[Concept 1: Benefit-risk assessment]**	24,674
23	"method*"[Title]	537,649
24	"Appraisal"[Title/Abstract]	42,055
25	"Framework"[Title/Abstract]	340,239
26	"Model"[Title/Abstract]	2,569,154
27	OR/23-26 **[Concept 2: Methods]**	3,342,355
28	"Guidance"[Title/Abstract]	149,210
29	"Guidelines"[Title/Abstract]	401,771
30	"Review"[Publication Type]	3,078,354
31	("systematic"[Filter] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR ("systematic"[Filter] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta analy*"[Text Word] OR "metanaly*"[Text Word] OR "metaanaly*"[Text Word] OR "met analy*"[Text Word] OR "integrative research"[Title/Abstract] OR "integrative review*"[Title/Abstract] OR "integrative overview*"[Title/Abstract] OR "research integration*"[Title/Abstract] OR "research overview*"[Title/Abstract] OR "collaborative review*"[Title/Abstract] OR "collaborative overview*"[Title/Abstract] OR "systematic review"[Publication Type] OR "systematic reviews as topic"[MeSH Terms] OR "systematic review*"[Title/Abstract] OR "technology assessment*"[Title/Abstract] OR "technology overview*"[Title/Abstract] OR "technology appraisal*"[Title/Abstract] OR "technology assessment, biomedical"[MeSH Terms] OR "HTA"[Title/Abstract] OR "HTAs"[Title/Abstract] OR "comparative efficacy"[Title/Abstract] OR "comparative effectiveness"[Title/Abstract] OR "outcomes research"[Title/Abstract] OR "indirect comparison*"[Title/Abstract] OR "Bayesian comparison"[Title/Abstract] OR (("indirect treatment"[Title/Abstract] OR "mixed-treatment"[Title/Abstract]) AND "comparison*"[Title/Abstract]) OR "embase*"[Title/Abstract] OR "cinahl*"[Title/Abstract] OR "systematic overview*"[Title/Abstract] OR "methodological overview*"[Title/Abstract] OR "methodologic overview*"[Title/Abstract] OR "methodological review*"[Title/Abstract] OR "methodologic review*"[Title/Abstract] OR "quantitative review*"[Title/Abstract] OR "quantitative overview*"[Title/Abstract] OR "quantitative	599,287

Line	Searches	Results
	synthes*"[Title/Abstract] OR "pooled analy*"[Title/Abstract] OR "Cochrane"[Title/Abstract] OR "Medline"[Title/Abstract] OR "Pubmed"[Title/Abstract] OR "Medlars"[Title/Abstract] OR "handsearch*"[Title/Abstract] OR "hand search*"[Title/Abstract] OR "meta regression*"[Title/Abstract] OR "metaregression*"[Title/Abstract] OR "data synthes*"[Title/Abstract] OR "data extraction"[Title/Abstract] OR "data abstraction*"[Title/Abstract] OR "mantel haenszel"[Title/Abstract] OR "peto"[Title/Abstract] OR "der-simonian"[Title/Abstract] OR "dersimonian"[Title/Abstract] OR "fixed effect*"[Title/Abstract] OR "multiple treatment comparison"[Title/Abstract] OR "mixed treatment meta analys*"[Title/Abstract] OR "umbrella review*"[Title/Abstract] OR ("multiple paramet*"[Title/Abstract] AND "evidence synthesis"[Title/Abstract]) OR ("multi paramet*"[Title/Abstract] AND "evidence synthesis"[Title/Abstract]) OR ("multiparameter*"[Title/Abstract] AND "evidence synthesis"[Title/Abstract]) OR "Cochrane Database Syst Rev"[Journal] OR "health technology assessment winchester england"[Journal] OR "evid rep technol assess full rep"[Journal] OR "evid rep technol assess summ"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "health technol assess rockv"[Journal] OR "Health Technol Assess Rep"[Journal]))	
32	OR/28-31 **[Concept 3: types of studies]**	3,784,327
33	#22 AND #27 AND #32 **[Concept 1 AND Concept 2 AND Concept 3]**	**1506**

Date of search: October 25, 2022

Supplemental Table 4. Sources of grey literature

#	ORGANIZATION	ABBREVIATION	COUNTRY
Health Technology Assessment (HTA) bodies and global HTA networks			
1	Adelaide Health Technology Assessment	AHTA	Australia
2	Agencia de Evaluación de Tecnologías Sanitarias de Andalucia	AETSA	Spain
3	Agency for Healthcare Research and Quality	AHRQ	United States
4	Association of Austrian Social Insurance Institutions	HVB	Austria
5	Austrian Institute for Health Technology Assessment	AIHTA	Austria
6	Canadian Agency for Drugs and Technologies in Health	CADTH	Canada
7	Centro Nacional de Excelencia Tecnológica en Salud	CENETEC	Mexico
8	Comissão Nacional de Incorporação de Tecnologias no SUS	CONITEC	Brazil
9	Dental and Pharmaceutical Benefits Agency	TLV	Sweden
10	European Network for Health Technology Assessment	EUnetHTA	Europa
11	Finnish Coordinating Center for Health Technology Assessment	FINCCHTA	Finland
12	Gemeinsamer Bundesausschuss	G-BA	Germany
13	Haute Autorité de Santé	HAS	France
14	Health Insurance Review and Assessment Agency	HIRA	South Korea
15	Health Technology Assessment International	HTAi	International
16	Healthcare Improvement Scotland	HIS	United Kingdom
17	Institute for Clinical and Economic Reviews	ICER	United States
18	Institute for Clinical Effectiveness and Health Policy	IECS	Argentine
19	Institute for Quality and Efficiency in Health Care	IQWiG	Germany
20	Instituto de Evaluación Tecnológica en Salud	IETS	Columbia
21	International Network of Agencies for Health Technology Assessment	INAHTA	International
22	Italian National Agency for Regional Healthcare Services	AGENAS	Italy
23	National Centre for Pharmacoeconomics	NCPE	Ireland
24	National Health Care Institute (Zorginstituut Nederland)	ZIN	Netherlands
25	National HTA Program for Medical Devices	PNHTADM	Italy
26	National Institute for Health and Care Excellence	NICE	United Kingdom
27	National Institute for Health and Disability Insurance	NIHDI	Belgium
28	National Institute for Health Technology Assessment	NIHTA	Taiwan
29	Network of HTA research agencies in Asia and Pacific regions	HTAsiaLink	Asia
30	Professional Society for Health Economics and Outcomes Research	ISPOR	International

#	ORGANIZATION	ABBREVIATION	COUNTRY
31	Red Española de Agencias de Evaluación de Tecnologías Sanitarias y Prestaciones del Sistema Nacional de Salud	REDETS	Spain
32	Rede de Avaliação de Tecnologia em Saúde das Américas	RedETSA	Latin America
33	Scottish Medicines Consortium	SMC	United Kingdom
34	Social & Health Services and Labour Market	DEFACTUM	Denmark
35	Swedish Agency for Health Technology Assessment and Assessment of Social Services	SBU	Sweden
36	Unidad Coordinadora de Evaluación y Ejecución de Tecnologías Sanitarias	UCEETS	El Salvador
Regulatory Agencies			
1	Agence Nationale de Sécurité du Médicament et des Produits de Santé	ANSM	France
2	Agência Nacional de Vigilância Sanitária	ANVISA	Brazil
3	Danish Medicines Agency	DMA	Denmark
4	European Medicines Agency	EMA	Europe
5	Health Canada/Santé Canadá	HC	Canada
6	Medical Products Agency	MPA	Sweden
7	Medicines and Healthcare products Regulatory Agency	MHRA	United Kingdom
8	Pharmaceuticals and Medical Devices Agency	PMAJ	Japan
9	Swiss Agency for Therapeutic Products	SATP	Switzerland
10	The Central Drugs Standard Control Organization	CDSCO	India
11	Therapeutic Goods Administration	TGA	Australia
12	U.S. Food and Drug Administration	FDA	United States

Supplemental Table 5. Excluded publications and reasons

#	Author	Reference	Reason
1	Angelis et al.	Value Health. 2020; 23(8):1040–1048. doi: 10.1016/j.jval.2020.04.1828	Other (It was not a concept of interest because it assessed methods exclusively for the harm or benefit outcomes, not the BRA balance)
2	Baltussen et al.	Value Health. 2019; 22(11):1283–1288. doi: 10.1016/j.jval.2019.06.014	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
3	Boada et al.	PLoS One. 2008;3(10):e3580. doi: 10.1371/journal.pone.0003580	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
4	Bouvy et al.	Patient. 2020 Apr;13(2):145-149. doi: 10.1007/s40271-019-00408-4	Other: paper addressed preferences methods but not as methods of BRA or in the BRA context
5	Chachoua et al.	Front Med. 2020 Oct 26;7:543046. doi: 10.3389/fmed.2020.543046	Other: paper addressed preferences methods but not as methods of BRA or in the BRA context
6	Chan et al.	Pharm Res 39, 1761–1777 (2022). doi: 10.1007/s11095-022-03201-5	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
7	Cruccu et al.	Pain Practice. 2007;7(3):230–233. doi: 10.1111/j.1533-2500.2007.00131.x	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
8	EL Masri et al.	Patient Prefer Adherence. 2022;16:2609-2637. doi: 10.2147/PPA.S375062	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
9	Frazão et al.	BMC Med Inform Decis Mak. 2018;18(1):90. doi: 10.1186/s12911-018-0663-1	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
10	Garrison et al.	Health Affairs. 2007;26(3):684–695. doi: 10.1377/hlthaff.26.3.684	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
11	Garrison et al.	Pharmacoeconomics. 2010;28(10):855-65. doi: 10.2165/11538640-000000000-00000	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
12	Hart et al.	Bundesgesundheitsblatt Gesundheitsforsch.Gesundheitsschutz. 2005;48:204–214. doi: 10.1007/s00103-004-0977-2	Other: paper addressed preferences methods but not as methods of BRA or in the BRA context
13	Khan et al.	Med Decis Making. 2022;42(2):262-274. doi: 10.1177/0272989X211019040	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
14	Lackey et al.	Ther Innov Regul Sci. 2021;55(1):170-179. doi: 10.1007/s43441-020-00203-6	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
15	Liberti et al.	Pharm Med. 2011;25(3):139-146. doi: 10.1007/BF03256855	Other: Opinion paper
16	Luteijin et al.	Food Chem Toxicol. 2012;50(1):26-32. doi: 10.1016/j.fct.2011.06.008	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
17	Maloney et al.	Int J Technol Assess Health Care. 2019;35(5):384-392. doi: 10.1017/S026646231900062X	Other: Methodological research using qualitative methods
18	Miller et al.	Value Health. 2017;20(2):296-298. doi: 10.1016/j.jval.2016.11.010	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA

#	Author	Reference	Reason
19	Moore et al.	Cureus. 2021;13(7):e16528. doi: 10.7759/cureus.16528	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
20	Norton et al.	Ther Innov Regul Sci. 2011;45:741–747. doi: 10.1177/009286151104500510	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
21	Ouellet et al.	Expert Opin Drug Saf. 2010 Mar;9(2):289-300. doi: 10.1517/14740330903499265.	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
22	Pane et al.	Pharmacoepidemiol Drug Saf. 2019;28(9):1155-1165. doi: 10.1002/pds.4859	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
23	Pignatti et al.	Mol Oncol. 2015;9(5):1034-41. doi: 10.1016/j.molonc.2014.10.003	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
24	Puhan et al.	BMC Med. 2015;13:250. doi: 10.1186/s12916-015-0493-2	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
25	Radawski et al.	Pharmacoepidemiol Drug Saf. 2020;29(12):1532-1539. doi: 10.1002/pds.5167	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
26	Rajczi et al.	J Law Med Ethics. 2004;32(2):338-48. doi: 10.1111/j.1748-720x.2004.tb00480.x	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
27	Rid et al.	Kennedy Inst Ethics J. 2011;21(2):141-79. doi: 10.1353/ken.2011.0007	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
28	Smith et al.	Ther Innov Regul Sci. 2021;55(2):415-425. doi: 10.1007/s43441-020-00230-3	Other: Qualitative research
29	Tervonen et al.	Med Decis Making. 2015;35(7):859-71. doi: 10.1177/0272989X15587005	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
30	van der Zanden et al.	Clin Pharmacol Ther. 2021;110(4):952-965. doi: 10.1002/cpt.2336	It was not a concept of interest because it was not a methodological document or guidelines for methods on BRA
31	Vass et al.	Pharmacoeconomics. 2017;35(9):859-866. doi: 10.1007/s40273-017-0518-0	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
32	Waddingham et al.	Biom J. 2016 Jan;58(1):28-42. doi: 10.1002/bimj.201300254	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA
33	Walker et al.	Clin Pharmacol Ther. 2011;89(2):179-82. doi: 10.1038/clpt.2010.290	Other: Discussions or lessons learned of a workshop conference
34	Wen et al.	Value Health. 2014;17(5):619-28. doi: 10.1016/j.jval.2014.04.008	It was not a concept of interest because it assessed a specific method approach or metric that can be used for BRA

Supplemental Table 6. Methodological approaches for BRA cited in <5 of the included documents

Approach	N of documents	% (from total of 83)
Descriptive frameworks		
Boers´ 3x3 table	4	4.8%
Outcome measures in rheumatology (OMERACT) 3x3	3	3.6%
Medical Device Innovation Consortium (MDIC) framework	3	3.6%
Benefit-risk analysis for foods (BRAFO)	2	2.4%
Benefit-Risk Assessment Framework Into the Common Technical Document for marketing authorization applications	2	2.4%
Centre for Innovation in Regulatory Science (CIRS) 7-step framework	2	2.4%
Benefit-risk assessment in new and old drugs (BRAIN)	1	1.2%
Benefit-risk assessment. communication. and evaluation (BRACE)	1	1.2%
Core structured benefit-risk assessment (cSBRA)	1	1.2%
Framework for BRA the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction or have endocrine-disrupting properties	1	1.2%
Quantitative frameworks		
Gail/National Cancer	4	4.8%
System dynamics	3	3.6%
Bayesian beliefs networks (BBN)	3	3.6%
Discrete event simulation (DES)	3	3.6%
Dynamic model	3	3.6%
Weighted net clinical benefit (wNCB)	3	3.6%
Benefit-risk assessment model (BRAM)	2	2.4%
Influence/relevance diagram	2	2.4%
Joint modeling framework for benefit-risk evaluation	2	2.4%
Bayesian decision analysis (BDA) method	1	1.2%
Bayesian Markov model	1	1.2%
Benefit-risk utility function and its corresponding ROC curve	1	1.2%
Hierarchical Bayesian Benefit-Risk (HBBR) Modeling	1	1.2%
ICER Value Assessment Framework (ICER Evidence Rating Matrix)	1	1.2%
Prospective BRA monitoring framework	1	1.2%
Statistical framework for periodic BRA	1	1.2%
Evidence-based benefit and risk model	1	1.2%
Threshold indices		
Minimal acceptable benefit (MAB)	3	3.6%
Ratio number needed to harm per number needed to treat (NNH/NNT)	3	3.6%
Threshold number needed to treat (NNTt)	3	3.6%
Number needed to vaccinate (NNV)	2	2.4%
Minimum target event risk for treatment (MERT)	2	2.4%
Probability of technical success (POTS)	1	1.2%
Minimally important difference (MID)	1	1.2%
Margin of Exposure (MoE)	1	1.2%
Margin of Safety (MoS)	1	1.2%
Number needed to treat for benefit (NNT-B)	1	1.2%
Unmitigated failure (NNHu)	1	1.2%
Unqualified success [treatment success without treatment induced side effects (NNTu)]	1	1.2%
Number needed to diagnose (NND)	1	1.2%
Number needed to misdiagnose (NNM)	1	1.2%
Number needed to screen (NNS)	1	1.2%
Number needed to benefit (NNB)	1	1.2%
Health indices		
Drug-attributed loss of quality-adjusted life year (DALQALY)	1	1.2%
Validated health-related quality of life measures	1	1.2%
Trade-off indices		

Approach	N of documents	% (from total of 83)
Incremental benefit-risk ratio (IBRR)	4	4.8%
Incremental net health benefit with relative-value-adjusted life year (INHB-RVALY)	2	2.4%
Incremental net health benefit with quality-adjusted life-year (INHB-QALY)	2	2.4%
Incremental net health benefit with maximum acceptable risk (INHB-MAR)	1	1.2%
Exposure-adjusted incidence rate (EAIR)	1	1.2%
Utility survey techniques		
Best-worst scaling exercise	4	4.8%
Threshold technique	4	4.8%
Ranking exercise	4	4.8%
Direct elicitation method	2	2.4%
Deliberative dialogue	2	2.4%
Direct assessment questions	2	2.4%
Outranking method	2	2.4%
Point allocation	2	2.4%
Indirect elicitation methods [Short Form–36 Health Survey (SF-36), Euro Quality-of-Life five-dimensions (EQ-5D), Health Utility Index]	2	2.4%
Delphi technique	1	1.2%
Graded pairs	1	1.2%
Index of Well-Being	1	1.2%
Nominal group	1	1.2%
Visual Analogue Scale (VAS)	1	1.2%
Utility survey technique	1	1.2%

BRA: benefit-risk assessment; ROC: receiver operating characteristic.

PRISMA Extension for Scoping Reviews (PRISMA-ScR)

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	6,7
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	8
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	8
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	9 and Supplementary material
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	9 and Supplementary material
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	9,10
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	published protocol (doi:10.1136/bmjopen-2023-075333)
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	10
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	11, Figure 2 and Supplementary material
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	11,12
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	13-17
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	13-17
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	17-18
Limitations	20	Discuss the limitations of the scoping review process.	18-19
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	20-21
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	21

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.