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REVIEW PROTOCOL

Quality of life of type 1 neurofibromatosis patients: a scoping review protocol

Qualidade de vida de portadores de neurofibromatose tipo 1: um protocolo de revisão de escopo

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ABSTRACT
Objective: To map concepts, findings, and limitations related to quality of life in children, adolescents, and young adults with neurofibromatosis type 1. **Method:** This is a scoping review protocol based on Joanna Briggs Institute (JBI) guidelines. Data searches will be conducted on PubMed/MEDLINE, EMBASE, Web of Science, Lilacs, CINAHL, Open Grey, and Google Scholar. The retrieved manuscripts will be organized using the Rayyan tool for duplicate identification and removal. Subsequently, the articles and other materials will be processed in the same tool for screening and selecting eligible studies by two independent researchers, and this entire process will be described in a flowchart adapted from the PRISMA-ScR checklist. As appropriate, data extracted from eligible manuscripts will be presented in tables, figures, and flowcharts. The data will be discussed and correlated to identify potential strengths and limitations related to the research topic.
Descriptors: Quality of Life; Neurofibromatosis 1; Review.

RESUMO
Objetivo: Mapear conceitos, achados e limitações acerca da qualidade de vida de crianças, adolescentes e adultos jovens portadores de neurofibromatose tipo 1. **Método:** Trata-se de um protocolo de revisão de escopo baseado nas diretrizes do Joanna Briggs Institute (JBI). A busca de dados será realizada nas plataformas PubMed/MEDLINE, EMBASE, Web of Science, Lilacs, CINAHL, Open Grey e Google Scholar. Os manuscritos encontrados serão organizados através da ferramenta Rayyan para identificação e exclusão de duplicatas. Na sequência, os artigos e demais materiais seguirão na mesma ferramenta para triagem e seleção de estudos elegíveis por dois pesquisadores independentes, sendo esse processo todo descrito em um fluxograma adaptado do Checklist PRISMA-ScR. Os dados extraídos dos manuscritos elegíveis serão apresentados em tabelas, quadros e fluxogramas, conforme pertinente. Os dados serão discutidos e inter-relacionados, com a finalidade de identificar potencialidades e limitações acerca do tema de pesquisa.
Descritores: Qualidade de Vida; Neurofibromatose 1; Revisão.

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a multisystem phacomatosis with an autosomal dominant inheritance pattern. Multiple café-au-lait macules, freckles, multiple neurofibromas, learning disabilities, behavioral problems, and other complications of varying severity and complexity characterize it. The expression of the disease and its various complications varies even among individuals within the same family. Advances in molecular biological analysis and imaging techniques have not only helped to elucidate the etiological and clinical characteristics of NF1 but have also provided better prospects for therapeutic intervention for those affected by the disease[1-2].

According to the United Kingdom Neurofibromatosis Association Clinical Advisory Board, the incidence of NF1 is estimated to be from 1 in 2,500

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to 1 in 3,000, with no evidence of the predominance of the disease in specific populations or sexes. However, studies indicate a symmetric distribution between cases resulting from genetic transmission (i.e., when one of the parents is an NF1 carrier) and cases resulting from new genetic mutations[1-3]. As a result, each child of an NF1 carrier has a 50% chance of inheriting the disease-causing variant, with an almost 100% chance of manifestation. Consequently, a child who inherits an NF1-causing variant is expected to develop some phenotypic features of NF1, which may vary even within the same family[2].

Regardless of how the disease is acquired, the diagnosis is predominantly clinical[1-3], based on criteria established by the National Institutes of Health in 1988 and still in use today[1-3]. Suspicion of NF1 arises when the patient presents with any clinical manifestations outlined in Figure 1[1-2].

- ✓ 6 or more café-au-lait macules (>5 mm in children or >15 mm in adults)
- ✓ ≥ 2 cutaneous and/or subcutaneous neurofibromas OR 1 plexiform neurofibroma
- ✓ Axillary or inguinal freckling
- ✓ Optic glioma
- ✓ ≥ 2 Lisch nodules or ≥ choroidal abnormalities
- ✓ Presence of bone dysplasia
- ✓ First-degree relative diagnosed with NF1

Source: Adapted from Ferner et al., 2007 and Friedman, 2022.

Figure 1 – Clinical criteria for diagnosing NF1. Porto Alegre, RS, Brazil, 2023

The diagnosis of NF1 is made when a patient has two or more features described in the suggestive findings[1-2] (Figure 1). A negative molecular test for NF1 does not necessarily exclude the diagnosis of the disease, as some patients have the above clinical features without a detectable NF1 variant. In addition, many of the clinical features of NF1 increase in frequency with age. Adults diagnosed with NF1 may not have been diagnosed in early childhood because these features were absent[1-4].

Currently, there is no cure for NF1, but patients must undergo multidisciplinary/professional follow-up at least once a year or more frequently in case of complications or new manifestations. Cutaneous neurofibromas can be surgically removed if they cause pain, interfere with daily life, or are aesthetically disfiguring. This approach is considered the gold standard for neurofibroma management.

Monitoring the neuropsychomotor development of infants is essential, as is tracking their educational progress to quickly identify and address issues such as attention-deficit/hyperactivity disorder, which is common in NF1 patients. Mental health problems are also common in NF1 carriers, caused by both the clinical manifestations of the disease (e.g., multiple neurofibromas) and the complex and unpredictable prognosis of the disease. These issues represent a health risk because they directly affect their quality of life (QoL).

According to the World Health Organization, QoL is "an individual's perception of his or her position in life in the context of the culture and value systems in which he or she lives and concerning his or her goals, expectations, standards, and concerns"[5]. In the field of health and its subsets, the growing interest in the concept of QoL has influenced not only public health policies but also care practices and protocols. This is because the process of health and illness is complex, dynamic, and multifactorial[6].

Numerous instruments have been developed to measure QoL in the population, of which the Pediatric Quality of Life Inventory™ (PedsQL™) is particularly prominent in pediatrics. Developed by Varni and colleagues in 1999[7], the PedsQL™ aims to provide a comprehensive tool for assessing QoL in children and adolescents. The questionnaire, known as the PedsQL™ Generic Core Scores, is a broad instrument[7]. With the discovery of new diseases and advances in health care, it has had to be adapted to different pathologies, including NF1, to allow more refined analyses of QoL in pediatric patients.

Because of the disease's complexity and potential impact throughout a patient's life, anyone diagnosed with NF1 requires continuous multidisciplinary follow-up to identify, treat, and/or monitor complications as early as possible. This often results in the patient and their support network (parents, family members, caregivers, etc.) making frequent and recurrent visits to different healthcare services and levels. The context of being a carrier of a complex, incurable disease with self-limited treatment can affect a patient's life and lead to a reduction in their quality of life. Therefore, this study aims to review the concepts and findings related to QoL in children, adolescents, and young adults

with NF1 and to identify limitations associated with this topic in the current literature.

METHOD

This is a protocol for a scoping review (SR) of the literature. SRs are commonly used to outline the key concepts that support and/or guide a particular field of research and clarify working definitions and even conceptual boundaries of a particular topic[8]. SR studies are gaining traction in the global scientific literature, and the contribution of this type of review to mapping relevant and current research is undeniable. It can significantly benefit professionals in their clinical practice and researchers in generating new research on a topic[9].

The current protocol is structured according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines[10]. PRISMA-P, originally a checklist to guide researchers in formulating a systematic review protocol, was adopted to develop this scoping review protocol to ensure a higher level of methodological rigor.

Protocol and registration

The SR will be conducted according to the Joanna Briggs Institute (JBI) guidelines[8], and the results will be structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist[11]. This protocol has been registered on the Open Science Framework (OSF) platform under osf.io/vcqdx[12].

Research question

The PCC mnemonic was used to formulate the research question, where P refers to population (children, adolescents, and young adults), C refers to concept (QoL), and C refers to context (being a carrier of NF1). Thus, the guiding research question is: How has the QoL of children, adolescents, and young adults with NF1 been addressed in Brazil and around the world?

Inclusion criteria

Population

Studies involving children, adolescents, and young adults aged 5 to 25 years with NF1 will be included.

Study concept

Studies must focus on the analysis of quality of life, regardless of how it is approached, treated, or analyzed.

Context

This review will be set in the context of NF1 carriers.

Types of evidence sources

As proposed by the JBI, a SR has a broader scope of research with less restrictive criteria. Following the JBI protocol, data from multiple sources of evidence with diverse study designs will be used. The broad nature of SR questions helps gather evidence from diverse and heterogeneous sources[8].

Search strategy

Based on the PCC mnemonic, search strategies will be constructed using the *Descritores em Ciência da Saúde* (DeCS)/Medical Subjects Headings (MeSH) Portuguese, English, and Spanish terms. An example of the systematization of the search strategy can be seen in Figure 2.

Eligibility criteria

The selected databases are PubMed/MEDLINE, EMBASE, Web of Science, Lilacs, and CINAHL. Open Grey and Google Scholar databases will be used. Studies published in Portuguese, English, and Spanish will be considered eligible for gray literature searches. The timeframe for inclusion will be from January 2018 to June 2023, with the possibility of extending the timeframe based on the availability of studies at the time of the search, supported by a clear rationale in the final manuscript. Included sources will include fully published articles, preprints, online handbooks, theses, and dissertations. If necessary, attempts will be made to contact the primary author to request the full manuscript/document for those unavailable during the initial search.

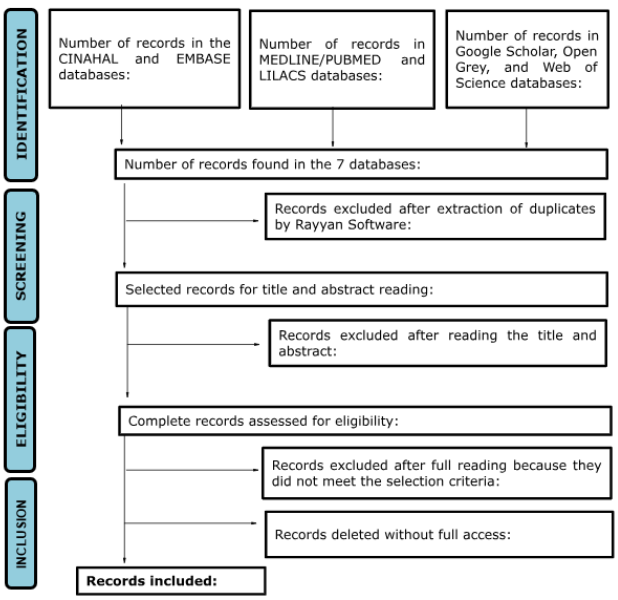
Study selection

After searching the databases, eligible studies will be selected systematically, in pairs, independently, and blinded, as recommended by JBI[8], using the Rayyan tool. In case of disagreements, a third reviewer will make the final decision. The study inclusion process will be organized following the PRISMA checklist[13] and presented in the "results" section of the final manuscript. The checklist has been adapted for

Objective	Mapping concepts, findings, and limitations regarding the quality of life of children, adolescents, and young adults with neurofibromatosis type 1.		
	P (Population)	C (Concept)	C (Context)
Extraction	Children, teenagers, and young adults	QoL	Be a NF1 holder
Combination	"Child", "Child Health", "Adolescent", "Adolescent Health", "Young Adult"	"Indicators of Quality of Life", "Quality of Life"	"Neurofibromatosis 1", "Neurofibromatosis Type 1", "Neurofibromatosis Type I", "Genes, Neurofibromatosis 1"
Construction	Child OR Child Health OR Adolescent OR Adolescent Health OR Young Adult	Indicators of Quality of Life OR Quality of Life	Neurofibromatosis 1 OR Neurofibromatosis Type 1 OR Neurofibromatosis Type I
Application	Child OR Child Health OR Adolescent OR Adolescent Health OR Young Adult AND Indicators of Quality of Life OR Quality of Life AND Neurofibromatosis 1 OR Neurofibromatosis Type 1 OR Neurofibromatosis Type I		

Figure 2 – Systematization of the search strategy. Porto Alegre, RS, Brazil, 2023

this review and is provided in Figure 3.



Source: Adapted from Page et al., 2021.

Figure 3 – Flowchart for the selection of eligible studies. Porto Alegre, RS, Brazil, 2023

First, the retrieved studies are analyzed using the Rayyan tool to identify duplicates, which are recorded and removed. After eliminating duplicate manuscripts, the systematic process of selecting eligible studies using the Rayyan tool will continue.

The first step in selecting eligible studies will be to read the title and abstract of all materials found to identify those that meet the inclusion and exclusion criteria. This step will be performed by a researcher trained according to the standards of this protocol. The selection will be carried out using the Rayyan tool, and in case of uncertainty, the material will automatically proceed to the second selection stage.

The second stage of selecting eligible studies, also within the Rayyan tool, will involve reading the full manuscripts of the materials screened in the previous stage. This blind selection phase will be performed by two different researchers, with a third reviewer to decide on the inclusion or exclusion of studies in case of disagreement. Manuscripts that meet the objectives and inclusion criteria will be included, and data will be extracted. At this stage, manuscripts unavailable for full reading will be excluded.

Data extraction

The synthesis of data from the selected manuscripts is presented to provide readers with a robust, up-to-date, and systematic overview of QoL in children, adolescents, and young adults with NF1. To achieve this, a synoptic table has been developed containing the authors' names, year of publication, aims or proposal of the manuscript, methodology, main results, and conclusions. The discussion of the results will be interrelated in a narrative manner, aiming to clarify the theoretical and methodological approaches of the research topic. Figure 4 illustrates the model of the synoptic table that will be used to synthesize the results.

Author	Journal	Year of publication	Aims	Methodology	Findings	Conclusions or concluding remarks

Source: Adapted from Peters et al., 2020.
Figure 4 – Data extraction summary table template. Porto Alegre, RS, Brazil, 2023

Data presentation
The data from the articles and other documents found will be extracted, synthesized, and organized into tables, figures, and flowcharts according to the relevance and nature of the findings. In addition, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method will be applied to the included manuscripts to assess the quality of evidence, which will be classified into four levels: high, moderate, low, or very low[14]. A discussion will then be presented that relates the findings to this SR's objective and guiding question. This will identify the potential strengths and limitations of the topic.

CONFLICT OF INTERESTS
The authors have declared that there is no conflict of interests.

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Data collection: Souza LP de, Diniz BL, Zen PRG
Data analysis and interpretation: Souza LP de, Diniz BL, Zen PRG
Writing and/or critical review of the intellectual content: Souza LP de, Diniz BL, Zen PRG
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