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Post-trial access to drugs for rare diseases: an integrative review

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Abstract

This study is an integrative literature review to analyze the scientific production about post-trial drug access by participants of clinical trials for rare diseases. The search was carried out in the Virtual Health Library, Embase, PubMed, SciELO, Scopus and Web of Science databases, covering 21 studies. Two categories emerged from the analysis: clinical research with orphan drugs and market regulation; and access to orphan drugs: background, globalization and the right to health. The first analyzes issues related to the number of patients with rare diseases, the efficacy and safety of these studies and the cost and price of medications. The second addresses the historical background of post-trial access, the globalization of clinical trials and the difficulties to ensure the right to post-trial access to orphan drugs. Few articles addressed post-trial drug access by participants with rare diseases as a central issue, which points to the importance of further studies on this subject.

Keywords: Ethics, research. Rare diseases. Bioethics. Clinical trial.

Resumo

Acesso a medicamentos para doenças raras no pós-estudo: revisão integrativa

A fim de analisar a produção científica acerca do acesso a medicamentos no pós-estudo por participantes de ensaios clínicos com doenças raras, realizou-se revisão integrativa da literatura nas bases Biblioteca Virtual em Saúde, Embase, PubMed, SciELO, Scopus e Web of Science, abrangendo 21 estudos. No processo analítico, surgiram duas categorias: pesquisa clínica com drogas órfãs e regulação do mercado; e acesso a drogas órfãs: história, globalização e direito à saúde. A primeira analisa questões relativas à quantidade de pacientes com doenças raras, à eficácia e à segurança dessas pesquisas e aos custos e preços dos medicamentos. A segunda trata do panorama histórico do acesso pós-estudo, da globalização dos ensaios clínicos e das dificuldades para efetivar o direito ao acesso a drogas órfãs no pós-estudo. Poucos artigos abordaram o acesso ao medicamento no pós-estudo por participantes com doenças raras como questão central, o que aponta a importância de mais estudos sobre esse tema.

Palavras-chave: Ética em pesquisa. Doenças raras. Bioética. Ensaio clínico.

Resumen

Acceso a medicamentos para enfermedades raras en el posestudio: una revisión integradora

Se pretende analizar la producción científica sobre el acceso a medicamentos para enfermedades raras en el posestudio a partir de una revisión integradora en las bases de datos Biblioteca Virtual en Salud, Embase, PubMed, SciELO, Scopus y Web of Science, que encontraron 21 estudios. Surgieron dos categorías en el análisis: investigación clínica con medicamentos huérfanos y regulación del mercado; y acceso a medicamentos huérfanos: historia, globalización y derecho a la salud. La primera examina el número de pacientes con enfermedades raras, la eficacia y seguridad de los estudios, así como los costes y precios de los medicamentos. La segunda aborda el panorama histórico del acceso posestudio, la globalización de los ensayos clínicos y las dificultades para materializar el derecho al acceso a medicamentos huérfanos en el posestudio. Pocos estudios plantean el acceso a estos medicamentos en el posestudio, y son necesarios más estudios sobre el tema.

Palabras clave: Ética en investigación. Enfermedades raras. Bioética. Ensayo clínico.

The authors declare no conflict of interest.

Research

Rare diseases affect a significant percentage of the population, which reveals an important health issue regarding the availability of treatment and the ethical aspects related to research and the need for public policies for these individuals [1-3]. Also known as orphan diseases, such pathologies mainly affect children. Diseases that affect 65 people per 100,000 [4-6] are classified as rare. When they affect one patient in every 50,000 people, they are defined as very rare, ultra-rare or super-rare [7].

There is no consensus on the number of rare and ultra-rare diseases [8]. However, it is estimated at around 8 thousand, accounting for a quarter of all known diseases worldwide. Most of these pathologies have a genetic origin, unlike others such as cancer and infectious, toxic and chronic diseases. Global infant mortality among people with rare diseases reaches 30%. This percentage is greater in peripheral countries such as Brazil, where diagnosis and access to experimental clinical research and to potential therapies from this process are deficient [8].

By its nature, an experimental clinical trial is not the same as a treatment and, in the case of rare diseases, the search for therapies and the belief in a cure can lead to therapeutic mistakes. In this sense, normative standards for research ethics in clinical trials of this type must be transparent and based on documents that regulate and guide research governance [9].

The process of searching for so-called orphan drugs consists of clinical trials aimed at developing safe therapies for such pathologies [10]. The development of these drugs is beneficial to the area of unmet needs; however, the pharmaceutical industry has little interest in developing and marketing them [11]. In addition, this process must be based on internationally established ethical foundations so that the design and practice of research are fair, especially in relation to drug supply [12,13].

The guarantee of access to beneficial interventions by participants of a clinical trial after its completion is called *post-trial access* [14]. This principle appears internationally from the year 2000, in the *Declaration of Helsinki* (DH) of the World Medical Association (WMA) [15], a guiding framework for Brazilian ethical standards, which aim to ensure the rights of research participants in relation to scientific objectives, during or after the clinical trial [16]. However, the latest version of DH, dated 2013, has not been applied to research in Brazil and the country's current official documents do not mention it for disagreeing with its positions regarding the use of placebos and post-trial access.

In this context, the Brazilian National Research Ethics Committee/Research Ethics Committees (CEP/Conep) system is responsible for evaluating human research ethics in Brazil and has advanced the defense of the rights of Brazilian research participants, especially for being part of the social control framework of the Unified Health System (SUS) [17].

The standard that broadly covers the issue of post-trial access is Resolution 466/2012 of the National Health Council (CNS), which approves guidelines and regulatory standards for research with humans. In Item III.3, this resolution provides that research with humans should:

d) ensure that when the study is over, the sponsor grants all participants free and indefinite access to the best prophylactic, diagnostic and therapeutic methods that have proven to be effective;
d.1) access will also be guaranteed in the interval between the end of individual participation and the end of the study, in which case said guarantee may be given through an extension study, according to a duly justified analysis of the participant's attending physician [18].

Conep's resolutions on research ethics also apply to rare diseases, and the resolutions of the Collegiate Board (RDC) of the National Health Surveillance Agency (Anvisa) regulate the availability of drugs for people with rare diseases that have not yet been approved to be marketed in Brazil. For example, RDC 38/2013[19] addresses expanded access, compassionate drug use and post-trial access in general, and is not specific to rare diseases. This resolution was amended in October 2019 by RDC 311/2019 [20], which refers the issue of the provision of post-trial drugs to Conep resolutions.

CNS Resolution 563/2017 [21], in turn, specifically addresses post-trial access to drugs for ultra-rare diseases, that is, it does not apply to rare diseases. With this resolution, mandatory post-trial access, previously unrestricted, indefinite and the exclusive responsibility of the industry, is now restricted to five years, counted from the definition of the price in reais by the Drug Market Regulation Chamber (CMED).

Currently, Bill 200/2015 [22], which has been approved by the Federal Senate and is being debated as Bill 7082/2017 [23] in the Chamber of Deputies, calls into question the protection of research participants in Brazil by proposing new resolutions for Brazilian research from an ethical-normative point of view, posing a threat to the right to post-trial access [24].

The production of drugs for rare diseases must be seen as a government issue to avoid the imposition of a capitalist and market-oriented view. Faced with the specificities of rare and ultra-rare diseases, added to the forces that tend to minimize the role of the state and maximize the health market, the market for limited use drugs presents ethical conflicts that evidence the collapse of public interests in relation to private ones.

This article analyzes the scientific production on access to post-trial drugs by participants in clinical trials for rare diseases.

Method

The integrative review [25-32] consisted of six steps:

1. Identification of the problem;
2. Sample selection;
3. Categorization of selected studies;
4. Critical analysis of the studies included in the review;
5. Description of results;
6. Interpretation and discussion of results in order to gather and synthesize existing knowledge on the subject [31].

The guiding question of the study was: "What ethical issues are found in the literature on access to pharmacotherapy by participants in clinical trials for rare diseases?" To answer it, a bibliographic search was carried out in the following databases: Virtual Health Library (VHL), Embase, PubMed, SciELO, Scopus and Web of Science. The search was adapted to the specificities of each database, leading to the development of thematic blocks associated with Boolean operators:

- Thematic block 1: "*doenças raras*," "rare diseases," "orphan diseases."
- Thematic block 2: "*ética*," "ethics," "*bioética*," "bioethics," "*pesquisa ética*," "ethical research."
- Thematic block 3: "*acesso ao pós-estudo*," "post-trial access," "access to post-clinical trial," "post-trial responsibilities," "post-trial obligation," "access to pharmaceuticals," "access to medicines and health technologies," "access to essential drugs and health technologies."

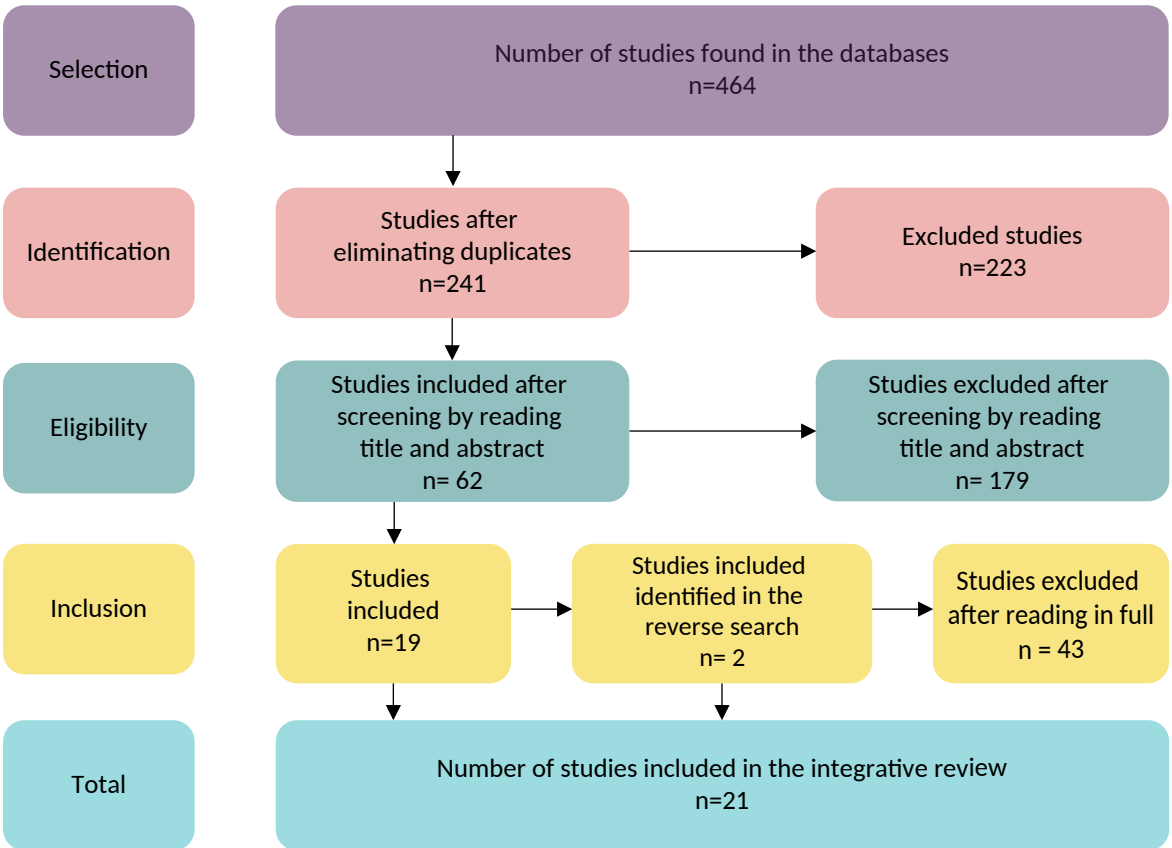
A reverse exploratory search was carried out based on studies found during the initial search process.

The inclusion criteria were studies published as scientific papers (original or review), in any language, between 2000 and 2020. Theses, dissertations, essays, reviews, books or abstracts of proceedings of scientific events were excluded, in addition to works published outside the established time frame.

Clarivate Analytics' EndNote X8 software was used as an auxiliary tool to build databases and select papers. Subsequently, the chosen studies were analyzed and identified, as shown in the flowchart (Figure 1) of the data collection process according to the PRISMA method [33]. The search for papers was carried out between September and October 2020.

In the initial step, the data were systematized into two categories determined a posteriori. In the final step, the data were discussed by grouping criteria, compiling information and important trends to address the theme.

Figure 1. Flowchart of the study selection steps of the integrative review (2021)



Results

The search in the databases resulted initially in 464 studies, of which 241 remained after the exclusion of duplicates. Following the screening of keywords, title and abstract, 179 did not fit the theme, leading to a total of 62, which were read in full, resulting in 19 studies, to which were added two works in the reverse search. The final sample consisted of 21 studies, according to the proposed selection criteria (chart 1).

Chart 1. Selected studies according to authors, year, country of origin, language, journal and database

Authors	no.	Year	Country/origin	Language	Journal/origin	Database
Annemans, Makady; 2020 [12]	1	2020	Belgium	English	*Orphanet Journal of Rare Diseases*	Scopus
Blin and collaborators; 2020 [34]	2	2020	France	English	*Therapies*	Embase, PubMed, Scopus, Web of Science
Bouwman, Sousa, Pina; 2020 [11]	3	2020	Portugal	English	*Health Policy and Technology*	Embase, Scopus, Web of Science
Dal-Ré and collaborators; 2020 [35]	4	2020	Spain	Spanish	*Anales de Pediatria*	PubMed, Scopus
Naud; 2019 [16]	5	2019	Brazil	Portuguese	*Revista Brasileira de Bioética*	Reverse search

continues...

Chart 1. Continuation

Authors	no.	Year	Country/origin	Language	Journal/origin	Database
Gelinas and collaborators; 2019 [36]	6	2019	USA	English	*Contemporary Clinical Trials*	Scopus
Saviano and collaborators; 2019 [37]	7	2019	Italy	English	*Sustainability*	Web of Science
Chaves Restrepo and collaborators; 2018 [38]	8	2018	Colombia	English	*Value in Health*	Embase
Pace and collaborators; 2018 [39]	9	2018	Australia	English	*Health Policy*	Scopus, Web of Science
van Egmond-Fröhlich, Schmitt; 2018 [40]	10	2018	Austria	German	*Monatsschrift Kinderheilkunde*	Embase, Scopus, Web of Science
Hasford, Koch; 2017 [1]	11	2017	Germany	German	*Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*	VHL, PubMed, Scopus, Web of Science
Rodriguez-Monguio, Spargo, Seoane-Vazquez; 2017 [41]	12	2017	USA	English	*Orphanet Journal of Rare Diseases*	VHL, PubMed, Scopus, Web of Science
Mastroleo; 2016 [42]	13	2016	Argentina	English	*Developing World Bioethics*	VHL, Scopus
Dallari; 2015 [43]	14	2015	Brazil	Portuguese	*Revista Bioética*	SciELO
Silva, Sousa; 2015 [7]	15	2015	Brazil	Portuguese	*Caderno de Saúde Pública*	VHL, SciELO
Rhee; 2015 [44]	16	2015	USA	English	*Ama Journal of Ethics*	VHL, Scopus
Rosselli, Rueda, Solano; 2012 [45]	17	2012	Colombia	English	*Journal of Medical Ethics*	Web of Science
Dainesi, Goldbaum; 2011 [46]	18	2011	Brazil	Portuguese	*Revista da Associação Médica Brasileira*	Reverse search
Barrera, Galindo; 2010 [47]	19	2010	Colombia	English	*Advances in Experimental Medicine and Biology*	VHL, PubMed, Scopus, Web of Science
Boy, Schramm; 2009 [48]	20	2009	Brazil	Portuguese	*Caderno de Saúde Pública*	VHL
Grady; 2005 [49]	21	2005	USA	English	*Yale Journal of Health Policy, Law, and Ethics*	VHL, PubMed, Scopus, Web of Science

VHL: Virtual Health Library; USA: United States of America

Bibliometric data indicate the number of studies published each year: four studies (19.1%) in 2020; three studies (14.3%) per year in 2019, 2018 and 2015; two studies (9.4%) in 2017; one study (4.8%) in 2016; one study per year in 2012, 2011, 2010, 2009 and 2005, totaling five studies (23.8%).

Regarding the origin of the studies and respective authors, Brazil has five (23.8%); United States, four (19.0%); Colombia, three (14.3%); and Germany, Austria, Argentina, Australia, Belgium, Spain, France, Italy and Portugal, one study each, totaling nine (42.9%). Regarding the language of publication, 13 studies (61.9%) are in English, five are in Portuguese (23%), two are in German (9.5%) and one is in Spanish (4.8%).

Based on content analysis, the studies were grouped into two categories:

a. Clinical research with orphan drugs and financial market regulation;

b. Access to orphan drugs: background, globalization and the right to health, comprising different themes (Chart 2).

Chart 2. Categories, emerging themes and descriptions identified in the articles on rare diseases (2021)

Clinical research with orphan drugs and market regulation	
Emerging theme	**Description**
Population of patients with rare diseases	Small size of patient population; characteristics of manifestation and geopolitical distribution of rare diseases converge on the problem of patient enrollment in clinical trials (Annemans, Makady; 2020 [12]; Barrera, Galindo; 2010 [47]; Dallari; 2015 [43]; Hasford, Koch; 2017 [1]; Rhee; 2015 [44]; Rodriguez-Monguio, Spargo, Seoane-Vazquez; 2017 [41]; Rosselli, Rueda, Solano; 2012 [45]).
Efficacy and safety	Compliance with efficacy and safety requirements in clinical research of drugs for rare diseases (Annemans, Makady; 2020 [12]; Barrera, Galindo; 2010 [47]; Chaves and collaborators; 2018 [38]; Hasford, Koch; 2017 [1]; Pace and collaborators; 2018 [39]).
Cost and price	The high cost of the development and post-marketing of drugs for rare diseases poses obstacles to access by the target population, revealing the industry's efforts to recover development costs, use of funding and judicialization to ensure access (Barrera, Galindo; 2010 [47]; Blin and collaborators; 2020 [34]; Boy, Schramm; 2009 [48]; Dal-Ré and collaborators; 2020 [35]; Rosselli, Rueda, Solano; 2012 [45]; Saviano and collaborators; 2019 [37]; van Egmond-Fröhlich, Schmitt; 2018 [40]).
Market regulation	The regulatory process for orphan drugs is carried out by regulatory bodies in each country, sometimes influenced by patient organizations, but market monopoly and price elasticity reveal regulatory flaws that reduce access and favor profit. (Bouwman, Sousa, Pina; 2020 [11]; Dallari; 2015 [43]; Rhee; 2015 [44]; Saviano and collaborators; 2019 [37]; van Egmond-Fröhlich, Schmitt; 2018 [40]).
Access to orphan drugs: background, globalization and the right to health	
Emerging themes	**Description**
Historical background	International and national documents/standards disseminate post-trial provision of beneficial orphan drugs (Dainesi, Goldbaum; 2011 [46]; Dallari; 2015 [43]; Gelinas and collaborators; 2019 [36]; Grady; 2005 [49]; Mastroleo; 2016 [42]; Naud; 2019 [16]; Silva, Sousa; 2015 [7]).
Globalization of clinical trials	Contemporary evolution of clinical trials through post-trial access to orphan drugs (Boy, Schramm; 2009 [48]; Dainesi, Goldbaum; 2011 [46]; Grady; 2005 [49]; Mastroleo; 2016 [42]; Rosselli, Rueda, Solano; 2012 [45]; Silva, Sousa; 2015 [7]).
Right to health	Post-trial provision of orphan drugs as a right to health (Dallari; 2015 [43]; Rodriguez-Monguio, Spargo, Seoane-Vazquez; 2017 [41]).

Discussion

Clinical research with orphan drugs

The themes related to the development of orphan drugs in clinical trials were addressed by 17 papers. The authors comprehensively report how the prevalence of rare diseases, which is lower than those of other diseases, becomes representative when they are grouped. The low prevalence justifies the difficulty of recruiting participants, spread around the world, and reveals problems in quantifying the size of the population and ensuring fair and equitable participation in research [1,12,41,43-45,47].

Annemans and Makady [12] argue that the incidence and prevalence of rare diseases can be seen as a set of uncertainties, since the exact size of the affected population, the characteristics of the subpopulations and the clinical manifestations of the diseases are variable. Rodriguez-Monguio, Spargo and Seoane-Vasquez [41] show that as there is no consensus on the size of the population of patients with rare diseases, practical intervention on this dimension is necessary.

The authors also cross population growth with the growth of the identification of new rare diseases [41]. The prevalence of the disease as a promoter of the clinical development of orphan drugs is problematized, since it conflicts with the concept of justice, as populations usually tend to grow, which, in percentage terms, would reduce and exclude people with rare diseases over time [41].

The scant and dispersed distribution of rare diseases in the population makes it difficult to recruit for clinical trials (particularly in phases I, II and III) the number of participants required for the approval of any drug, including orphan drugs. The authors also define this population as vulnerable and unprotected when it comes to access in peripheral countries [47,48].

Accessible participation in clinical trials of drugs for patients with rare diseases requires relevant policies and reflection, mainly from the population point of view, to provide justice and equity [49]. In this sense, Silva, Ventura and Castro [50] discuss equal opportunities in the use of healthcare services and access to clinical trials for orphan drugs. This shows that the distribution of such opportunities is hindered by obstacles related to geographic location and eligibility criteria for study participants, with exclusions of population groups in clinical trials and consequent loss of benefit.

In Brazil, Bill 231/2012 [51] provided the creation of the National Research Fund for Rare and Neglected Diseases (FNPDRN), reserving 30% of funds from the Health Research Promotion Program, an important initiative to fight inequalities in research fostered by the development of drugs, vaccines and therapies for rare diseases. However, the bill was vetoed in its entirety by President Jair Bolsonaro in 2019 for allegedly compromising the feasibility of said program and reducing private interest in the matter [52].

When the principle of justice is absent in clinical trials for rare diseases, the consequence is poor access to health care, as equitable distribution is affected by several issues, such as disease prevalence, population size and characteristics, and research inclusion criteria [1,12,41,43-45,47].

Seeking distributive justice in the case of rare diseases means questioning the rules and format with which this distribution is done according to the characteristics of the population. For Boy and Schramm [48], access to clinical research and drugs to treat rare diseases in peripheral countries, places with blatant social asymmetries and inequalities, affects the vulnerable population harshly. Those authors advocate the need for legitimate public policies based on the principle of equity, guaranteeing formal equality.

In general, the articles analyzed argue that the ethical standards that guide the requirements of efficacy and safety in the development of clinical research and production of drugs for rare diseases must be respected [1,34,39,47]. Ethical standards of information, consent and conduct of studies must be followed regardless of disease frequency [1].

Barrera and Galindo [47] add that research on drugs for rare diseases must also strictly comply with the requirements of efficacy and safety, ideally at the lowest possible cost, as these drugs will be used in highly vulnerable and unprotected people. Treatment effect and durability must also be provided, based on confidence interval, group heterogeneity, dosage and adverse events [12].

However, Blin and collaborators state that *some clinical trials that may not be ethical for frequent diseases may be acceptable for rare diseases* [statement regarding lack of power due to small number of available patients and heterogeneity, short trials that do not address the most relevant clinical outcome and early use of biomarkers before their qualification...]. *Otherwise, there is a risk that new drugs will never be developed for complicated rare diseases and that efforts will be concentrated on relatively frequent diseases with a well-known and controllable development pipeline* [53].

This shows the need to criticize the defense of easing of post-trial access, as it is essential to strengthen the perspective of the right to access as a right to health. This view is adopted by Pace and collaborators [39] when they address the ethical framework for the creation, governance and evaluation of accelerated access programs, presenting an overview of the case of rare diseases. Accelerating the process of obtaining orphan drugs, the authors argue, may have built-in risks, whether physical (resulting from adverse drug effects) or psychological [39].

In turn, Hasford and Koch [1] stress that methodological limits in clinical research exist regardless of whether it relates to rare or frequent diseases and must be respected, showing the importance of planning the study in the best way possible so as to minimize harm.

Hasford and Koch [1] argue that an important aspect in ethical evaluation in clinical trials for rare diseases is the biometric quality of the study's design, size, sample and statistical analysis,

as weak methodologies proposed in clinical trials with humans are considered unethical. Therefore, there is a need to ensure methodological criteria based on ethical standards that certify the efficacy and safety of clinical trials in the development of these drugs.

Several studies focus on such efficacy and safety. Most argue that the research method should be guided by ethical rigor. However, some authors suggest that, on the other hand, ethical rigor may limit clinical research, due to the very heterogeneity of diseases [34]. Such rigor must ensure compliance with the requirements of efficacy and safety in planned trials for common diseases and, especially, the safety of participants and respect for human rights. Malleability and acceleration in the rare disease research process put participants at risk.

For Blin and collaborators [34], clinical trials are intervention studies that aim to analyze and evaluate one or more drugs in order to intervene in the progression of a rare disease or a group of them, implying high economic costs. The guarantee of access to participation in clinical studies and the benefits arising from them may be jeopardized by commercial clinical research, and it is up to research ethics and public health policies to problematize this issue [34,35,37,40,43,45,47,48].

The high prices of orphan drugs may reflect the need to recover development costs with a small group of patients [34]. However, Saviano and collaborators [37] question whether those prices fairly reflect the costs incurred in development or are aimed at generating profit. The fact is that all clinical research is costly, which, in the case of rare diseases, gives rise to an unregulated market [40].

In addition to the possible benefits, some authors reflect on how patients have access to multicenter clinical trials and orphan drugs [35,48] (the debate on the responsibility for guaranteeing the provision of the post-study drug will be addressed in the second section of this paper). Thus, mechanisms such as funding and judicialization are mentioned. The development of clinical trials for rare diseases may be thwarted by lack of funding, although there are alternatives.

Dal-Ré and collaborators [35] describe how patients occasionally finance clinical trials through crowdfunding. This mechanism has been used in the United States for about 40 years and raises ethical questions, mainly because it prioritizes the research needs of wealthy people rather than society as a whole. Self-financing is also advocated as long as ethical research requirements are met [35].

Boy and Schramm [48] address the search for access to orphan drugs in developing countries and use the example of Brazil, where many drugs already approved in the European Union, United States, Australia and Asian countries are not on the Ministry of Health's list of exceptional drugs, with provision depending on judicialization. The literature also stresses that access via judicialization to drugs in experimental or non-approved phases may pose risks to patients [54].

Although it can ensure fair access to drugs by patients, judicialization implies costly and ethically questionable public spending, especially in countries with scarce public resources for health. The regulatory process for the production, development and control of orphan drugs is usually done by competent bodies, such as the Food and Drugs Administration (FDA) in the United States, the European Medicines Agency (EMA) in Europe and Anvisa in Brazil. Despite the extensive regulatory process required by these bodies, Rhee [44] states that many orphan drugs are currently available but not always accessible due to their high cost.

The author points out that the lack of market regulation raises concerns about pharmaceutical companies creating a monopoly that prevents buyers from negotiating prices [44]. The combination of monopoly and price elasticity results from faulty market regulation, with drug producers setting profitable prices under pressure from investors.

The search for profit is evident in the behavior of drug producers, showing that the economic risk assumed, given the relatively small market for orphan drugs, can be offset by financial incentives (flexibilization, tax credits and patents), which is observed especially in developed countries, as stated by Dallari [43].

Patient organizations, such as the European Organization for Rare Diseases (Eurordis) in Europe and the National Organization for Rare Disorders (Nord) in the United States, play important roles in the field of rare diseases, mainly by encouraging the development of research and

providing funding [11]. In addition, they work to raise public awareness, collecting information, providing support and information to those affected, keeping patient records and networking with universities, industry and health authorities. The analyzed authors also emphasize that patient organizations can influence standards and the problematization of market monopoly [11].

Access to orphan drugs

The theme related to the provision of post-trial orphan drugs was addressed in nine articles. The authors reported that ethical aspects related to research with humans are historically governed by several documents.

Each author provides a documentary historical background of corrections and incorporations of guiding ethical principles, identifying DH, the *Belmont Report*, the *International Ethical Guidelines for Biomedical Research Involving Humans Subjects*, of the World Health Organization (WHO), the *Universal Declaration on Bioethics and Human Rights* (UDBDH) and the *International Declaration on Human Genetic Data* [7,16,36,42,43,46,49] as the main documents in guiding ethical research with humans. DH and DUBDH are highlighted as regulations that address access to post-trial drugs.

HD is recognized worldwide as a benchmark for ethical research [46]. Silva and Sousa [7] explain that access to post-trial technologies by research participants has been problematized since 2000. The authors reveal that DH incorporated the principle of post-trial access in clinical research in the 2000s—in its fifth revision—and that such endorsement produced differing interpretations. Therefore, WMA issued a clarification in 2004, triggering the debate on post-trial access in interventions that proved to be beneficial [7,16,36,42,43,46,49].

The latest version of DH [55], revised in 2013, concisely addresses this principle, explaining in Article 34 the need for provisions, agreed between sponsors, researchers and governments of the host countries of the clinical research, for post-trial access to all participants who still need intervention identified as beneficial in the study. DH recommends that relevant information during the informed consent process and the study outcomes be disclosed to the participants in the consent form [43].

Mastroleo [42] argues that the 2013 revision of DH abandons the ambiguous language found in previous versions and identifies the responsible agents. However, the author criticizes the removal of references to access to appropriate care other than drug-related and to obligatory access to post-trial information [42].

In Brazil, the evolution of regulations on post-trial access began with CNS Resolution 196/1996 [17], complemented by CNS Resolution 251/1997 [56], which specifically addresses research for new drugs, vaccines and diagnostic tests.

The Brazilian ethical regulation that addresses the principle of post-trial access currently in force is Resolution CNS 466/2012 [18], which regulates ethics in clinical research, protects research participants and defines post-trial access as a sponsor's duty [17,18,56]. The National Policy for Comprehensive Care for People with Rare Diseases was only implemented in 2014 by Ordinance 199/2014 [4], expanding previous restrictive conduct with a predominant focus on medicine.

Grady [49] and Dainesi and Goldbaum [46] consider the issue of the principle of post-trial access a challenge, revealing that it has been a subject of discussion since the late 1980s, when it was associated with the continuity of treatment of participants in HIV/AIDS studies. Other articles also address the development of antiretrovirals [57-63]. International and national regulations reveal an extensive debate on the incorporation of the principle of post-trial access.

Naud [16] addresses the complexity of this debate, revealing that regulations are not capable of covering all types of diseases. The author also points to the fact that all research must have its own evaluation, based on the singularities of each disease, population and their needs [16]. The position defended by Naud [16] is considered to relate to the "easing" of ethical research standards based on those singularities.

Dainesi and Goldbaum [46] view the dissemination of the principle of post-trial access as a contemporary concern, especially in the context of other illnesses. It is noted that the organization of HIV patients played a role in inducing this principle, which gained

momentum when it was inserted in HD in 2000. In the case of the provision of orphan drugs to participants with rare diseases, usually chronic and progressive, the challenges relate to a specific context that hinders access to medicines.

Different authors address the effect of globalization on the expansion of clinical research [42,46,49]. For Dainesi and Goldbaum [46], globalization raises new questions in the scientific community and the principle of post-trial access emerges as a demand in this period. Similarly, Mastroleo [42] states that providing the transition of research participants to appropriate health care when the study ends is a global problem. Thus, continuity of medical care, including treatment, is based on an ethical responsibility to compensate volunteering participants who subjected themselves to clinical research biases [46].

Before the 1980s, development of drugs for rare diseases was insufficient and focused on palliative measures that aimed to circumvent the seriousness of those diseases [7]. At that time, initial concerns emerged about methodological, regulatory and ethical aspects in the development and production of orphan drugs. Reflecting on the healthcare aspect of post-trial access in that period was remarkably hypothetical.

The scientific development that enabled the creation of enzyme and gene therapies, which are the basis of most drugs for rare diseases, was boosted after the 1980s. Boy and Schramm [48] point to a contemporary evolution of clinical trials based on biotechnical, scientific progress, which can be seen in current pharmaceutical research of drugs for rare diseases.

The authors also state that the global insertion of orphan drugs occurred progressively, with developed countries as pioneers, and explain that drugs are currently being developed for patients with rare diseases, but with a focus on economic aspects. The rarity of the disease and the prevalence in peripheral countries slow down development for purely profitable reasons [48].

Dainesi and Goldbaum [46] reveal that clinical trials of rare diseases and treatment with orphan drugs after the conclusion of a research require attention particularly in developing countries, where participants are more vulnerable. This ethical issue relates to social conditions that interfere with the autonomy of the investigated subjects, putting their interests at risk.

Rosselli, Rueda and Solano [45] analyze the situation of social vulnerability in developing countries in research on mucopolysaccharidosis VI. This rare disease affects indigenous ethnic groups in Colombia, where access to developed drugs is compromised by geographic marginalization and frequent institutional distrust.

Dallari [43] mentions that the need to provide ethical protection in developing countries must go beyond research participants to benefit the community. Dainesi and Goldbaum [46] state that adequately designed and conducted clinical research, with methodologies that comply with maximum ethical rigor, must be extended to the entire community.

Mastroleo [42] stresses that access to post-trial orphan drugs is not just a problem for countries with few or average resources. The author highlights cases of uninsured or underinsured research participants in the United States and of former participants of clinical trials in the United Kingdom whose therapy was not provided by the United Kingdom National Health Service (NHS) [42].

In a 2003 editorial, the scientific journal *The Lancet* [64] states that participants from wealthy nations are usually able to obtain the best available treatment at the end of a clinical trial, while in the developing world researchers leave the respective countries where the research was conducted and the participants may be left with nothing. It adds that the obligation to provide post-trial access is closely linked to the vulnerability of the participants.

In analyzing the distributive justice of post-trial drugs in Brazil, Deucher [65] observed, based on a qualitative and exploratory study, that patients with serious and life-threatening diseases do not suffer negligence in access to post-trial drugs. The author also highlighted that foreign pharmaceutical companies without national representation have difficulty understanding the need to provide post-trial drugs.

Therefore, it is perhaps appropriate to reflect that pharmaceutical multinationals and conglomerates choose to ignore the problems of countries with few resources, especially in terms of social vulnerability. Dallari [43] argues that the world community must remain committed

to providing access to necessary health care and treatment, especially post-trial access.

The globalization of clinical trials for rare diseases is currently growing and sheds light on ethical issues that guide post-trial access to orphan drugs, both in peripheral and rich countries. It is noted that the outsourcing of clinical trials to peripheral countries is marked by economic issues that often hinder the right of access to post-trial drugs by research participants who need them. In this context, the right to health supports the fundamental guarantee of post-trial access to orphan drugs [41,43].

Dallari [43] analyzes the ethical conflict involved in post-trial access and in rare diseases, showing that essential products, such as orphan drugs, cannot be viewed solely from the point of view of health, as they are associated with predominant social, economic and technological factors.

The constitutional law of Western countries often includes the right to life as one of its basic moral principles. Based on that and on DUBDH, Rodriguez-Monguio, Spargo and Seoane-Vasquez [41] proposed that the above-stated principle can be understood as a right to health when related to the use of orphan drugs in the treatment of potentially fatal diseases. That makes it possible to analyze the right of access to orphan drugs as part of the right to health.

Thus, the state fulfills its constitutional duty to protect the right to health when it regulates clinical research, creating duties between sponsors and researchers and thereby protecting participants entering in an asymmetrical relationship of information and power that subjects them to high risk. It is in this perspective that the obligation to ensure post-trial access must be understood, a condition that must be guaranteed by the state within the scope of its duty to protect, and not as a means of exempting itself from the duty to provide. Access to post-trial orphan drugs is considered a right of access to medicine, regardless of how that access is made possible.

Final considerations

During the process of reading and composing the categories resulting from the bibliographic survey, issues emerged that address not only post-trial access to drugs by participants affected by rare diseases, but also questions about clinical research with orphan drugs. Although this theme, configured in the first category, does not directly address the main theme of the research, it is nevertheless relevant to a comprehensive understanding of post-trial access to orphan drugs.

The reduced size of the population of patients with rare diseases is a factor that narrows down the discussion of post-trial drug access, given that the production of orphan drugs is basically market-oriented rather than guided by the health needs of that population. The geopolitical distribution of these diseases also encourages discussion about the issue of enrolling in clinical trials and increases global asymmetries. The high costs of the production of orphan drugs and their reduced and unregulated market are obstacles to guaranteeing post-trial access and favorable to industry profits.

Although this is a relatively recent issue, different regulations address in different ways specific questions about the principle of post-trial access by participants in research with rare diseases, and there is no international consensus on the provision of orphan drugs to patients who need them. Furthermore, it was observed that the globalization of clinical trials is due to commercial interests, especially to lower the costs of drug development. This economic factor is another barrier to post-trial access to orphan drugs.

Lastly, the authors address the right to health and the right to life as principles that guide and defend the right to post-trial access. In Brazil, post-trial access to researched products is ensured by ethical regulations in unequivocal and non-negotiable terms. In times of budget cuts in the health area, the only sure way to guarantee this right to Brazilian citizens with rare diseases who are volunteers in clinical research is to ensure that the sponsor continues providing them with the medication that benefits them for as long as needed.

Discussions on research ethics from the perspective of social justice contribute to ensure the right to post-trial drug access, insofar as they highlight the need for public policy in this regard. It is therefore essential to reflect and take a stand against threats that may place that right in jeopardy.

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