Research, Society and Development, v. 13, n. 12, e97131247669, 2024
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Repercussions of the diagnostic delay of rare diseases: A scoping review protocol

Repercussões do atraso diagnóstico de doenças raras: Um protocolo de revisão de escopo

Repercusiones del retraso diagnóstico de enfermedades raras: Un protocolo de revisión del alcance

Received: 11/25/2024 | Revised: 12/03/2024 | Accepted: 12/04/2024 | Published: 12/07/2024

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Abstract
Rare diseases (RDs) are life-threatening conditions affecting 263 to 446 million people globally. However, diagnosing these diseases often takes years, leading to a "diagnostic odyssey." The impact of these delays is often underreported, leaving patients' consequences unclear. This protocol intends to guide a scoping review about the current knowledge on RDs, identify gaps and clarify reasons for diagnostic delays, focusing on global trends and Brazil. Following PRISMA-ScR guidelines and using the Joanna Briggs Institute's framework, searches will be conducted in five databases (PubMed, LILACS, Embase, Cochrane Library, and IBECS) and grey literature from reputable sources. Two authors will independently screen and extract data, resolving discrepancies with a third reviewer. Data will be analyzed qualitatively and presented through figures and narrative synthesis, with statistical analysis applied when pertinent. This protocol will supply a step-by-step guide for a scoping review that is going to provide critical insights into the effects of diagnostic delays in rare diseases, offering valuable information to improve diagnostic process and patient care. This protocol has been registered in the Open Science Framework (https://osf.io/zte3c/?view_only=90c5abadfbb646d6a64bc284314e696c).
Keywords: Delayed diagnosis; Rare diseases; Neglected diseases; Undiagnosed diseases.

Resumo
Doenças raras (DRs) são condições que ameaçam a vida e afetam entre 263 e 446 milhões de pessoas globalmente. No entanto, o diagnóstico dessas doenças frequentemente leva anos, resultando em uma "odisséia diagnóstica". O impacto desses atrasos muitas vezes é subnotificado, o que deixa as consequências para os pacientes pouco claras. Este protocolo tem como objetivo orientar uma revisão de escopo sobre o conhecimento atual acerca das DRs, identificar lacunas e esclarecer as razões para os atrasos no diagnóstico, com foco em tendências globais e no Brasil. Seguindo as diretrizes do PRISMA-ScR e utilizando a metodologia do Instituto Joanna Briggs, as buscas serão realizadas em cinco bases de dados (PubMed, LILACS, Embase, Biblioteca Cochrane e IBECS) e na literatura cinzenta de fontes renomadas. Dois autores irão, de forma independente, selecionar e extrair os dados, resolvendo discrepâncias com a ajuda de um terceiro revisor. Os dados serão analisados qualitativamente e apresentados por meio de figuras e uma síntese narrativa, com análise estatística aplicada quando pertinente. Este protocolo fornecerá um guia passo a passo para uma revisão de escopo que oferecerá insights críticos sobre os efeitos dos atrasos diagnósticos em doenças raras, proporcionando

informações valiosas para melhorar o processo de diagnóstico e o cuidado com esses pacientes. Este protocolo foi registrado na plataforma Open Science Framework (https://osf.io/zte3c/?view_only=90c5abadfbb646d6a64bc284314e696c).
Palavras-chave: Diagnóstico tardio; Doenças raras; Doenças negligenciadas; Doenças não diagnosticadas.

Resumen
Las enfermedades raras (ER) son condiciones que amenazan la vida y afectan a entre 263 y 446 millones de personas en todo el mundo. Sin embargo, el diagnóstico de estas enfermedades frecuentemente lleva años, resultando en una "odisea diagnóstica". El impacto de estos retrasos a menudo está subreportado, lo que deja poco claras las consecuencias para los pacientes. Este protocolo tiene como objetivo orientar una revisión de alcance sobre el conocimiento actual acerca de las ER, identificar lagunas y aclarar las razones de los retrasos en el diagnóstico, con un enfoque en las tendencias globales y en Brasil. Siguiendo las directrices de PRISMA-ScR y utilizando la metodología del Instituto Joanna Briggs, se realizarán búsquedas en cinco bases de datos (PubMed, LILACS, Embase, Biblioteca Cochrane e IBECS) y en literatura gris de fuentes reconocidas. Dos autores, de manera independiente, seleccionarán y extraerán los datos, resolviendo discrepancias con la ayuda de un tercer revisor. Los datos serán analizados cualitativamente y presentados mediante figuras y una síntesis narrativa, con análisis estadístico aplicado cuando sea pertinente. Este protocolo proporcionará una guía paso a paso para una revisión de alcance que ofrecerá conocimientos críticos sobre los efectos de los retrasos en el diagnóstico de enfermedades raras, proporcionando información valiosa para mejorar el proceso de diagnóstico y la atención a estos pacientes. Este protocolo ha sido registrado en la plataforma Open Science Framework (https://osf.io/zte3c/?view_only=90c5abadfbb646d6a64bc284314e696c).
Palabras clave: Diagnóstico tardío; Enfermedades raras; Enfermedades desatendidas; Enfermedades no diagnosticadas.

1. Introduction

Rare Diseases (RDs) are a diverse group of conditions frequently characterized by their progressive, complex, and degenerative nature, demanding ongoing care and multidisciplinary support (Ministério da Saúde, 2024). According to the European Union, RDs are generally defined as pathologies in which the prevalence is below 5 cases per 10,000 inhabitants (EUR-Lex, 2016), while the Orphan Drug Act in the United States defines them as conditions affecting fewer than 200,000 people (FDA, 2022) and the World Health Organization (WHO) specifies a rare disease as a disorder that affects less than 65 out of every 100,000 individuals (World Health Organization, 2024), a definition also adopted in Brazil (Ministério dos Direitos Humanos e da Cidadania, 2022). Despite their low prevalence, between 6,000 and 10,000 known RDs have been identified, with 80% having a genetic etiology (Plaiasu et al, 2010; The Global Genes, 2023). It is estimated that 263-446 million people are affected by RDs (Wakap et al., 2019), with 13 million of those in Brazil alone (Pfizer Brasil, 2019), thus representing a significant public health concern.

Moreover, the burden of having a rare disease is intensely felt by the patients with several impacts, including difficulties in performing daily activities, maintaining proper communication with others, and accessing healthcare services (Courbier et al., 2017). They also face social isolation and deteriorated mental health, highlighting the psychological burden (Uhlenbusch et al., 2019; Uhlenbusch et al., 2019), limitations in one's career or work environment (Uhlenbusch et al., 2019) and financial costs (Yang et al., 2022).

However, it is not only the burden of the disease itself that takes a toll on patients; the diagnostic journey towards an accurate diagnosis can be equally draining, often referred to as a "diagnostic odyssey" (Teutsch et al, 2023; Bauskis et al, 2022). During this pathway, the search for a definitive diagnosis lasts 5 to 6 years on average (Global genes, 2018; Benito-Lozano et al., 2022) Most patients visit more than three doctors before reaching the diagnosis, and feel that their diagnosis was delayed (Molster et al, 2016; Anderson et al., 2013) This also affects patients' families, since parents of children with RDs experience negative emotions, often linked to the uncertainty they feel regarding the future (Bauskis et al, 2022; Withers et al., 2020), adding significant impacts caused by a late diagnosis.

Much attention has been given to the importance of an early diagnosis for RDs, as it prevents unnecessary treatments and procedures, reduces the risk of misdiagnosis, and allows earlier access to the right therapy (Bygum et al, 2015; Mehta et al.,

2017; Zanello et al., 2022). Hence, The International Rare Diseases Consortium (IRDiRC) has established three goals to be accomplished by 2027, one of which is that all patients with a known RD should be diagnosed within one year (Bertolini et al, 2023). Therefore, this goal represents a crucial milestone that can facilitate patients in receiving an accurate diagnosis and proper disease management, especially for those who bear the consequences of a late diagnosis.

In Brazil, challenges mirror those observed globally. In January 2014, the Ministry of Health launched the Brazilian Policy of Comprehensive Care for People with Rare Diseases, aiming to reduce morbimortality rates and improve the quality of life for RD patients by focusing on prevention and early diagnoses (Giugliani et al., 2016). RD patients still face substantial delays in receiving a correct diagnosis. This is primarily due to a lack of access to specialized physicians, specific medications, and genetic tests. This shortage frequently leads to judicial actions to obtain necessary treatments, which increases healthcare costs and highlights significant flaws in the care policy for rare diseases (Iriart et al., 2019).

Moreover, regional disparities exacerbate the problem, as patients in remote areas may need to travel extensively to reach specialized medical centers (Iriart et al., 2019; Félix et al., 2022). This delay not only prolongs patient suffering but also increasingly weighs the emotional and financial burden on families.

1.1 Study rationale

Regarding the consequences of a delayed diagnosis, while some studies have cited few repercussions in psychological (Benito-Lozano et al., 2023; Páramo-Rodríguez et al., 2023), social (Tanaka et al., 2023; Benito-Lozano et al., 2022), financial (Gimenez-Lozano et al., 2022; Nunn et al., 2017), and emotional aspects (Nunn et al., 2017), the depth of understanding on this subject remains limited. The effects of diagnostic delay on rare disease patients need further investigation, since the literature lacks information on the specific impacts of diagnostic delay on the lives of individuals affected.

This knowledge gap can only be filled with a more comprehensive overview of the impact of delayed diagnosis on rare disease patients. Therefore, a scoping review was chosen due to its exploratory nature for mapping and summarizing what is known about the repercussions of the diagnostic delay of RDs for pointing further research and intervention.

1.2 Aims

We aim to provide a protocol to serve as a guiding tool to enable a review that will allow us to (1) comprehend and summarize the characteristics of published studies on the topic (origin of studies, sample size, type of study, and diseases addressed); (2) illustrate the existing knowledge on the impacts of a late diagnosis on individuals both globally and specifically in Brazil; and (3) describe the contributing reasons attributed to the diagnostic delay of RDs.

2. Methodology

This protocol was developed following the Joanna Briggs Institute Manual for Evidence Synthesis on scoping review protocols (Aromataris et al., 2024) and finalized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews Checklist (PRISMA-ScR) guidelines. (Tricco et al., 2018).

2.1 Identifying the review questions

This protocol aims to answer the following key questions: (1) What are the characteristics of the studies conducted to evaluate the repercussions of the diagnostic delay of RDs? (2) What is known in the literature regarding the consequences of a late diagnosis on patients with RDs? (3) What are the reasons attributed to the diagnostic delay of RDs by the authors or participants of the selected studies?

2.2 Eligibility criteria

First, we will establish a time criterion, defining a diagnosis as delayed if the time from symptom onset or the first medical appointment exceeds one year. This timeframe is consistent with the International Rare Diseases Consortium (IRDiRC) goal to facilitate timely diagnosis (Bygum et al., 2015). Second, studies with patients with all types of RDs will be included in the search, and no publication date limit will be applied, aiming to capture the current state of knowledge in the field. The selection will be done only if the article addresses the question: "What are the repercussions of the diagnostic delay of RDs?" Additionally, we intend to include studies written in Portuguese, Spanish, and English.

Studies are going to be excluded if: (1) they do not report the outcomes specified in the inclusion criteria; (2) the participants report being diagnosed late but receive the definitive diagnosis in less than a year; (3) they are case reports or dissertations; (4) the studies were published in languages other than those included. See Table 1.

Table 1 - Review eligibility criteria based on study population, concept, context and type of evidence.

	Inclusion	**Exclusion**
Population	▶Patients with any type of rare disease or description (eg, adults, children, adolescents, or older adults)	▶ None
Concept	▶ Studies that refer to and explore the consequences of diagnostic delay in various aspects of the lives of patients with rare diseases (eg, psychological, economic, social) ▶ Studies in which the diagnostic delay exceeded 1 year	▶ Studies that did not explore the repercussions of diagnostic delay in rare disease patients ▶ Studies in which the diagnostic delay did not exceed 1 year
Context	▶ Any geographical location or setting of any nature (including online studies)	▶ None
Types of evidence	▶ Primary empirical research studies (eg, cross-sectional studies, case-control studies, qualitative studies, historic cohort studies, case-control studies, and meta-analysis) ▶ Articles written in English, Spanish, or Portuguese ▶ Full-text articles ▶ Reviews (eg, systematic reviews) ▶ Abstracts or posters	▶ Articles for which we can not obtain the full text or that were not written in English, Spanish, or Portuguese ▶ Case series with 3 participants or less ▶ Case studies ▶ Dissertations

Legend: The question of interest is guided by the PCC acronym. It is recommended for structuring objectives, defining the scope of the work, and outlining the eligibility criteria for the review. *Source:* developed by the authors

2.3 Identifying relevant studies

To ensure a thorough inclusion of relevant studies, a comprehensive search strategy was developed based on the review questions. We identified key concepts and keywords related to the population of interest ('rare disease patients') and the concept of interest ('diagnostic delay'). Specific search terms were then formulated using the Medical Subject Headings (MeSH) vocabulary, allowing us to capture a wide array of synonyms and related studies. The indexing terms were combined using Boolean operators to create a structured search strategy. Later, the search was conducted in Pubmed, LILACS, Embase, Cochrane Library, and IBECS, resulting in the use of 5 databases, as well as websites with a focus on RDs, to include the grey literature.

The databases were chosen based on their global and regional importance in medical and clinical research, and the

websites due to their relevance in disseminating information regarding RDs. Two authors will conduct the screening process independently and the conflicts will be solved by the third author. Titles and abstracts will be first screened according to the inclusion and exclusion criteria. Those that fulfilled the inclusion criteria are going to be selected for full-text review. No publication date limits were applied.

2.4 Search strategy and terms

The search terms were strategically crafted to maximize the relevance of the retrieved articles, ensuring a comprehensive capture of literature related to rare diseases, and diagnostic delays. These terms were consistently applied across all databases, with minor modifications tailored to the specific search functionalities of each platform. All searches were conducted on February 21st, 2024.

The search terms used were: (“Rare disease” OR “Rare diseases” OR “Orphan disease” OR “Orphan diseases”) AND (”Delayed diagnoses” OR “Delayed diagnosis” OR “Late diagnosis” OR “Late diagnoses” OR “Diagnosis delay”).

2.5 Grey literature

"Grey literature” encompasses documents and sources produced outside traditional publishing channels often containing emerging research findings and insights that may not be captured in peer-reviewed articles. This inclusion enhances the comprehensiveness of our review.

We will conduct online research to include grey literature. We believe that such information will be found in two non-governmental and four governmental sources.

Additionally, the last five editions of the Brazilian Medical Genetics Congress (CBGM) annals are going to be screened by the first author. The pre-selected abstracts will be reviewed by the second author, and the findings will be discussed between the two. See Table 2.

Table 2 - Websites searched for grey literature.

Non-Governmental websites	Governmental websites
Resource Development (UK) (Frankish et al, 2022)	NHS England (Marley et al, 2018)
EURORDIS (Eurordis, 2024)	National Center of Advancing Translational Science (National Institutes of Health, 2024)
Brazilian Genetic Medical Congress (CBGM) annals (Sociedade Brasileira De Genética Médica E Genômica, 2023)	Brazilian Department of Health (Jorge et al, 2014)
	RARAS network (RARAS, 2024)

Legend: this table shows the websites elected for grey literature screening. *Source:* Developed by the authors.

2.6 Data charting

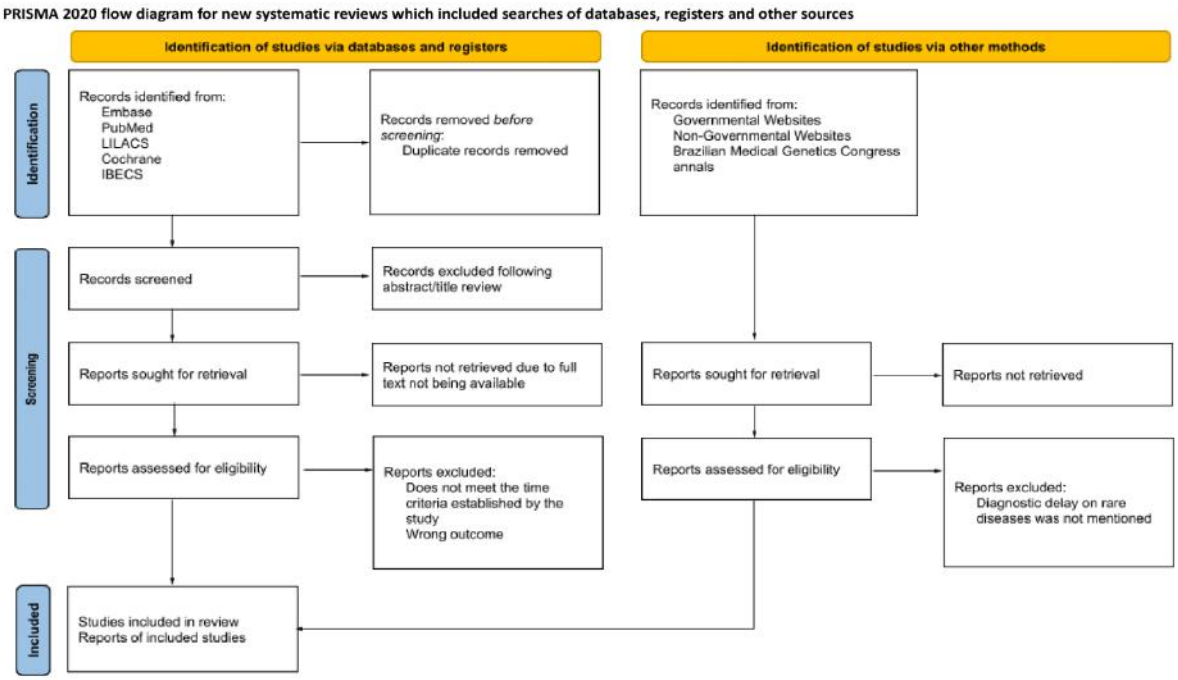
Two authors will conduct data charting simultaneously and independently while reading all the selected articles. Articles containing the information needed to address the research question will have their main information extracted.

For charting, each author will use a spreadsheet specifically created for this review to record the articles' information. This will include the title, author's name, year of publication, and country of origin. It will also be noted whether the study focuses on a specific rare disease or addresses rare diseases as a whole. Later, other authors will be responsible for including the type of study and the sample size used in each article in the spreadsheet.

A second spreadsheet will be created by the authors responsible for the screening process. It will objectively document the main results presented in each study, including the consequences of late diagnosis for rare disease patients. Each study's limitations and the primary causes of diagnostic delay identified in the studies will also be recorded.

At the end of the process, a third author will produce a PRISMA flow diagram (Prisma, 2020) (Figure 1) to properly record the number of articles found with the search strategy, how many of them were included or excluded, and the reasons for inclusion or exclusion.

Figure 1 - PRISMA flow diagram.



Legend: This diagram explains the methodology used in the study and each arrow represents the path of which the studies have been included or excluded from the screening. *Source:* Developed by the authors.

2.7 Data synthesis

Once the data charting will be conducted individually by each author, it will result in two spreadsheets containing similar information. The authors will discuss their results and unify them, a task that will be performed by the second author, which will result in a single spreadsheet encompassing both sets of findings. The final spreadsheet will facilitate the analysis of the information extracted from the studies, making it easier to notice recurrent themes and less likely to overlook unique ones.

3. Results

All yielded articles will be imported into Rayyan, a web or mobile app commonly used for systematic reviews (Ouzanni et al, 2016). Other authors, the ones not responsible for the screening, will remove duplicate articles from the platform.

All articles will be screened based on their titles and abstracts by two independent authors. Articles that do not meet the inclusion criteria or that meet any of the exclusion criteria will be automatically excluded. A third author will be assigned to resolve any conflicts by reviewing the titles and abstracts. This process will identify which articles need to be read in their full length.

All selected articles will undergo an independent full-text review by the two authors responsible for the screening. The articles that address the main research question will be included in the scoping review.

4. Discussion

This protocol aims to develop a step-by-step guide for a future scoping review that aims to recognize and comprehend the main consequences of delayed diagnosis for patients with rare diseases, as the authors have identified a gap in the existing literature regarding this issue.

Implications of our findings can enable future research to concentrate on assisting patients in coping with these consequences or even preventing them altogether, as the specific impacts and their mechanisms will be better understood. For example, understanding the psychological impact on these patients can lead to the development of targeted mental health interventions.

5. Conclusion

This project on the impacts of diagnostic delays in rare diseases will be instrumental in shedding light on the critical challenges faced by patients and their families. By documenting and analyzing these delays, the research will provide actionable insights that can drive improvements in early diagnosis and treatment strategies. The outcomes will not only enhance our understanding of the broader implications of diagnostic inefficiencies but also contribute to the development of targeted interventions, ultimately paving the way for more timely and effective care in the realm of rare diseases.

Ethics and Dissemination

As a scoping review protocol, this article will not involve direct participation of human subjects or use unpublished secondary data; therefore, it does not require approval from any human research ethics committee. It's important to highlight that only existing research studies will be used to conduct this work, involving no patients or members of the public.

The authors responsible for this protocol intend to disseminate it through publication in scientific journals and conference presentations.

This research has not received specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

The authors declare no competing interests.

Ethics approval or participants' consent to participate was not needed in this research, since it is a literature review.

Consent for publication was also not needed in this research.

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