DOI: 10.53660/CLM-4176-24T10

Rare diseases, trends and challenges for scientific advances: a snapshot of a decade of research in Brazil

Received: 10-08-2024 | Accepted: 15-09-2024 | Published: 23-09-2024

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ABSTRACT

Brazil is home to around 13 million rare disease patients, which represents a significant challenge for biomedical research and public health. This descriptive and exploratory study analyzed research protocols on rare diseases submitted to Plataforma Brasil between 2013 and 2023, with the aim of identifying trends, challenges and opportunities for scientific progress in this area. The research evaluated variables such as the number of studies submitted and approved, sample characteristics, type of study, experimental design, research phase, participation in international networks, and epidemiological data (ICD). The results indicate a substantial increase in the number of protocols submitted over the period analyzed, with an average approval rate of 87.26%. Most of the studies were conducted in public institutions, highlighting the fundamental role of the public sector in rare disease research in Brazil. These findings suggest a growing investment and interest in research in this area, which could boost the development of new therapies and interventions, as well as supporting the formulation of more effective public policies to meet the needs of patients with rare diseases.

Keywords: Rare Diseases; Database; Clinical Trial; Public Policy

INTRODUCTION

According to the World Health Organisation (WHO), in Brazil, a disease is considered rare when it affects up to 65 people in every 100,000 individuals, i.e. 1.3 cases for every 2,000 people (Brasil, 2014). Rare diseases are largely genetic in origin, involving one or more genes or chromosomal abnormalities, manifesting in childhood in around 75 per cent of cases; others are caused by infections (bacterial or viral), allergies or degenerative, proliferative or toxic processes (chemicals, radiation) (Brasil, [2024]b).

It is estimated that, globally, more than 400 million people live with a rare disease, totalling around 5 to 6% of the world's population, with approximately 7,000 different conditions indicated. In Brazil, around 13 million citizens have rare diseases, according to data from the Ministry of Health (MS) (Brasil, [2024]a).

The field of rare diseases suffers from a huge lack of medical and scientific knowledge. Although there are no specific treatments for many rare diseases, there is adequate care with the aim of improving the quality of life and prolong the survival of those living with this condition (Raras, [2024]).

Research into rare diseases plays a fundamental role in advancing health technologies and improving the health conditions of the population. In Brazil, clinical research is regulated by government bodies and specific legislation. The National Health Surveillance Agency (ANVISA) (Brasil, [2024]c), for example, regulates clinical trials whose results will be used to subsidise the registration of medicines or medical devices; it also conducts inspections to verify adherence to Good Clinical Practices. The National Research Ethics Commission (CONEP) (Brasil, [2024]d), on the other hand, works closely with the Research Ethics Committees (CEPs) in the process of reviewing and approving research protocols involving human subjects before they are carried out and supervising them during and after the conclusion of the study, with a view to protecting research participants.

Given the above, the relevance of this study is due not only to the growing numbers of diagnosis of new rare diseases, but also to the urgency of developing effective, safe treatments and comprehensive care for patients with rare diseases. Understanding the trends and challenges of rare disease research can foster collaboration between institutions, optimise resources, target public and private funding sources and promote a more integrated and effective approach to the treatment and management of these conditions.

OBJECTIVE

The aim of this study was to analyse and characterise the research protocols on rare diseases in Brazil submitted via the Brazil Platform (PB) to the 898 CEPs (CEP/CONEP System) in the period 2013-2023, in terms of the number of studies submitted and approved, sample size, type of study, design, phase, international study, ICD (International Classification of Diseases) code, ICD description, proposing region, sponsor, among other developments.

METHOD

Study pattern

A retrospective and exploratory descriptive study was carried out by reviewing data and information on research carried out on rare diseases and submitted to the 898 CEPs in Brazil, registered via PB, the CONEP database, National Health Council (CNS), from January 2013 to December 2023.

Data

The CEP/CONEP system was set up in 1996 to carry out ethical analyses of research projects involving human subjects in Brazil, by means of resolutions and regulations issued by the CNS, which is linked to the Ministry of Health. It is made up of CONEP and the 898 CEPs in Brazil. Ethical analyses are sent to the CEP/CONEP system via a tool called Plataforma Brasil (Brasil, [2024]d).

The BP is a national, publicly accessible, digital and unified database of research records involving human beings for the entire CEP/CONEP System, which allows research to be monitored at its different stages, from submission to final approval by the CEP and CONEP. When necessary, PB makes it possible to monitor the field phase, send partial reports and final research reports (when completed). The system allows transparency of work and access to public data on research submitted by society in general.

The data from the research protocols on rare diseases submitted to PB in the period 2013-2023 was provided by the Data, Technology and Innovation Management Centre (NDTI) of the Department of Science and Technology (DECIT) of the Ministry of Health, which is responsible for managing the Plataforma Brasil tool, after documented authorisation from the person responsible for the service and a commitment from the researchers to guarantee the secrecy and confidentiality of the data in accordance with current CNS regulations (Brasil, 2012).

Data collection for this survey followed the following criteria: Brazilian Platform and Clinical Trials >> Public tab >> Consultations>> Consult Research Projects>> Search for research projects>> Research Project Title>> "rare disease and rare diseases". In addition, the projects listed had to include the expression 'rare disease' in at least one of the fields: Public Title, Introduction and Methodology. The period considered for data collection was from January 2013 to December 2023 and the variables defined for the research were: date of submission to the platforms, public title of the study, sample size, UF of origin of the institution, type of study, study design, disease researched, ICD-10 of the diseases and experimental drug.

Within the database search, research protocols (studies) related to 'Rare Diseases' using the following categories were considered: OP (Original Projects); date of the opinion between 01/01/2013 and 31/12/2023; status of the opinion (approved, not approved and pending); CAAE number (Certificate of Submission for Ethical Appraisal - numbering generated to identify the research project that comes up for ethical appraisal in the CEP/CONEP System); public title; proposed methodology; sample size; type of study; phase of the study; country of origin of the study (international/national); type of descriptor (general and specific); ICD code; description of the ICD; proposing institution; state of origin of the proposing institution; Brazilian geographical region of the proposing institution; type of sponsor (public or private).

STATISTICAL DATA ANALYSIS

Was structured in three stages:

1) Data organisation - the following variables were selected: opinion date, opinion status, CAAE, CEP name, sample size, type of study, type of design, phase, international study, type of descriptor, ICD code, ICD description, proposing

region and sponsor; using the CAAE code, which is unique for each study, duplicates in the database were eliminated, resulting in the identification of nine duplicate studies. In addition, the year of each study was extracted from the 'date of opinion' variable;

2) Classification of the studies - a search was carried out using the variable 'name of the REC' to classify the studies as 'public' or 'private'; it is worth noting that some studies were conducted in more than one institution, one of which was public and the other private; in these cases, the studies were classified as 'public and private'; and
3) Statistical analysis - the approved studies were selected and descriptive statistics, measures of central tendency and measures of dispersion were analysed. The data was presented in tables, graphs and heat maps. All analyses were carried out using Microsoft Excel spreadsheets version 2020 and R software version 4.2.3 (The R Project for [...], [2024].).

RESULTS

A total of 1,500 research protocols on rare diseases from 2013-2023 were analysed. Initially, the data was processed to eliminate all duplicates present in the dataframe, using the CAAE code as a reference. This procedure resulted in the identification of 9 duplicate studies among the 1500 found in the search. In the subsequent stage, the 1491 unique studies were classified as coming from public or private institutions, according to the origin of the proposing institution. In the last phase of data processing, only studies with an approved opinion were selected. Thus, 1301 studies (87.26%) were classified as approved, 38 (2.55%) as not approved and 152 (10.19%) as pending (see table 1).

Table 1. Descriptive statistics of opinion of the studies, period 2013-2023

Situation	Absolute freq.	%
Approved	1301	87,26
Not approved	38	2,55
Pending	152	10,19

Source: developed in-house

A descriptive statistical analysis was also carried out on the sample sizes of the studies included in the dataset. The average sample size of the studies was 153 individuals, with a standard deviation of 817.03. In addition, other statistical parameters were calculated, such as the median (n = 22), the minimum value (n = 0) and the maximum value (n = 20,000) (see table 2).

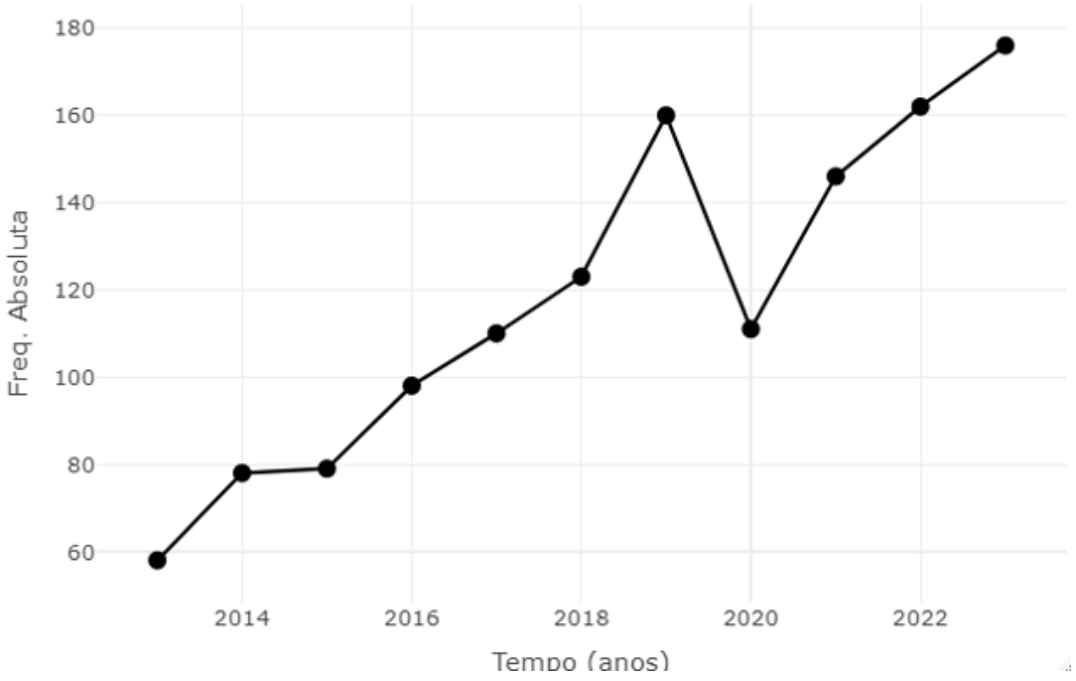
Table 2. Descriptive statistics for the sample size variable of studies from 2013 to 2023

Statistic	Sample size
Average	153,00
Median	22,00
Standard deviation	817,03
Minimum	0,00
Maximum	20000,00

Source: developed in-house

Over the period 2013-2023, there was a significant increase in the number of studies related to rare diseases in Brazil. In 2013, 58 studies were registered, representing 4.46 per cent of the total; in contrast, 2023 had the highest number of studies, with 176 registrations, corresponding to 13.53 per cent (see illustration 1 and table 3).

Ilustration 1. Number of studies related to rare diseases approved in the period 2013-2023



Source: Brasil (2023)

It can be seen that over the 2013-2019 period, there was an increasing number of studies, ranging from 58 (4.46%) in 2013 to 160 (12.30%) in 2019. However, in the 2020-2021 period, there was a decrease in the number of studies related to rare diseases (see table 3), which increased again in the 2022-2023 period, when it reached 176 studies for the year.

Table 3. Number of studies related to rare diseases in the period 2013-2023

year	Approved studies
2013	58 (4,46%)
2014	78 (6,00%)
2015	79 (6,07%)
2016	98 (7,53%)
2017	110 (8,46%)
2018	123 (9,45%)
2019	160 (12,30%)
2020	111 (8,53%)
year	**Approved studies**
2021	146 (11,22%)
2022	162 (12,45%)
2023	176 (13,53%)

Source: developed in-house

In order to obtain a comprehensive view of studies on rare diseases in Brazil, a descriptive statistical analysis of the variables of interest was carried out (see table 04).

Table 4. Descriptive statistics of the variables of interest related to rare disease studies in Brazil in the period 2013-2023

Variable\Statistic	Absolute freq.	%
Type of study		
Multicentric	101	7,76
Unicentric	1200	92,24
Type of pattern\design		
Experimental intervention	159	12,22
Observational	1142	87,78

Study phase		
phase 1	31	19,50
phase 2	11	6,92
phase 3	35	22,01
phase 4	8	5,03
phase 1/2	4	2,52
phase 2/3	6	3,77
others	48	30,19
No classification	16	10,06
International study		
No	1216	93,47
Yes	85	6,53
Origin		
Public	883	67,87
Private	401	30,82
Public\Private	17	1,31

Variable\Statistic	Absolute freq.	%
Type of descriptor		
general	666	51,19
specific	635	48,81
Region		
North	47	3,61
Northeast	256	19,68
Central-west	61	4,69
Southeast	719	55,27
South	218	16,76
Federal unit (state)		
AC Acre	3	0,23
AL Alagoas	11	0,85
AM Amazonas	12	0,92
AP Amapa	2	0,15
BA Bahia	49	3,77
CE Ceara	48	3,69
DF Distrito Federal	33	2,54
ES Espirito Santo	32	2,46

GO Goais	19	1,46
MA Maranhao	9	0,69
MG Minas Gerais	87	6,69
MS Mato Grosso do Sul	5	0,38
MT Mato Grosso	4	0,31
PA Para	27	2,08
PB Paraiba	38	2,92
PE Pernambuco	80	6,15
PI Piaui	5	0,38
PR Parana	90	6,92
RJ Rio do Janeiro	134	10,30
RN Rio Grande do Norte	5	0,38
RO Rondonia	1	0,08
RS Rio Grande do Sul	92	7,07
SC Santa Catarina	36	2,77
SE Sergipe	11	0,85
Variable\Statistic	**Absolute freq.**	**%**
Federal unit (state)		
SP Sao Paulo	466	35,82
TO Tocantins	2	0,15
RR Roraima	0	0,00

Where: AC – Acre; AL – Alagoas; AM – Amazonas; AP – Amapá; BA – Bahia; CE – Ceará; DF – Distrito Federal; ES – Espírito Santo; GO – Goiás; MA – Maranhão; MG – Minas Gerais; MS – Mato Grosso do Sul; MT – Mato Grosso; PA – Pará; PB – Paraíba; PE – Pernambuco; PI – Piauí; PR – Paraná; RN – Rio Grande do Norte; RO – Rondônia; RS – Rio Grande do Sul; SC – Santa Catarina; SE – Sergipe; SP – São Pualo; TO – Tocantins; e, RR – Roraima.

Source: developed in-house

In order to screen and understand possible relationships between the specific characteristics of the studies, a comparative descriptive analysis was carried out between the categories of variables (see table 5). In addition, all the variables of interest mentioned above were also analysed over the years 2013 to 2023 (see table 6).

Table 5. Descriptive/comparative statistics of the variables of interest related to each other, to the Federative Units and Regions of Brazil in the period 2013-2023

Variables	Type of Study		Tyoe of pattern\design		International study		Origin		
	unicentric	multicentric	Experimental\intervention	Observational	No	Yes	Public	Private	Public\Private
Study type									
Multicentric	-	-	40 (25,16%)	61 (5,34%)	49 (4,03%)	52 (61,18%)	85 (9,63%)	16 (3,99%)	0 (0,00%)
unicentric	-	-	119 (74,84%)	1081 (94,66%)	1167 (95,97%)	33 (38,82%)	798 (90,37%)	385 (96,01%)	17 (100,00%)
Type of pattern\design									
Experimental/intervention	119 (9,92%)	40 (39,60%)	-	-	116 (9,54%)	43 (50,59%)	119 (13,48%)	40 (9,98%)	0 (0,00%)
Observational	1081 (90,08%)	61 (60,40%)	-	-	1100 (90,46%)	42 (49,41%)	764 (86,52%)	361 (90,02%)	17 (100,00%)
Study phase									
phase 1	31 (26,05%)	0 (0,00%)	31 (19,50%)	-	30 (25,86%)	1 (2,33%)	15 (12,61%)	16 (40,00%)	0 (0,00%)
phase 2	7 (5,88%)	4 (10,00%)	11 (6,92%)	-	9 (7,76%)	2 (4,65%)	7 (5,88%)	4 (10,00%)	0 (0,00%)
phase 3	11 (9,24%)	24 (60,00%)	35 (22,01%)	-	8 (6,90%)	27 (62,79%)	32 (26,89%)	3 (7,50%)	0 (0,00%)
phase 4	4 (3,36%)	4 (10,00%)	8 (5,03%)	-	5 (4,31%)	3 (6,98%)	7 (5,88%)	1 (2,50%)	0 (0,00%)
phase 1/2	3 (2,52%)	1 (2,50%)	4 (2,52%)	-	3 (2,59%)	1 (2,33%)	3 (2,52%)	1 (2,50%)	0 (0,00%)
phase 2/3	3 (2,52%)	3 (7,50%)	6 (3,77%)	-	3 (2,59%)	3 (6,98%)	6 (5,04%)	0 (0,00%)	0 (0,00%)
others	44 (36,97%)	4 (10,00%)	48 (30,19%)	-	42 (36,21%)	6 (13,95%)	37 (31,09%)	11 (27,50%)	0 (0,00%)
No classification	16 (13,45%)	0 (0,00%)	16 (10,06%)	-	16 (13,79%)	0 (0,00%)	12 (10,08%)	4 (10,00%)	0 (0,00%)
International study									
No	1167 (97,25%)	49 (48,51%)	116 (72,96%)	1100 (96,32%)	-	-	808 (91,51%)	391 (97,51%)	17 (100,00%)
Yes	33 (2,75%)	52 (51,49%)	43 (27,04%)	42 (3,68%)	-	-	75 (8,49%)	10 (2,49%)	0 (0,00%)
Origin									
Public	798 (66,50%)	85 (84,16%)	119 (74,84%)	764 (66,90%)	808 (66,45%)	75 (88,24%)	-	-	-
Private	385 (32,08%)	16 (15,84%)	40 (25,16%)	361 (31,61%)	391 (32,15%)	10 (11,76%)	-	-	-

Variables	Type of Study		Tyoe of pattern\design		International study		Origin		
	unicentric	multicentric	Experimental\intervention	Observational	No	Yes	Public	Private	Public\Private
Public\Private	17 (1,42%)	0 (0,00%)	0 (0,00%)	17 (1,49%)	17 (1,40%)	0 (0,00%)	-	-	-
Type of descriptor									
General	618 (51,50%)	53 (52,48%)	79 (49,69%)	587 (51,40%)	621 (51,07%)	45 (52,94%)	447 (50,62%)	213 (53,12%)	6 (35,29%)
Specific	582 (48,50%)	48 (47,52%)	80 (50,31%)	555 (48,60%)	595 (48,93%)	40 (47,06%)	436 (49,38%)	188 (46,88%)	11 (64,71%)
Region									
North	47 (3,92%)	0 (0,00%)	3 (1,89%)	44 (3,85%)	46 (3,78%)	1 (1,18%)	43 (4,87%)	4 (1,00%)	0 (0,00%)
Northeast	244 (20,33%)	12 (11,88%)	18 (11,32%)	238 (20,84%)	254 (20,89%)	2 (2,35%)	171 (19,37%)	84 (20,95%)	1 (5,88%)
Central-west	60 (5,00%)	1 (0,99%)	3 (1,89%)	58 (5,08%)	59 (4,85%)	2 (2,35%)	49 (5,55%)	11 (2,74%)	1 (5,88%)
Southeast	651 (54,25%)	68 (67,33%)	101 (63,52%)	618 (54,12%)	665 (54,69%)	54 (63,53%)	486 (55,04%)	233 (58,10%)	0 (0,00%)
South	198 (16,50%)	20 (19,80%)	34 (21,38%)	184 (16,11%)	192 (15,79%)	26 (30,59%)	134 (15,18%)	69 (17,21%)	15 (88,24%)
Federal unit (state)									
AC	3 (0,25%)	0 (0,00%)	0 (0,00%)	3 (0,26%)	3 (0,25%)	0 (0,00%)	3 (0,34%)	0 (0,00%)	0 (0,00%)
AL	11 (0,92%)	0 (0,00%)	1 (0,63%)	10 (0,88%)	11 (0,90%)	0 (0,00%)	7 (0,79%)	4 (1,00%)	0 (0,00%)
AM	12 (1%)	0 (0,00%)	1 (0,63%)	11 (0,96%)	11 (0,90%)	1 (1,18%)	11 (1,25%)	1 (0,25%)	0 (0,00%)
AP	2 (0,17%)	0 (0,00%)	1 (0,63%)	1 (0,09%)	2 (0,16%)	0 (0,00%)	2 (0,23%)	0 (0,00%)	0 (0,00%)
BA	45 (3,75%)	4 (3,96%)	4 (2,52%)	45 (3,94%)	47 (3,87%)	2 (2,35%)	33 (3,74%)	15 (3,74%)	1 (5,88%)
CE	44 (3,67%)	4 (3,96%)	6 (3,77%)	42 (3,68%)	48 (3,95%)	0 (0,00%)	34 (3,85%)	14 (3,49%)	0 (0,00%)
DF	32 (2,67%)	1 (0,99%)	1 (0,63%)	32 (2,8%)	31 (2,55%)	2 (2,35%)	26 (2,94%)	6 (1,50%)	1 (5,88%)
ES	32 (2,67%)	0 (0,00%)	4 (2,52%)	28 (2,45%)	32 (2,63%)	0 (0,00%)	13 (1,47%)	19 (4,74%)	0 (0,00%)
GO	19 (1,58%)	0 (0,00%)	2 (1,26%)	17 (1,49%)	19 (1,56%)	0 (0,00%)	15 (1,7%)	4 (1,00%)	0 (0,00%)
MA	9 (0,75%)	0 (0,00%)	0 (0,00%)	9 (0,79%)	9 (0,74%)	0 (0,00%)	7 (0,79%)	2 (0,50%)	0 (0,00%)
MG	82 (6,83%)	5 (4,95%)	4 (2,52%)	83 (7,27%)	83 (6,83%)	4 (4,71%)	46 (5,21%)	41 (10,22%)	0 (0,00%)
MS	5 (0,42%)	0 (0,00%)	0 (0,00%)	5 (0,44%)	5 (0,41%)	0 (0,00%)	5 (0,57%)	0 (0,00%)	0 (0,00%)
MT	4 (0,33%)	0 (0,00%)	0 (0,00%)	4 (0,35%)	4 (0,33%)	0 (0,00%)	3 (0,34%)	1 (0,25%)	0 (0,00%)

Variables	Type of Study		Tyoe of pattern\design		International study		Origin		
	unicentric	multicentric	Experimental\intervention	Observational	No	Yes	Public	Private	Public\Private
PA	27 (2,25%)	0 (0,00%)	1 (0,63%)	26 (2,28%)	27 (2,22%)	0 (0,00%)	24 (2,72%)	3 (0,75%)	0 (0,00%)
PB	38 (3,17%)	0 (0,00%)	3 (1,89%)	35 (3,06%)	38 (3,12%)	0 (0,00%)	25 (2,83%)	13 (3,24%)	0 (0,00%)
PE	78 (6,5%)	2 (1,98%)	3 (1,89%)	77 (6,74%)	80 (6,58%)	0 (0,00%)	49 (5,55%)	31 (7,73%)	0 (0,00%)
PI	5 (0,42%)	0 (0,00%)	0 (0,00%)	5 (0,44%)	5 (0,41%)	0 (0,00%)	3 (0,34%)	2 (0,50%)	0 (0,00%)
PR	89 (7,42%)	1 (0,99%)	6 (3,77%)	84 (7,36%)	87 (7,15%)	3 (3,53%)	42 (4,76%)	33 (8,23%)	15 (88,24%)
RJ	126 (10,5%)	8 (7,92%)	26 (16,35%)	123 (10,77%)	128 (10,53%)	6 (7,06%)	110 (12,46%)	24 (5,99%)	0 (0,00%)
RN	4 (0,33%)	1 (0,99%)	1 (0,63%)	4 (0,35%)	5 (0,41%)	0 (0,00%)	4 (0,45%)	1 (0,25%)	0 (0,00%)
RO	1 (0,08%)	0 (0,00%)	0 (0,00%)	1 (0,09%)	1 (0,08%)	0 (0,00%)	1 (0,11%)	0 (0,00%)	0 (0,00%)
RS	73 (6,08%)	19 (18,81%)	26 (16,35%)	66 (5,78%)	70 (5,76%)	22 (25,88%)	68 (7,7%)	24 (5,99%)	0 (0,00%)
SC	36 (3%)	0 (0,00%)	2 (1,26%)	34 (2,98%)	35 (2,88%)	1 (1,18%)	24 (2,72%)	12 (2,99%)	0 (0,00%)
SE	10 (0,83%)	1 (0,99%)	0 (0,00%)	11 (0,96%)	11 (0,9%)	0 (0,00%)	9 (1,02%)	2 (0,50%)	0 (0,00%)
SP	411 (34,25%)	55 (54,46%)	82 (51,57%)	384 (33,63%)	422 (34,70%)	44 (51,76%)	317 (35,9%)	149 (37,16%)	0 (0,00%)
TO	2 (0,17%)	0 (0,00%)	0 (0,00%)	2 (0,18%)	2 (0,16%)	0 (0,00%)	2 (0,23%)	0 (0,00%)	0 (0,00%)
RR	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)

Souce: developed in-house

Table 6. Descriptive/comparative statistics of the variables of interest versus time - period 2013-2023

Variables	Category/Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Type of study	Unicentric	9 (15,52%)	2 (2,56%)	9 (11,39%)	7 (7,14%)	4 (3,64%)	5 (4,07%)	15 (9,38%)	6 (5,41%)	15 (10,27%)	15 (9,26%)	14 (7,95%)
	Multicentric	49 (84,48%)	76 (97,44%)	70 (88,61%)	91 (92,86%)	106 (96,36%)	118 (95,93%)	145 (90,63%)	105 (94,59%)	131 (89,73%)	147 (90,74%)	162 (92,05%)
Type of pattern\design	Experimental\Intervention	10 (17,24%)	17 (21,79%)	15 (18,99%)	16 (16,33%)	11 (10%)	12 (9,76%)	19 (11,88%)	10 (9,01%)	16 (10,96%)	15 (9,26%)	18 (10,23%)
	Observational	48 (82,76%)	61 (78,21%)	64 (81,01%)	82 (83,67%)	99 (90%)	111 (90,24%)	141 (88,13%)	101 (90,99%)	130 (89,04%)	147 (90,74%)	158 (89,77%)

Variables	Category/Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Study phase	Phase 1	2 (3,45 %)	1 (1,28 %)	3 (3,8%)	3 (3,06 %)	3 (2,73%)	2 (1,63%)	8 (5%)	2 (1,8%)	1 (0,68%)	4 (2,47%)	2 (1,14%)
	Phase 2	0 (0%)	1 (1,28 %)	1 (1,27 %)	1 (1,02 %)	1 (0,91%)	2 (1,63%)	1 (0,63%)	0 (0%)	0 (0%)	1 (0,62%)	3 (1,7%)
	Phase 3	5 (8,62 %)	3 (3,85 %)	4 (5,06 %)	1 (1,02 %)	0 (0%)	1 (0,81%)	5 (3,13%)	3 (2,7%)	6 (4,11%)	4 (2,47%)	3 (1,7%)
	Phase 4	0 (0%)	1 (1,28 %)	0 (0%)	1 (1,02 %)	1 (0,91%)	0 (0%)	1 (0,63%)	0 (0%)	3 (2,05%)	1 (0,62%)	0 (0%)
	Phase 1/2	0 (0%)	0 (0%)	2 (2,53 %)	0 (0%)	0 (0%)	1 (0,81%)	0 (0%)	1 (0,9%)	0 (0%)	0 (0%)	0 (0%)
	Phase 2/3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,81%)	0 (0%)	1 (0,9%)	2 (1,37%)	0 (0%)	2 (1,14%)
	Others	2 (3,45 %)	5 (6,41 %)	5 (6,33 %)	8 (8,16 %)	4 (3,64%)	3 (2,44%)	4 (2,5%)	3 (2,7%)	2 (1,37%)	5 (3,09%)	7 (3,98%)
	No classification	1 (1,72 %)	6 (7,69 %)	0 (0%)	2 (2,04 %)	2 (1,82%)	2 (1,63%)	0 (0%)	0 (0%)	2 (1,37%)	0 (0%)	1 (0,57%)
International study	No	54 (93,1 %)	72 (92,31 %)	71 (89,87 %)	93 (94,9 %)	110 (100%)	117 (95,12 %)	152 (95%)	104 (93,69 %)	136 (93,15 %)	148 (91,36 %)	159 (90,34 %)
	Yes	4 (6,9%)	6 (7,69 %)	8 (10,13 %)	5 (5,1%)	0 (0%)	6 (4,88%)	8 (5%)	7 (6,31%)	10 (6,85%)	14 (8,64%)	17 (9,66%)
Origin	Public	39 (67,24 %)	53 (67,95 %)	54 (68,35 %)	71 (72,45 %)	71 (64,55 %)	89 (72,36 %)	105 (65,63 %)	75 (67,57 %)	101 (69,18 %)	101 (62,35 %)	124 (70,45 %)
	Private	16 (27,59 %)	25 (32,05 %)	23 (29,11 %)	27 (27,55 %)	37 (33,64 %)	34 (27,64 %)	55 (34,38 %)	35 (31,53 %)	44 (30,14 %)	58 (35,8%)	47 (26,7%)
	Public\Private	3 (5,17 %)	0 (0%)	2 (2,53 %)	0 (0%)	2 (1,82%)	0 (0%)	0 (0%)	1 (0,9%)	1 (0,68%)	3 (1,85%)	5 (2,84%)
Type of descriptor	General	28 (48,28 %)	38 (48,72 %)	38 (48,1 %)	51 (52,04 %)	61 (55,45 %)	64 (52,03 %)	80 (50%)	57 (51,35 %)	79 (54,11 %)	70 (43,21 %)	100 (56,82 %)
	Specific	30 (51,72 %)	40 (51,28 %)	41 (51,9 %)	47 (47,96 %)	49 (44,55 %)	59 (47,97 %)	80 (50%)	54 (48,65 %)	67 (45,89 %)	92 (56,79 %)	76 (43,18 %)
Region	North	3 (5,17 %)	4 (5,13 %)	3 (3,8%)	2 (2,04 %)	2 (1,82%)	7 (5,69%)	9 (5,63%)	4 (3,6%)	3 (2,05%)	6 (3,7%)	4 (2,27%)
	Northeast	7 (12,07 %)	15 (19,23 %)	9 (11,39 %)	27 (27,55 %)	21 (19,09 %)	25 (20,33 %)	39 (24,38 %)	21 (18,92 %)	26 (17,81 %)	27 (16,67 %)	39 (22,16 %)
	Central-west	2 (3,45 %)	2 (2,56 %)	5 (6,33 %)	3 (3,06 %)	5 (4,55%)	4 (3,25%)	7 (4,38%)	7 (6,31%)	8 (5,48%)	6 (3,7%)	12 (6,82%)
	Southeast	36 (62,07 %)	41 (52,56 %)	46 (58,23 %)	56 (57,14 %)	59 (53,64 %)	70 (56,91 %)	82 (51,25 %)	62 (55,86 %)	82 (56,16 %)	92 (56,79 %)	93 (52,84 %)

Variables	Category/Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
	South	10 (17,24 %)	16 (20,51 %)	16 (20,25 %)	10 (10,2 %)	23 (20,91 %)	17 (13,82 %)	23 (14,38 %)	17 (15,32 %)	27 (18,49 %)	31 (19,14 %)	28 (15,91 %)
Federal unit (state)	AC	1 (1,72 %)	1 (1,28 %)	0 (0%)	0 (0%)	1 (0,91%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	AL	0 (0%)	0 (0%)	1 (1,27 %)	2 (2,04 %)	0 (0%)	0 (0%)	4 (2,5%)	1 (0,9%)	2 (1,37%)	1 (0,62%)	0 (0%)
	AM	1 (1,72 %)	1 (1,28 %)	2 (2,53 %)	0 (0%)	1 (0,91%)	1 (0,81%)	2 (1,25%)	1 (0,9%)	0 (0%)	2 (1,23%)	1 (0,57%)
	AP	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,81%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,57%)
	BA	0 (0%)	6 (7,69 %)	3 (3,8%)	6 (6,12 %)	6 (5,45%)	5 (4,07%)	4 (2,5%)	3 (2,7%)	3 (2,05%)	6 (3,7%)	7 (3,98%)
	CE	0 (0%)	3 (3,85 %)	2 (2,53 %)	6 (6,12 %)	5 (4,55%)	2 (1,63%)	9 (5,63%)	4 (3,6%)	5 (3,42%)	6 (3,7%)	6 (3,41%)
	DF	1 (1,72 %)	1 (1,28 %)	3 (3,8%)	2 (2,04 %)	2 (1,82%)	1 (0,81%)	3 (1,88%)	5 (4,5%)	3 (2,05%)	4 (2,47%)	8 (4,55%)
	ES	1 (1,72 %)	1 (1,28 %)	1 (1,27 %)	3 (3,06 %)	0 (0%)	2 (1,63%)	6 (3,75%)	4 (3,6%)	5 (3,42%)	5 (3,09%)	4 (2,27%)
	GO	1 (1,72 %)	0 (0%)	2 (2,53 %)	0 (0%)	3 (2,73%)	2 (1,63%)	3 (1,88%)	1 (0,9%)	4 (2,74%)	1 (0,62%)	2 (1,14%)
	MA	0 (0%)	0 (0%)	0 (0%)	2 (2,04 %)	0 (0%)	1 (0,81%)	0 (0%)	1 (0,9%)	2 (1,37%)	0 (0%)	3 (1,7%)
	MG	6 (10,34 %)	7 (8,97 %)	3 (3,8%)	9 (9,18 %)	7 (6,36%)	6 (4,88%)	6 (3,75%)	5 (4,5%)	13 (8,9%)	12 (7,41%)	13 (7,39%)
	MS	0 (0%)	0 (0%)	0 (0%)	1 (1,02 %)	0 (0%)	0 (0%)	0 (0%)	1 (0,9%)	0 (0%)	1 (0,62%)	2 (1,14%)
	MT	0 (0%)	1 (1,28 %)	0 (0%)	0 (0%)	0 (0%)	1 (0,81%)	1 (0,63%)	0 (0%)	1 (0,68%)	0 (0%)	0 (0%)
	PA	1 (1,72 %)	2 (2,56 %)	1 (1,27 %)	2 (2,04 %)	0 (0%)	5 (4,07%)	6 (3,75%)	2 (1,8%)	3 (2,05%)	3 (1,85%)	2 (1,14%)
	PB	3 (5,17 %)	3 (3,85 %)	0 (0%)	2 (2,04 %)	1 (0,91%)	6 (4,88%)	12 (7,5%)	5 (4,5%)	3 (2,05%)	1 (0,62%)	2 (1,14%)
	PE	3 (5,17 %)	3 (3,85 %)	2 (2,53 %)	7 (7,14 %)	6 (5,45%)	8 (6,5%)	8 (5%)	5 (4,5%)	10 (6,85%)	11 (6,79%)	17 (9,66%)
	PI	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,91%)	1 (0,81%)	0 (0%)	1 (0,9%)	0 (0%)	1 (0,62%)	1 (0,57%)
	PR	5 (8,62 %)	6 (7,69 %)	5 (6,33 %)	3 (3,06 %)	9 (8,18%)	7 (5,69%)	11 (6,88%)	8 (7,21%)	8 (5,48%)	14 (8,64%)	14 (7,95%)

Variables	Category/Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
	RJ	6 (10,34 %)	4 (5,13 %)	7 (8,86 %)	12 (12,24 %)	8 (7,27%)	19 (15,45 %)	8 (5%)	11 (9,91%)	15 (10,27 %)	22 (13,58 %)	22 (12,5%)
	RN	0 (0%)	0 (0%)	1 (1,27 %)	0 (0%)	2 (1,82%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,62%)	1 (0,57%)
	RO	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,63%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	RS	4 (6,9%)	9 (11,54 %)	11 (13,92 %)	4 (4,08 %)	9 (8,18%)	9 (7,32%)	11 (6,88%)	7 (6,31%)	11 (7,53%)	11 (6,79%)	6 (3,41%)
	SC	1 (1,72 %)	1 (1,28 %)	0 (0%)	3 (3,06 %)	5 (4,55%)	1 (0,81%)	1 (0,63%)	2 (1,8%)	8 (5,48%)	6 (3,7%)	8 (4,55%)
	SE	1 (1,72 %)	0 (0%)	0 (0%)	2 (2,04 %)	0 (0%)	2 (1,63%)	2 (1,25%)	1 (0,9%)	1 (0,68%)	0 (0%)	2 (1,14%)
	SP	23 (39,66 %)	29 (37,18 %)	35 (44,3 %)	32 (32,65 %)	44 (40%)	43 (34,96 %)	62 (38,75 %)	42 (37,84 %)	49 (33,56 %)	53 (32,72 %)	54 (30,68 %)
	TO	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,9%)	0 (0%)	1 (0,62%)	0 (0%)
	RR	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total		58 (100,0 0%)	78 (100,0 0%)	79 (100,0 0%)	98 (100,0 0%)	110 (100,0 0%)	123 (100,0 0%)	160 (100,0 0%)	111 (100,0 0%)	146 (100,0 0%)	162 (100,0 0%)	176 (100,0 0%)

Source: developed in-house

DISCUSSION

For a more comprehensive discussion and comparison with other studies dealing with similar data and objectives, an extensive literature review was carried out. However, no studies were found that used data from Brazil, and that were dedicated to this topic, which provides this work with a somewhat ‘pioneering’ and significant character in understanding the profile of research into rare diseases in the country.

A comparative analysis between the data from the study by Santoro et al. (2015) and the data collected in Brazil reveals a significant and evolving panorama in the field of rare diseases, highlighting both similarities and differences in research approaches between the European Union and Brazil. The study by Santoro et al. (2015) was based on a questionnaire applied to 220 rare disease registries (RDRs) active in Europe as part of the EPIRARE project, which aims to create consensus and synergies for the development of a European platform for rare disease registry. This study includes three main RDR

typologies: Public Health Registries, which focus on epidemiological research and surveillance; Clinical Research and Genetics Registries, which address the genotype-phenotype splendour; and Treatment Registries, dedicated to the evaluation and monitoring of therapeutic interventions. The analysis of the data found emphasised the importance of interoperability between RDRs, which is essential for optimising patient recruitment and treatment validation, as well as enabling more robust epidemiological estimates.

As seen in this work; data on research into rare diseases in Brazil, obtained between 2013 and 2023, shows a notable increase in the number of studies, from 58 in 2013 to 176 in 2023. This increase reflects a growing recognition of the importance of study into rare diseases, which affect between 7 and 13 million Brazilians. The approval of 87.26 per cent of the 1,491 studies detailed suggests a favourable environment for research, although a decline in the number of studies was observed during the critical phase of the COVID-19 pandemic, indicating that external factors can impact scientific production.

The predominance of single-centre studies (92.24%) and the low proportion of multicentre studies (7.76%) in Brazil indicates a significant opportunity to expand collaboration between institutions and diversify the types of research done. This reality contrasts with the diversity observed in European registries, which seek to integrate different profiles and informational requirements or needs. Furthermore, the majority of Brazilian studies are carried out at public institutions (67.87%), which may reflect a prioritisation of funding aimed at integrating data into broader health policies.

While the study by Santoro et al. (2015) provides an analytical framework for understanding RDRs in Europe, the Brazilian data reveals a rapidly evolving scenario with the potential to strengthen rare disease research. The interconnection between EU registries and Brazilian studies can promote fruitful collaborations, contributing to the development of new therapies and interventions that meet the differing needs of a diverse population affected by rare diseases.

Thus, the data shows weak points that need to be strengthened, such as the low proportion of multicentre studies (7.76%), which indicates a restriction in collaboration between institutions - that can limit the generalisability of the results and the scope of the proposed interventions; plus, the predominance of observational studies suggests a lack of more specific clinical trials - fundamental for validating new therapies and disciplines. The identification of research gaps and the predominance of observational studies in

Brazil also suggest the need for greater investment in clinical trials, in line with the search for harmonisation and data sharing by European facilities in general.

CONCLUSION

Research and development efforts into rare diseases, which are marginalised in terms of financial and technological incentives plus scientific research, are focused only on those that affect a considerable number of patients, resulting in the development and approval of orphan drugs to improve patients' quality of life and health. However, as well as covering a small fraction of the different types of rare diseases that exist, the cost limits their access to treatment (Rodriguez-Monguio; Spargo; Seoane-Vazquez, 2017).

The results of the survey on the profile of studies related to rare diseases in Brazil, covering the period 2013-2023, provided a substantial contribution to understanding and advancing this topic. The evidence that rare diseases significantly impact the quality of life of patients and their families emphasises the urgency of investing in research that not only deepens knowledge about these conditions, but also promotes the development of new technologies and effective treatments.

Analysing the data reveals an intrinsic visibility between the volume of studies carried out and the growing visibility of rare diseases in Brazil, the increase in the number of research studies over the years, culminating in a peak in 2023; which can possibly be interpreted as a reflection of the increase in public knowledge and\or interest, and government support, evidenced by the implementation of specific policies for these diseases. In addition, the data suggests that, despite the challenges posed by the interruption of study submissions during the novel coronavirus pandemic, the scientific community in rare diseases in Brazil is adapting and expanding, with positive post-pandemic indicators.

The integration of research and public policies can result in a virtuous cycle that not only improves knowledge about these diseases, but also fosters inclusion and support for patients, contributing to a more holistic and effective approach to the management of rare diseases.

In conclusion, the results of rare disease research in Brazil not only emphasise the importance of the topic, but also offer a clear path for the future. Although there are challenges to be faced, such as the need for increased collaboration and diversification of the types of studies done, an upward trajectory in rare disease research is an optimistic

sign. With the continued commitment of all those involved - government, research institutions, healthcare professionals and patient organisations - it is possible to transform the reality of millions of Brazilians affected by these conditions into something more favourable. The expectation that clinical research and public policies will align to provide better treatments and quality of life for patients with rare diseases is a goal that must be pursued with determination and innovation.

REFERENCES

BRASIL. Health ministry. Agência Nacional de Vigilância Sanitária. Brasília, DF, [2024]c. Available at: https://www.gov.br/anvisa/pt-br. Accessed on: 23 jul. 2024.

BRASIL. Health ministry. Brasília, DF, [2024]a. Available at: https://www.gov.br/saude/pt-br. Accessed on: 23 jul. 2024.

BRASIL. Health ministry. Composição: Atenção Especializada à Saúde: doenças raras. Brasília, DF, [2024]b. Available at: https://www.gov.br/saude/pt-br/composicao/saes/doencas-raras. Accessed on: 23 jul. 2024.

BRASIL. Health ministry. Conselho Nacional de Saúde. Comissão Nacional de Ética em Pesquisa. Brasília, DF, [2024]d. Available at: https://conselho.saude.gov.br/comissoes-cns/conep/. Accessed on: 23 jul. 2024.

BRASIL. Health ministry. Conselho Nacional de Saúde. **Resolução nº 466, de 12 de dezembro de 2012**. Brasília, DF, 2012. Available at: https://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf. Accessed on: 23 jul. 2024.

BRASIL. Health ministry. Secretaria de Atenção à Saúde. Departamento de Atenção Especializada e Temática. Coordenação Geral de Média e Alta Complexidade. **Diretrizes para Atenção Integral às Pessoas com Doenças Raras no Sistema Único de Saúde – SUS**: Portaria GM/MS nº 199 de 30/01/2014. Brasília, DF: Health ministry, 2014. 41 p.

BRASIL. Ministério da Saúde. Conselho Nacional de Saúde. **Plataforma Brasil**. Brasília, DF, 2023. Available at: https://conselho.saude.gov.br/plataforma-brasil-conep?view=default. Accessed on: 23 jul. 2024.

REDE NACIONAL DE DOENÇAS RARAS – RARAS. [*S. l.*], [2024]. Available at: https://raras.org.br/. Accessed on: 23 jul. 2024.

RODRIGUEZ-MONGUIO, R.; SPARGO, T.; SEOANE-VAZQUEZ, E. Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs? **Orphanet Journal of Rare Diseases**, [*s. l.*], v. 12, n. 1, p.1-8, 2017. DOI: https://doi.org/10.1186/s13023-016-0551-7. Available at: https://www.researchgate.net/publication/312106852_Ethical_Imperatives_of_Timely_Access_to_Orphan_Drugs_Is_Possible_to_Reconcile_Economic_Incentives_and_Patients'_Health_Needs. Accessed on: 23 jul. 2024.

SANTORO, M.; COI, A.; DI PAOLA, M. L.; BIANUCCI, A. M.; GAINOTTI, S.; MOLLO, E.; TARÚSCIO, D. de; VITTOZZI, L.; BIANCHI, F. Classificação e caracterização dos registros de doenças raras: uma mineração de dados Abordagem. **Genômica em Saúde Pública**, [s. l.], v. 18, p. 113-122, 2015. DOI: https://doi.org/10.1159/000369993.

THE R PROJECT FOR STATISTICAL COMPUTING. [*S. l.*], [2024]. Available at: https://www.r-project.org/. Accessed on: 23 jul. 2024.