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Study protocol

Economic Evaluation of Health Technologies in the Context of Ultra-Rare Diseases: A Rapid Scoping Review Protocol

Avaliação econômica em saúde no contexto de doenças ultrarraras: um protocolo de revisão rápida de escopo

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ABSTRACT

Background: Ultra-rare diseases pose unique challenges for the economic evaluation of health technologies due to the scarcity of robust evidence, high uncertainty, and often elevated costs. **Objective**: To identify and characterize the economic modeling approaches used in the evaluation of health technologies in the context of ultra-rare diseases. **Methods**: This is a rapid scoping review that will be conducted in accordance with the Joanna Briggs Institute methodological guidance. Conceptual studies, methodological papers, and systematic reviews addressing models, methods, adaptations, and alternative proposals for economic evaluation in this context will be included. The search will be performed in major secondary databases, as well as sources of grey literature. The selection process will involve independent screening by pairs and cross-checking of exclusions. Data extraction will follow a pre-tested form. Results will be presented narratively, in tables, and graphically, describing the types of economic modeling identified, their methodological characteristics, and the main reported limitations. **Expected Results**: This synthesis is expected to help inform decision-makers, researchers, and health technology assessment agencies about more appropriate and transparent approaches for incorporating technologies targeting ultra-rare diseases. **Conclusion:** The findings may guide both researchers and policymakers on more appropriate strategies for incorporating technologies aimed at small and clinically complex populations, promoting practices that balance economic efficiency, equity, and sustainability of health systems.

Keywords: Rare Diseases; Economic Models; Cost-Effectiveness Analysis; Scoping Review.

RESUMO

Introdução: As doenças ultrarraras apresentam desafios singulares para a avaliação econômica de tecnologias em saúde, devido à escassez de evidências robustas, alta incerteza e custos frequentemente elevados. **Objetivo**: Identificar e caracterizar as modelagens econômicas utilizadas na avaliação de tecnologias em saúde no contexto de doenças ultrarraras. **Métodos**: Trata-se de uma revisão rápida de escopo que será conduzida conforme as orientações metodológicas do *Joanna Briggs Institute*. Serão incluídos estudos conceituais, metodológicos e revisões sistemáticas que abordem modelos, métodos, adaptações e propostas alternativas de avaliação econômica nesse contexto. A busca será realizada nas principais bases de dados secundários, além de fontes de literatura cinzenta. O processo de seleção contará com leitura independente por pares e checagem cruzada de exclusões. A extração dos dados seguirá formulário previamente testado. Os resultados serão apresentados de forma narrativa, tabular e gráfica, descrevendo os tipos de modelagem econômica identificados, suas características metodológicas e principais limitações relatadas. **Resultados esperados**: Espera-se que esta síntese contribua para informar tomadores de decisão, pesquisadores e agências de avaliação de tecnologias em saúde sobre abordagens mais adequadas e transparentes para incorporar tecnologias voltadas às doenças ultrarraras. **Conclusão:** Os achados poderão orientar tanto pesquisadores quanto formuladores de políticas sobre estratégias mais adequadas para incorporar tecnologias destinadas a populações pequenas e clinicamente complexas, promovendo práticas que equilibrem eficiência econômica, equidade e sustentabilidade dos sistemas de saúde.

Palavras-chave: Doenças Raras; Modelos Econômicos; Análise de Custo-Efetividade; Revisão de Escopo.

Introduction

Although there is still no legally established definition for the term "ultra-rare disease," this category was informally created by the National Institute for Health and Care Excellence (NICE) to refer to medicines intended for the treatment of conditions with a prevalence of fewer than 1 case per 50,000 people, which has become the reference most commonly attributed to the term.[1,2] In Brazil, Resolution No. 563/2017 of the Conselho Nacional de Saúde defined an ultra-rare disease as one that is chronic, debilitating, or life-threatening, with an incidence less than or equal to 1 case per 50,000 inhabitants.[3] It is also common to adopt the more conservative threshold of 1 case per 100,000 people, in contrast to the World Health Organization (WHO) definition of rare disease, which considers up to 65 cases per 100,000 people.[4]

Regardless of the definition adopted, these conditions are characterized by high clinical complexity, limited therapeutic options, and frequently high treatment prices, which impose constraints on the application of conventional economic evaluation methods, such as the use of quality-adjusted life years (QALYs) as a health outcome measure.[5] In addition to being challenging due to the context of high uncertainty and scarcity of robust evidence, the application of these traditional approaches may fail to adequately capture the clinical, social, and economic value of technologies intended for these populations.[6]

Several studies have discussed how these conditions further exacerbate these challenges by combining extremely high upfront costs, small patient populations, and potential long-term benefits, often supported by single-arm studies and surrogate outcomes.[7] In parallel, an umbrella review of economic evaluations in rare diseases and orphan drugs showed that such analyses remain scarce, heterogeneous, and frequently limited.[8] Taken together, these contributions reinforce the need for methodological adaptations in the economic evaluation of rare diseases, yet they remain focused on the broader group of rare diseases and do not systematically describe how economic modeling has been operationalized specifically in ultra-rare diseases, nor how these choices interact with regulatory contexts such as that of the Unified Health System (SUS).

To the best of our knowledge, there is no review that systematically maps the economic modeling approaches used in this context, integrating the international literature with Brazilian institutional guidelines and reports. Understanding how economic evaluation methods are being applied and adjusted to address these conditions is essential to inform decisions that are fairer, more transparent, and more consistent with the principles of efficiency and equity in the incorporation of technologies within the SUS.

From this perspective, the aim of this review is to identify and characterize the economic modeling approaches, including novel approaches or adaptations, used in health technology assessments in the context of ultra-rare diseases, as well as to explore their interface with Brazilian institutional guidelines and economic evaluation reports.

Methods

Context

The present study protocol is one of the components of the research project "Strengthening health technology assessment for ultra-rare diseases: Decision Analysis in the Unified Health System (SUS)," coordinated by the Instituto Nacional de Cardiologia, in Rio de Janeiro (INC-RJ), in partnership with the University of York, in England. The project aims to support the Departamento de Gestão e Incorporação de Tecnologias em Saúde of the Ministério da Saúde in the formulation of national guidelines for the assessment of technology incorporation within the SUS.

Type of study

This review does not aim to evaluate a specific intervention, but rather to synthesize the scope of economic modeling applied to ultra-rare diseases. It is therefore characterized as a scoping review, a design recommended when the objective is to describe the extent, nature, and gaps of the available evidence, without requiring the homogeneity of outcomes, comparators, and study designs that is necessary for traditional systematic reviews focused on effectiveness.

The study was planned and will be conducted in accordance with the methodological guidance of the Joanna Briggs Institute[9], and its reporting will follow the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, extension for Scoping Reviews (PRISMA-ScR)[10] (Appendix A). Considering the feasibility of conducting the research within a timeframe that supports the formulation of national guidelines currently under discussion, a rapid review strategy was adopted, in accordance with the methodological proposal of the Cochrane Collaboration[11] and based on the World Health Organization (WHO) guide.[12] In line with good practices for conducting reviews, the complete study protocol was formulated a priori and finalized before study selection and data extraction. Given that, as of June 2025, the International Prospective Register of Systematic Reviews, known as PROSPERO (https://www.crd.york.ac.uk/prospero) , limits its scope to traditional review protocols and does not accept the registration of scoping review protocols, this protocol was registered in the Open Science Framework database (DOI: 10.17605/OSF.IO/Z9F6W).

Stakeholder consultation

Stakeholder consultation was conducted throughout the development of the protocol, with the aim of increasing the applicability of its results and supporting the communication of findings to the community. For this purpose, different stakeholders were informally consulted, including consumers, such as health policy makers, health professionals, and patients, who contributed to refining the topic, clarifying definitions, and presenting their understanding of concepts and methods, in a process designed to increase the relevance of the scoping review and reduce potential research waste; experts in ultra-rare diseases, who assessed the relevance of the review to the field of knowledge and assisted in identifying resources that preliminary searches of data sources might not capture; methodological experts, who supported the development and conduct of the scoping review and provided clarification on methodological issues throughout the process; and information specialists, who collaborated in defining a relevant search strategy and identifying the most appropriate databases for the topic.

Eligibility criteria

Population

Studies including individuals with ultra-rare diseases will be considered eligible, regardless of age, sex, or disease severity. For the purposes of this review, ultra-rare diseases will be defined as those with an estimated prevalence of fewer than 1 case per 50,000 people. Conditions explicitly described as "ultra-rare," "very rare," or "ultra-orphan," as well as those whose prevalence and clinical characteristics align with these criteria, as defined by the study authors, will be included.

Concept

Studies that describe or discuss economic modeling frameworks applied to the assessment of health technologies in ultra-rare conditions will be included.

Context

Studies applied to health technology assessment from the perspective of society, governments, and health systems in any country and time period will be included.

Types of evidence

Systematic reviews addressing economic modeling applied to ultra-rare diseases will be prioritized. Conceptual and methodological studies that explicitly explore methods, challenges, adaptations, or alternative proposals related to the conduct of economic evaluations in this context will also be included.

Exclusion criteria

Publications that do not present the methods used in economic modeling, that contain incomplete or unavailable data for extraction, and study protocols without results will be excluded. In addition, studies with duplicate data already reported in another included publication will be excluded, in which case the most complete and recent publication will be prioritized.

Information sources and search strategies

Bibliographic searches will be conducted in the Medical Literature Analysis and Retrieval System Online (MEDLINE, via PubMed), Excerpta Medica dataBASE (Embase, via Elsevier), the Cochrane Library (via Wiley), and Epistemonikos. In addition, if updates of included reviews are identified, complementary manual searches will be conducted in the gray literature databases of three major international HTA agencies, NICE, CAD, and PBAC. Manual searches will also be performed in reference lists of relevant studies and through contact with content experts.

The primary search strategy was developed by one reviewer, based on controlled vocabulary (MeSH) and non-controlled terms (keywords and synonyms) in the MEDLINE database (via PubMed), structured around two main components, ultra-rare diseases and economic modeling. The strategy was validated by a second reviewer with experience in health search strategies, using the PRESS protocol (Peer Review of Electronic Search Strategies) (Appendix A). After validation, the strategy was adapted for the other databases (Appendix B). Searches will be conducted in July 2025 and updated until submission of the final version of the review.

Study selection process

The selection process will be conducted in two stages with the support of the Rayyan platform[13]. In the first stage, after duplicate removal, titles and abstracts will be screened. In the second stage, full texts will be assessed to confirm study eligibility. Reasons for exclusion of all studies at the second stage will be documented. As this is a rapid scoping review, full duplicate screening will not be performed, and screening will be conducted by a single reviewer with experience in systematic reviews, adopting this arrangement as one of the methodological shortcuts recommended by the Cochrane Collaboration for rapid reviews[11]. In cases of uncertainty regarding study eligibility, the reviewer will consult a second researcher, and any disagreements will be resolved by consensus.

Data extraction

Included studies will be divided between two reviewers for data extraction using a pre-established electronic cloud-based extraction form (Google Sheets), which will be pilot-tested with five studies. A second reviewer will validate all data extracted by their counterpart. Study authors will be contacted to request missing or additional data when necessary. The data extraction form will include, but not be limited to, the following elements: study information (document ID, author, year of publication, country, type of source, source category, study scope); clinical and technology characteristics (definition of ultra-rare disease, source of definition, condition or indication, medicine, comparators); and economic modeling characteristics (type of model, time horizon, extrapolation methods, perspective adopted, cost data sources, utility data sources, clinical data sources, health outcomes, methods for estimating utilities and outcomes, discount rates, cost-effectiveness thresholds, and sensitivity analyses) (Appendix C).

This set of variables may be refined after the extraction pilot, with any necessary adaptations duly recorded.

Critical appraisal of included studies

As scoping reviews do not aim to produce a synthesis to answer a specific question, but rather to provide an overview or map of the evidence, methodological quality assessment or risk of bias appraisal of the identified evidence will not be conducted.[9,14]

Data synthesis and presentation of results

The results of each included evidence source will be synthesized descriptively and presented in tables, organized according to methodological axes of economic modeling approaches applied to ultra-rare conditions. The definition of these axes was inspired by the catalogue of research and HTA challenges for rare diseases proposed by Nestler-Parr et al.[15], adapted to focus specifically on economic modeling components. For each axis, the following will be described: (i) the main challenges, (ii) the approaches reported in the studies, and (iii) the consistency

of these approaches with Brazilian economic evaluation guidelines.[16,17]

Expected Results

Expected results include the identification and characterization of economic modeling methods employed, particularly in health technology assessments for ultra-rare diseases, including detailed descriptions of approaches such as weighted QALYs, differentiated cost-effectiveness thresholds, adjustments for single-arm studies, and survival extrapolation methods. The review is also expected to map the main methodological adaptations reported, the challenges faced, and the recommendations proposed by authors to reduce uncertainty and improve the applicability of economic results in this context. The study should produce a narrative synthesis to support the formulation of guidelines on economic evaluation in ultra-rare diseases.

Conclusion

The use of evidence for public health policy formulation is a fundamental principle of transparency in decisions regarding the incorporation of technologies into the SUS. This rapid scoping review protocol seeks to enable the conduct of an evidence synthesis on methodological approaches used in the economic evaluation of health technologies for ultra-rare diseases, thereby contributing to informed, transparent, and evidence-based decision-making. The findings may guide both researchers and policy makers on more appropriate strategies for incorporating technologies intended for small and clinically complex populations, promoting practices that balance economic efficiency, equity, and sustainability of health systems.

Author contributions and authorship statement

KRCA, RRAF, ENS, MSS, IRZ: Conceptualization and design of the project; responsibility for all aspects of the manuscript, ensuring the accuracy and integrity of any part of the work. KRCA and IRZ: Manuscript drafting and data interpretation. KRCA, RRAF, and IRZ: Critical revision and final approval of the version to be published.

Conflicts of interest

The authors declare that there are no personal, commercial, academic, political, or financial conflicts of interest in the process of review and publication of this protocol.

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Declaration and availability of data
The underlying content of the research text is contained in the manuscript.

Responsible editor
Lindemberg Assunção Costa

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Anexo A. Diretrizes de relato para revisão de escopo.

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE
TITLE			
Title	1	Identify the report as a scoping review.	Click here to enter text.
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.	Click here to enter text.
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.	Click here to enter text.
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.	Click here to enter text.
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.	Click here to enter text.
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.	Click here to enter text.
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.	Click here to enter text.
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Click here to enter text.
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Click here to enter text.
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.	Click here to enter text.
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Click here to enter text.
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).	Click here to enter text.
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Click here to enter text.

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.	Click here to enter text.
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Click here to enter text.
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Click here to enter text.
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.	Click here to enter text.
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Click here to enter text.
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.	Click here to enter text.
Limitations	20	Discuss the limitations of the scoping review process.	Click here to enter text.
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.	Click here to enter text.
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.	Click here to enter text.

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.

Apêndice A. Revisão da estratégia de busca pela Diretriz PRESS — Submissão da Estratégia de Busca e Avaliação de Revisão por Pares.

Submissão de estratégia de busca: esta seção deve ser preenchida pelo pesquisador

Pesquisador: Keitty Regina Cordeiro de Andrade	**Email:** keitty.andrade@unb.br
Data da submissão: 23/6/2025	**Solicitada para a data:** 27/6/2025

Tópico da pesquisa ou título

Avaliação econômica em saúde no contexto de doenças ultrarraras: revisão rápida de escopo

Esta estratégia de busca é:
Minha estratégia de busca na base de dados PRIMÁRIA (core)
☐ Esta é minha primeira submissão ☐ Esta é submetida após o retorno da avaliação

Esta estratégia de busca é:
Minha estratégia de busca na base de dados SECUNDÁRIA (complementar):
☐ Esta é minha primeira submissão ☐ Esta é submetida após o retorno da avaliação

Base(s) de dados
(por exemplo., MEDLINE, CINAHL, Embase): **[obrigatório]**
MEDLINE

Plataforma(s) de acesso à base de dados
(por exemplo, Ovid, EBSCO): **[obrigatório]**

PubMed

*Se a base de dados ou a plataforma que você escolheu provê um link para o histórico da busca, por favor, forneça aqui:

Pergunta(s) de pesquisa
(Descreva o propósito da busca) **[obrigatório]**

Quais são os métodos para avaliação econômica em doenças ultrarraras?

PICO(S) ou formato relacionado
(Descreva o PICOs, SPIDER, PEPSI, etc. de sua pergunta — ou seja, Paciente, Intervenção, Comparação, Resultado (Outcome) e Desenho do Estudo — quando aplicável)

Fenômeno de interesse	Serão considerados elegíveis estudos que abordem o uso de modelagem econômica aplicada à avaliação de tecnologias em saúde voltadas para doenças ultrarraras. Para fins desta revisão, doenças ultrarraras serão aquelas com prevalência estimada inferior a 1 caso para cada 50.000 pessoas, frequentemente associadas a alta complexidade clínica. Serão incluídas condições explicitamente descritas como “ultrarraras”, “muito raras” ou “ultra-órfãs”, bem como aquelas cuja prevalência e características clínicas se alinhem a esses critérios, conforme definido pelos autores dos estudos.
Contexto	Serão incluídos estudos aplicados à avaliação de tecnologias em saúde na perspectiva da sociedade, governos e sistemas de saúde em todo o mundo e em qualquer período.
Tipos de evidências	Serão elegíveis prioritariamente revisões sistemáticas que abordem modelagens econômicas aplicadas a doenças ultrarraras. Também serão incluídos estudos conceituais e metodológicos que explorem, de forma explícita, os métodos, os desafios, as adaptações ou as propostas alternativas relacionadas à condução de avaliações econômicas nesse contexto.

Critérios de inclusão
(Liste os critérios a serem incluídos, tais como grupos etários, desenhos de estudo, e assim por diante) [opcional]

Serão incluídos estudos de qualquer país, período e perspectiva (sociedade, governo ou sistema de saúde) que abordem modelagem econômica na avaliação de tecnologias em saúde voltadas a doenças ultrarraras. A revisão incluirá principalmente revisões sistemáticas, mas também estudos conceituais ou metodológicos que discutam de forma clara os métodos, desafios ou adaptações na avaliação econômica dessas doenças.

Critérios de exclusão
(Liste os critérios a serem excluídos, tais como desenhos de estudo, limites de data e assim por diante) [opcional]

Serão excluídos estudos que: (1) não apresentem foco explícito em modelagem econômica aplicada a doenças ultrarraras; (2) tratem exclusivamente de tecnologias em saúde sem relação com avaliação econômica; (3) não estejam disponíveis na íntegra para leitura e extração de dados

Foram aplicados filtros de busca? [obrigatório]
☐ Sim ☐ Não
Caso SIM, quais foram utilizados (por exemplo, filtro Cochrane RCT, Guia de filtros da CADTH, filtros PubMed Perguntas Clínicas)? Forneça a fonte se este for um filtro publicado. **[obrigatório caso a resposta for SIM]** Outras notas ou comentários que você acha que seriam úteis para o revisor (por exemplo, decisão sobre limites de data ou idioma, artigos usados para extrair termos de busca)? **[opcional]**

Enter any content that you want to repeat, including other content controls. You can also insert this control around table rows in order to repeat parts of a table.

Copie e cole sua estratégia de busca aqui, exatamente como executada, incluindo o número de resultados por linha. **[obrigatório]**

ID	Elemento	Termos	Resultado
#1	Doença raras e ultrarraras	("ultra-rare"[all fields] or "URD"[all fields] or "ultrarare"[all fields] or "very rare"[all fields] or "ultra-orphan"[all fields] or "ultra orphan"[all fields] or "rare diseases"[mesh] or "orphan disease"[all fields] or "disease rare"[all fields] or "disease orphan"[all fields] or "orphan condition"[all fields] or "rare condition"[all fields])	90.050
#2	Estudos econômicos	("cost-effectiveness analysis"[mesh terms] or ("cost-effectiveness"[all fields] and "analysis"[all fields]) or "cost-effectiveness analysis"[all fields] or ("cost"[all fields] and "effectiveness"[all fields]) or "cost effectiveness"[all fields] or "cost-utility analysis"[all fields] or "cost-benefit analysis"[mesh]) or ("models, economic"[mesh terms] or ("models"[all fields] and "economic"[all fields]) or "economic models"[all fields] or "models, economic"[all fields] or "economic analyses" [all fields] or "economic evaluation"[all Fields]) or ("budgets"[mesh] or budget*[all fields])	281.236
#3	Revisão sistemática	((("review literature as topic"[mesh] or "systematic review"[ti] or "systematic literature review"[ti] or "systematic scoping review"[ti] or "systematic narrative review"[ti] or "systematic qualitative review"[ti] or "systematic evidence review"[ti] or "systematic quantitative review"[ti] or "systematic meta-review"[ti] or "systematic critical review"[ti] or "systematic mixed studies review"[ti] or "systematic mapping review"[ti] or "systematic cochrane review"[ti] or "systematic search and review"[ti] or "systematic integrative review"[ti]) not comment[pt] not (protocol[ti] or protocols[ti])) not medline [subset]) or ("cochrane database syst rev"[ta] and review[pt]) or "systematic review"[pt]	354.329
#4		#1AND #2AND #3	30

*atualizado em 23 de junho de 2025.

Avaliação de revisão por pares: esta seção é para ser preenchida pelo revisor

Revisor: Click or tap here to enter text.	**Email:** Click or tap here to enter text.
Data da conclusão: Click or tap here to enter text.	

1. Tradução da pergunta de pesquisa

☐ A) Sem revisões

☐ B) Revisão(ões) sugeridas

☐ C) Revisão(ões) necessárias

☐ Se "B" ou "C", por favor forneça uma explicação ou exemplo:

Quais são os métodos para avaliação econômica em doenças ultrarraras aplicadas à avaliação de tecnologias em saúde?

2. Operadores booleanos e de proximidade

☐ A) Sem revisões

☐ B) Revisão(ões) sugeridas

☐ C) Revisão(ões) necessárias

Se "B" ou "C", por favor forneça uma explicação ou exemplo:

Clique ou toque aqui para inserir o texto.

3. Cabeçalhos de assunto

☐ A) Sem revisões

☐ B) Revisão(ões) sugeridas

☐ C) Revisão(ões) necessárias

Se "B" ou "C", por favor forneça uma explicação ou exemplo:

Clique ou toque aqui para inserir o texto.

4. Busca por palavras

☐ A) Sem revisões

☐ B) Revisão(ões) sugeridas

☐ C) Revisão(ões) necessárias

Se "B" ou "C", por favor forneça uma explicação ou exemplo:

Clique ou toque aqui para inserir o texto.

5. Ortografia, sintaxe e número de linhas

☐ A) Sem revisões

☐ B) Revisão(ões) sugeridas

☐ C) Revisão(ões) necessárias

Se "B" ou "C", por favor forneça uma explicação ou exemplo:

Enter any content that you want to repeat, including other content controls. You can also insert this control around table rows in order to repeat parts of a table.

6. Limites e filtros

☐ A) Sem revisões

☐ B) Revisão(ões) sugeridas

☐ C) Revisão(ões) necessárias

Se "B" ou "C", por favor forneça uma explicação ou exemplo:

Avaliação geral (Nota: Se 1 ou mais dos elementos anteriores foram respondidos com "revisão necessária", esta resposta deve ser "revisão necessária").

☐ A) Sem revisões

☐ B) Revisão(ões) sugeridas

☐ C) Revisão(ões) necessárias

Comentários adicionais (incluindo as fontes de termos adicionais de busca, tais como o uso de programas de mineração de texto ou recursos como ChemID):

Clique ou toque aqui para inserir o texto.

1. Por favor, selecione a resposta mais apropriada para cada elemento

Elemento	**Sem revisões**	**Revisão(ões) sugerida(s)**	**Revisão(ões) necessária(s)**
1. Tradução da pergunta de pesquisa	☐	☐	☐
2. Operadores booleanos e de proximidade	☐	☐	☐
3. Cabeçalhos de assunto	☐	☐	☐
5. Ortografia, sintaxe e número de linhas	☐	☐	☐
6. Limites e filtros	☐	☐	☐
Avaliação geral	☐	☐	☐

Se forem sugeridas ou necessárias revisões, por favor forneça uma explicação ou exemplo:
Apenas sugiro incluir o contexto da ATS na pergunta de pesquisa

Apêndice B. Estratégia de busca para cada fonte de dados.

Fonte	Termos	Resultado*
Cochrane	#1 MeSH descriptor: [Rare Diseases] explode all trees #2 ("ultra-rare":ti,ab OR "ultrarare":ti,ab OR "very rare":ti,ab OR "ultra orphan":ti,ab OR "ultra-orphan":ti,ab OR "rare disease":ti,ab OR "orphan disease":ti,ab OR "orphan condition":ti,ab OR "rare condition":ti,ab OR "rare disorder":ti,ab OR "orphan disorder":ti,ab) #3 #1 or #2 #4 MeSH descriptor: [Cost-Effectiveness Analysis] explode all trees #5 ("cost-effectiveness":ti,ab OR "economic evaluation":ti,ab OR "cost-utility":ti,ab OR "cost-benefit":ti,ab OR "budget impact":ti,ab OR "budget impact analysis":ti,ab OR "budgetary impact":ti,ab OR "budget impact model":ti,ab) #6 #4 or #5 # #3 and #6	2
Embase	#1 ('ultra-rare':ab,ti OR 'ultrarare':ab,ti OR 'very rare':ab,ti OR 'ultra orphan':ab,ti OR 'ultra-orphan':ab,ti OR 'rare disease'/exp OR 'orphan disease':ab,ti OR 'orphan condition':ab,-ti OR 'rare condition':ab,ti) #2 ('cost effectiveness analysis'/exp OR 'cost effectiveness':ab,ti OR 'cost-utility analysis':ab,ti OR 'cost-benefit analysis'/exp OR 'economic model'/exp OR 'economic evaluation':ab,ti OR 'economic analysis':ab,ti OR budget*:ab,ti) #3 ('systematic review'/de OR 'systematic review':ab,ti) #4 [medline]/lim #5 #1 and #2 and #3 not #4	82
Epistemonikos	#1 (title:("ultra-rare" or "urd" or "ultrarare" or "very rare" or "ultra-orphan" or "ultra orphan" or "rare disease" or "orphan disease" or "disease rare" or "disease orphan" or "orphan condition" or "rare condition") or abstract:("ultra-rare" or "urd" or "ultrarare" or "very rare" or "ultra-orphan" or "ultra orphan" or "rare disease" or "orphan disease" or "disease rare" or "disease orphan" or "orphan condition" or "rare condition")) #2 (title:("cost-effectiveness" or "cost effectiveness" or "cost utility" or "cost-benefit" or "economic model" or "economic models" or "economic evaluation" or "economic analysis" or "economic analyses" or "budget impact" or "budget") or abstract:("cost-effectiveness" or "cost effectiveness" or "cost utility" or "cost-benefit" or "economic model" or "economic models" or "economic evaluation" or "economic analysis" or "economic analyses" or "budget impact" or "budget")) #3 #1 and #2 Filter: publication type (systematic review)	23
Pubmed	# 1 ("ultra-rare"[all fields] or "URD"[all fields] or "ultrarare"[all fields] or "very rare"[all fields] or "ultra-orphan"[all fields] or "ultra orphan"[all fields] or "rare diseases"[mesh] or "orphan disease"[all fields] or "disease rare"[all fields] or "disease orphan"[all fields] or "orphan condition"[all fields] or "rare condition"[all fields]) # 2 ("cost-effectiveness analysis"[mesh terms] or ("cost-effectiveness"[all fields] and "analysis"[all fields]) or "cost-effectiveness analysis"[all fields] or ("cost"[all fields] and "effectiveness"[all fields]) or "cost effectiveness"[all fields] or "cost-utility analysis"[all fields] or "cost-benefit analysis"[mesh]) or ("budgets"[mesh] or budget*[all fields]) or ("models, economic"[mesh terms] or ("models"[all fields] and "economic"[all fields]) or "economic models"[all fields] or "models, economic"[all fields] or "economic analyses" [all fields] or "economic evaluation"[all Fields]) # 3 ((("review literature as topic"[mesh] or "systematic review"[ti] or "systematic literature review"[ti] or "systematic scoping review"[ti] or "systematic narrative review"[ti] or "systematic qualitative review"[ti] or "systematic evidence review"[ti] or "systematic quantitative review"[ti] or "systematic meta-review"[ti] or "systematic critical review"[ti] or "systematic mixed studies review"[ti] or "systematic mapping review"[ti] or "systematic cochrane review"[ti] or "systematic search and review"[ti] or "systematic integrative review"[ti]) not comment[pt] not (protocol[ti] or protocols[ti])) not medline [subset]) or ("cochrane database syst rev"[ta] and review[pt]) or "systematic review"[pt] #4 #1AND #2AND #3	30
Total		137

*Atualizado em: 23 de junho de 2025

Apêndice C. Modelagem econômica aplicada em doenças ultrarraras identificadas nos documentos incluídos

Variável	Descrição
ID do documento	Identificador único do estudo ou número do relatório
Autor	Sobrenome do primeiro autor ou instituições responsáveis
Ano de publicação	Ano em que o documento foi publicado
País de realização	Local onde o documento foi desenvolvido ou aplicado
Tipo de fonte	Categoria documental
Categoria da fonte	Tipo de categoria da fonte
Escopo do estudo	Ultrarrara e rara, apenas ultrarrara
Definição de doença ultrarrara	Descreve como o estudo define o que é considerado “doença ultrarrara”, incluindo o critério de prevalência
Fonte da definição de doença ultrarrara	Indica a origem ou autoridade que fundamenta a definição utilizada no estudo
Condição/indicação	Doenças ultrarraras específicas ou grupos de doenças mencionados, se aplicável
Medicamento	Intervenção analisada
Comparadores	Alternativa usada como referência
Tipo de modelo	Tipo de modelo econômico usado
Horizonte temporal	Tempo considerado na modelagem
Métodos de extrapolação	Estratégia e justificativa para extrapolar dados além do observado
Perspectiva adotada	Perspectiva econômica utilizada
Fontes de dados de custos	Origem das informações de custos
Fontes de dados de utilidade	De onde vêm os dados
Fontes de dados clínicos	Base usada para eficácia
Estimativa de efetividade	Quantificação do efeito em saúde ajustado por custos
Métodos de estimação das utilidades e desfechos	Como foram derivadas as utilidades e desfecho
Taxas de desconto	Valor aplicado e justificativa
Limiares de custo-efetividade	Valores explícitos de limiar
Sensibilidade	Tipo e forma