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Transforming uncertainties into legitimate regulation? NICE and CONITEC agencies' decisions on rare diseases

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Abstract *As a scientific and technological practice, the evaluation of health technologies (HTA) is, at the same time, a challenge to determine the value of the technologies to be incorporated. This study aimed to explore and compare the results and technical elements of the evaluations issued for rare diseases between the English (NICE) and the Brazilian agency (CONITEC). The first part of the study involved the systematic search for evaluations from 2013 to 2019. In the second stage, the reports were analyzed based on: (i) descriptive narrative review; and (ii) calculation of the absolute and relative frequency according to each domain and component (element) applied in the European HTA network model. Twenty-four medicines were distinctly assessed during the study period. Through 126 questions (elements) distributed among nine domains, the analysis revealed that 67 (53.2%) and 44 (35.0%) were described in the reports, 42 (33.3%) and 59 (47.0 %) were only considered partially, and 17 (13.5%) and 23 (18.0%) were not considered in the NICE and CONITEC reports, respectively. We identified a relatively low agreement between the Brazilian agency with the English agency in the reports issued for rare diseases. It remains to be seen whether the agencies are able to capture the various values of these medicines, as well as manage uncertainties in the evaluations.*

Key words *Health technology assessment, Rare diseases, Government regulation, Uncertainty*

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Introduction

In universal health systems, such as Brazil and England, the institutionalization of health technology assessment (HTA) is a historic landmark[1]. Conceptually, HTA is a multidisciplinary process that uses explicit methods to determine the value of health technology at different points in its life cycle, thus seeking to guide decision-making to promote an equitable, efficient, and high quality[2].

In England, the development of HTA dates back to the 1990s, creating an evidence-based level of assessment (analyzed in terms of cost per quality-adjusted life years (QALY))[3]. This change provided a transparent reform in the English healthcare system, emphasizing transparency and public involvement in the decisions introduced and programmed by establishing the National Institute of Health and Care Excellence (NICE) (a globally recognized HTA agency)[4,5]. Currently, the agency has a significant role in cost-effective drug evaluation for use in the National Health Service (NHS), particularly where there is a significant impact on resource allocation[5].

In Brazil, the National Commission for the Incorporation of Technologies in the Unified Health System (CONITEC) was established in 2011, given the need for an efficient allocation of resources with explicit criteria for incorporating technologies. This body acts as an advisor to the Brazilian Ministry of Health, providing recommendations to public managers for decisions regarding the incorporation, exclusion, or change of new medicines, products, and procedures, and the preparation and review of Clinical Protocols and Therapeutic Guidelines (PCDT)[6]. CONITEC still has some distinctions despite showing many similarities with other regulatory agencies. Among them is the authority in decision-making, the scope of the evidence used, and the lack of the production of a previous stage of selection or prioritization of topics to be analyzed[1].

Due to the multidimensional nature of the evaluation processes and the high involvement of stakeholders (namely health care providers, funding agencies, industry, patients, and health policymakers), the evaluation of incorporation of new treatments has become highly technical, political, and socially complex process. Many agencies, such as NICE, have struggled to keep their legitimacy[7,8]. On some occasions, decision-making has explicitly or implicitly considered the pressures of specific groups, such as those from the public, patient organizations, and the pharmaceutical industry itself, which achieve the acceptance of their claims through a regulatory bias[3,4,7,8].

In an analysis involving NICE, British researchers have shown that decision-making in evaluating high-priced medicines occurs with negotiation and navigation between using practical methods and managing layers of uncertainty in the evaluation. In the assessments carried out by NICE, the authors identified epistemological uncertainties and uncertainties related to technical processes/procedures and to interpersonal contexts and relationships[9,10].

The complexity involved in evaluating new technologies for their incorporation into health systems takes on specific contours in certain settings, such as in the case of evaluating medicines for rare diseases, due to the scarce studies with thorough methodology and different values supporting the stakeholders[11,12]. The vast uncertainties surrounding the evaluation of treatments for rare diseases are related to the growth of risk-sharing or managed entry agreements in health systems in several countries[13]. Such agreements seek to manage the fact that the proposed new treatments do not show the desirable level of scientific evidence about their effectiveness and produce a tremendous economic impact for health systems or plans[13,14].

Most countries use data related to prevalence limits to define the term rare diseases, with few countries considering indicators related to severity or absence of treatment[15]. The European Union legislation defines rare diseases as those with a prevalence of no more than 50 cases per 100,000 inhabitants, which can be considered the highest prevalence for fatal, severely chronic, and debilitating conditions[16]. In England, the term "ultra-rare diseases" has also been proposed, such as life-threatening diseases or debilitating conditions that affect ≤ 1: 50,000 people[17]. Brazil corroborates the concept employed by the World Health Organization (WHO), which considers the prevalence of 65 individuals per 100,000 inhabitants as a rare disease[18].

This study aimed to explore and compare the results of HTA processes that resulted in the incorporation by risk-sharing or managed entry of medicines by the NICE and CONITEC agencies, identifying the extent to which they considered the internationally agreed technical criteria in the evaluation of medicines for rare diseases.

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Methods

Study design and sample definition

This exploratory study is based on qualitative and quantitative documentary analysis of drug recommendation reports for rare diseases, from January 2017 to December 2019, published by CONITEC. The individual medicines assessed by CONITEC were searched on the NICE data platform and compared when available to the respective assessment across countries. The data evaluated are in the public domain and were collected through secondary sources available on CONITEC (http://conitec.gov.br/) and NICE (https://www.nice.org.uk/) websites. The comparative analysis countries were chosen due to their time to consolidate and structure their HTA agencies, associated with a universal health system context. The quantitative analysis of positive or negative recommendations was performed after selecting the reports that met the definition of rare disease, as established in the National Policy for the Comprehensive Care of People with Rare Diseases in Brazil[16] from 2013 to 2019. The evaluation of medicines interrupted or still under development in data collection (June to December 2019) was not considered for the analysis.

Based on the previous assessment conducted in the first stage of the study (Chart 1), we found that, in Brazil, Eculizumab, Nusinersen, and Elosulphase Alpha were the only medicines for rare diseases incorporated based on commercial agreements (of outcomes or price). The same medicines are also subject to managed entry agreements in the English healthcare system. In this sense, this excerpt was chosen to apply the European Union analysis model and comparison with the respective reports issued by NICE.

Analysis model

The model of the European HTA network (HTA Core Model® version 3.0)[19-20] was used to analyze the content of the reports issued by CONITEC and NICE. Analyses of the reports selected from the exclusion and inclusion criteria (Figure 1) were conducted by two independent evaluators. The model applied concerns a structured format for the production of HTA, which lists the main attributes of a medication evaluation. The model consists of nine domains. Each domain is divided into components, consisting of several questions (elements) that must be addressed throughout the HTA process. This analysis of domains, components, and elements was conducted and compared by the researchers reporting the results as domain (component) present and described in the reports (when the element question could be fully answered), absent and not described in the reports (when the element question could not be answered and the reports did not address the issue) or partially described in the reports (when despite the issue being considered in the reports, it was not possible to obtain or project data and calculations). These domains and components were then compared across agencies and with the European Union model.

Data analysis

The information from the first stage of the work was analyzed from the agencies' website reports and presented in descriptive tables. In the second stage, the analysis excerpt was chosen to apply the European Union model. The qualitative and quantitative results of this step were analyzed by Microsoft Excel® descriptive tables for calculations. The reports were analyzed in two parts in the second stage of the study for comparison purposes: (i) descriptive narrative review data; (ii) calculating the absolute and relative frequency per each domain and component with the following equation: %=number of elements described or not described or partially described in the reports *100/total number of elements in the domain (total n of the model= 126).

Results

General profile of agency recommendations

In total, twenty-three recommendation reports for rare diseases were issued by CONITEC from 2017 to 2019, thirteen medicines were recommended for incorporation, and ten were recommended for non-incorporation. During this period, a total of nine recommendations were issued by NICE through the Highly Specialized Technology Assessment Program. A systematic search carried out on the NICE website for different years resulted in comparing twelve medicine, also respectively evaluated by CONITEC (Chart 1). However, we observed that the agencies received different demands for the incorporation

Chart 1. Medicines evaluated for rare diseases by NICE and CONITEC and their respective recommendations.

Medicine	Indication	NICE	CONITEC
Elosulphase Alpha	Type IV A muco-polysaccharidosis (Morquio syndrome)	Recommended for treatment based on a risk-sharing agreement	Recommend the incorporation of Elosulphase Alpha under conditions *
Brentuximab	Treatment of adult patients with refractory or relapsed Hodgkin's lymphoma after autologous stem cell transplantation	Recommended as an option for the treatment of CD30 positive. Hodgkin's lymphoma in adults with relapsed or refractory disease, under certain clinical conditions and based on commercial agreement	Incorporate brentuximab for the treatment of adult patients with refractory or relapsed Hodgkin's Lymphoma after autologous hematopoietic stem cell transplantation, through price negotiation and CPTG
Canakinumab	Treatment of Systemic Juvenile Idiopathic Arthritis	Does not recommend, as it believes that there are not enough data to propose a robust evaluation of the medicine to be considered in clinical practice in England	Do not incorporate canakinumab for the treatment of systemic juvenile idiopathic arthritis
Eculizumab	Treatment of patients with Atypical Hemolytic Uremic Syndrome (aHUS)	Recommended only if all conditioning criteria are met *	Do not incorporate eculizumab for the treatment of Atypical Hemolytic Uremic Syndrome
Eltrombopag olamine	Chronic Idiopathic Thrombocytopenic Purpura (ITP)	Recommended if refractory to standard treatments and rescue therapies or with severe illness and a high risk of bleeding that requires frequent courses of rescue therapies through a managed patient access scheme	Recommend the incorporation of eltrombopag olamine for the treatment of refractory ITP using CPTG
Evolocumab	Homozygous familial hyperlipidemia (HoFH)	Recommended in certain clinical conditions and good basis for managed patient access scheme	Recommend the non-incorporation of Evolocumab for the treatment of HoFH
Nintedanib	Idiopathic pulmonary fibrosis (IPF)	Recommended under certain clinical features and based on manufacturer-provided discount, patient access scheme	Do not incorporate Nintedanib for IPF treatment
Nusinersen	Spinal Muscle Atrophy (SMA) 5q	Recommended as a treatment option for SMA 1,2,3 through a risk-sharing agreement	Incorporate Nusinersen for spinal muscular atrophy (SMA) 5q type I through a risk-sharing agreement
Pirfenidone	Idiopathic pulmonary fibrosis (IPF)	Recommended under certain clinical features and based on manufacturer-provided discount, patient access scheme	Non-incorporation of Pirfenidone for the treatment of IPF
Romiplostim	Chronic Idiopathic Thrombocytopenic Purpura (ITP) in refractory adults and at high bleeding risk.	Recommended under certain clinical features and based on manufacturer-provided discount, patient access scheme	Non-incorporation of Romiplostim for the treatment of ITP

Captions: CPTG: Clinical Protocol and Therapeutic Guidelines. Note: *Conditions: 1) coordination of use through a specialized center; 2) monitoring systems to record the number of people diagnosed with the disease and the number of individuals using the medicine, the dose, and duration of treatment; 3) national protocol for starting and stopping for clinical reasons; 4) a research program with robust methods to assess (collect data), when to discontinue treatment, or need to adjust the dose.

Source: Prepared by the authors based on data from the digital platform of the National Commission for the Incorporation of Technologies in the SUS (CONITEC) and the National Institute for Health and Care Excellence (NICE).

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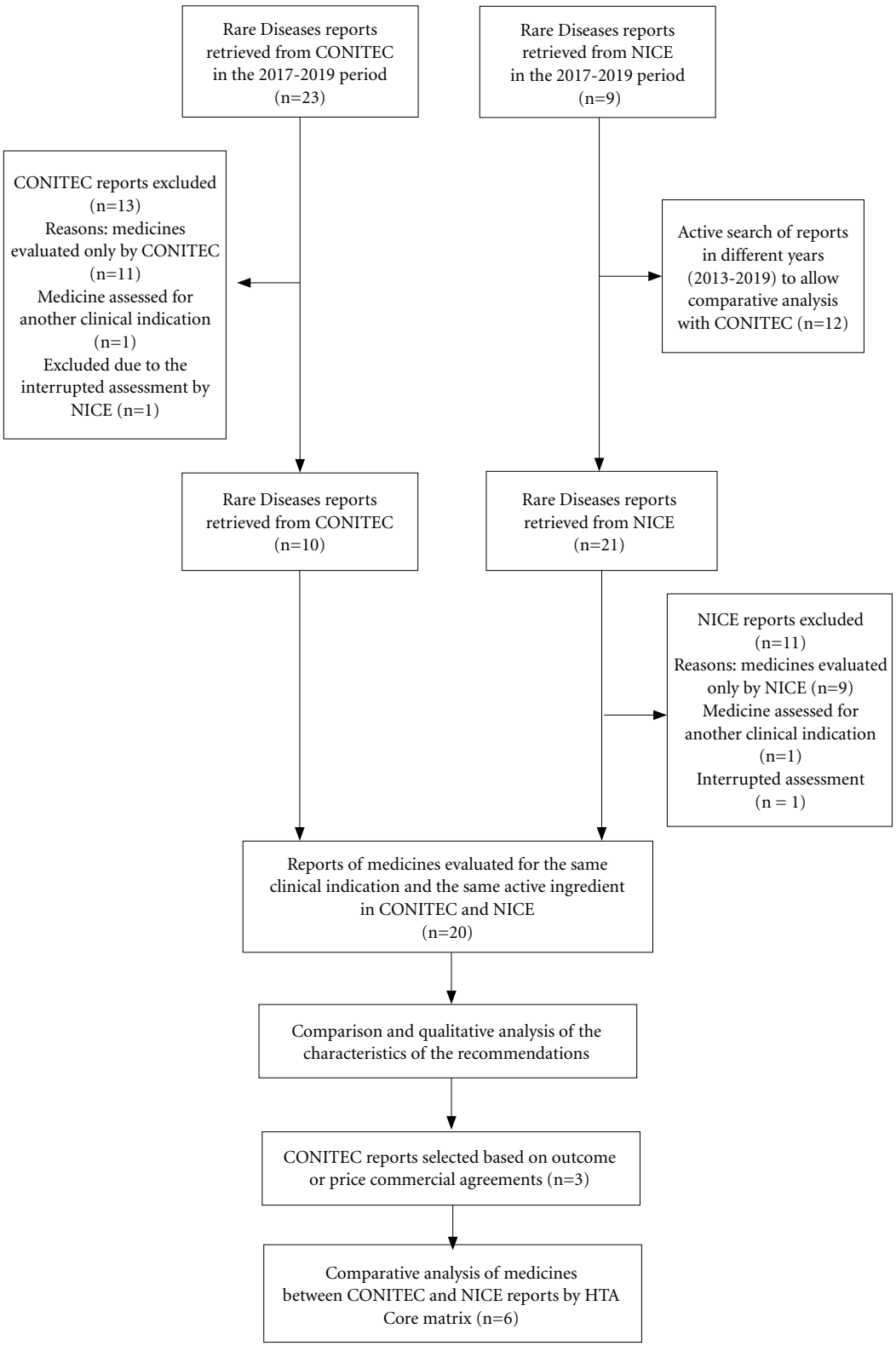

Figure 1. Flowchart of the steps involved in the study excerpt.

Source: Authors' elaboration.

of different medicines.

Ten medicines were assessed solely by NICE from 2013 to 2019 (Chart 2), and twelve medicines were assessed only by the CONITEC agency from 2017 to 2019 (Chart 3). An interagency comparison was not possible for this group of medicines, as they were not submitted to evaluate the same active ingredient or the same clinical indication.

After this search stage, the total number of possible comparisons was collected between the agencies, which addressed the same clinical indication as the applicant and the same active ingredient (Chart 1), resulting in ten drug comparisons. In this subgroup mentioned above, nine medicines obtained a favorable recommendation based on use criteria and one (Canakinumab), a negative recommendation by NICE. CONITEC recommended four medicines for incorporation with pre-established criteria and six for non-incorporation (Chart 1).

Comparative analysis of agencies in the HTA Core Model®

The result of applying the European network model (Core Model®) revealed that 67 of the 126 questions (elements) (53.2%) distributed between components I to IX were relevant (described) in the NICE reports for the medicines Eculizumab, Nusinersen, and Elosulphase Alpha. In the CONITEC reports, 44 of 126 questions (elements) (35.0%) were relevant and described in the drug reports evaluated by the Brazilian agency for the same medicines. In the analysis of the most significant number of elements described by the agencies, we found that these were from the following domains in NICE: I – Health problem and current use of technology, with 83.3%; II – Description and technical characteristics of the technology, with 53.3%, and IX – Legal aspects, 83.3% of elements described. Some of the best-described elements at CONITEC are the following domains: I – Health problem and current use of technology, 83.3%; V – Cost and economic evaluation, 50%, and VIII – Social aspects, 50.0%.

In the analysis of the group of elements that were not described in the reports, 17 of the 126 questions (elements) (13.5%) were not described in the NICE reports. Also, 23 of the 126 questions (elements) (18.0%) were not described in the CONITEC reports. The domains least described in the NICE reports were: II – Description and technical characteristics of the technology, 33.3%, and III – Security, 33.3%. At CONITEC, the domains were: VII – Organizational aspects, 50.0%, and IX – Legal aspects, 50.0%.

Regarding the categorization of elements partially described in the reports, 42 of 126 questions (33.3%) were categorized to this group in the NICE reports, and the prevalent domains were: V – Economic assessment cost, with 66.7%; VI – Ethical analysis, 55.6%; VII – Organizational aspects, 50.0%, and VIII – Social aspects, 50.0%. In CONITEC, 59 of 126 questions (47.0%) belonged to this group, and the prevalent domains were: III – Safety, 66.7% and IV – Clinical Effectiveness, 83.3%, and VI – Ethical analysis (66.7%).

When comparing the three descriptive categories between the agencies to the recommended model applied, we found that NICE had a higher percentage of elements described in its reports (53.2%), and CONITEC had a higher number of undescribed (18.0%) or partially described elements (47.0%).

Considering medicines and both agencies, the only domain that converged in the group of "described" elements was the domain I – health problems and current use of technology. Among the analysis domains with the highest occurrence of "undescribed" or "partially described" elements, those related to the organization of health services and professionals involved in the treatment stand out (domain VII – materials, facilities, qualified personnel, equipment; required training and information; technology dispensing model; process, resource and management analysis), those related to evidence of safety and effectiveness, or treatment benefits (domains III and IV – health and quality of life benefit (QALY); effectiveness and safety; identification and measurement of price, value and comparison of cost and technology outcomes based on value-based price judgment and priority setting across different healthcare technologies; damage risk reduction; direct and indirect harm to patients) and those related to the ethical analysis (domain VI – social and moral prevalence, norms and relevant value of technology, ethical issue of technology and consequence of implementing and non-implementing, and identification of ethical and moral problems inherent in the assessment technology).

Chart 2. Medicines for rare diseases evaluated only by CONITEC and not by NICE.

Medicine	Indication	Recommendation (CONITEC)
Alfa, beta, Agalsidase	Fabry disease	Do not incorporate alpha-agalsidase and beta-agalsidase as enzyme replacement therapy in Fabry disease, within the SUS
Eftrenonacog alfa (Factor XI)	Treatment of patients with Hemophilia B	Recommends the non-incorporation of Eftrenonacog alfa (Fc recombinant coagulation factor XI) into the SUS for the treatment of patients with hemophilia B
Efmoroctocog alfa (Factor VIII)	Induction of immunotolerance in patients with hemophilia A and inhibitors	Do not incorporate Efmoroctocog alfa (recombinant Fc coagulation factor VIII) for induction of immunotolerance in patients with hemophilia A and inhibitors, within the SUS
Taliglucerase alfa	Treatment of Gaucher Disease	Recommends the incorporation of Taliglucerase alfa for pediatric use in Gaucher Disease
Alglucosidase alfa	Pompe disease	Recommends the incorporation Alglucosidase alfa for the treatment of the early form of Pompe's disease within the SUS, according to PCDT
Eculizumab	Paroxysmal Nocturnal Hemoglobinuria	Incorporate Eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH), within the SUS, under conditions*
Emicizumab	Treatment of individuals with hemophilia A and factor VIII inhibitors refractory to immunotolerance treatment	Incorporate Emicizumab for the treatment of individuals with hemophilia A and factor VIII inhibitors refractory to the treatment of immunotolerance, within the SUS
Galsulfase	Type VI Mucopolysaccharidosis (Maroteaux-Lamy syndrome)	Incorporate Galsulfase for long-term enzyme replacement therapy in patients with a confirmed diagnosis of type VI mucopolysaccharidosis (N-acetylgalactosamine 4-sulfate deficiency), within the SUS, under conditions*
Idursulfase	Type II Mucopolysaccharidosis	Incorporate Idursulfase alfa as enzyme replacement therapy in type II mucopolysaccharidosis under the SUS according to PCDT
Laronidase	Enzyme replacement in type I mucopolysaccharidosis	Recommends the incorporation of Laronidase for enzyme replacement in patients with type I mucopolysaccharidosis according to PCDT
Miglustat	Neurological manifestations of Niemann-Pick type C disease (NPC)	Does not recommend the incorporation of Miglustat for neurological manifestations of Niemann-Pick type C disease (NPC)
Tafamidis meglumine	Treatment of transthyretin-associated amyloidosis in adult patients with early-stage symptomatic polyneuropathy and not undergoing liver transplantation	Incorporate Tafamidis meglumine for adult patients with early-stage symptomatic polyneuropathy and not undergoing liver transplantation, through price negotiation and PCDT in the SUS

Captions: PCDT: Clinical Protocol and Therapeutic Guidelines; SUS; Unified Health System. Note: *Conditions: 1) coordination of use through a specialized center; 2) monitoring systems to record the number of people diagnosed with the disease and the number of individuals using the medicine, the dose and duration of treatment; 3) national protocol for starting and stopping for clinical reasons; 4) a research program with robust methods to assess (collect data) when treatment is discontinued or dose adjustment is required.

Source: Prepared by the authors based on data from the digital platform of the CONITEC agency.

Chart 3. Medicines for rare diseases evaluated only by NICE and not by CONITEC.

Medicine	Indication	Recommendation (NICE)
Asphotase alpha	Perinatal/infant and juvenile hypophosphatasia	Recommended as an option for pediatric treatment in hypophosphatasia only: for people who meet the treatment criteria within the managed access and for the duration of this agreement, and as per the other specified conditions, and when the company supplies Asphotase alpha to confidential business terms under the health system
Brentuximab	Cutaneous CD 30+ T-cell lymphoma	Recommended as an option for the treatment of CD30-positive cutaneous T-cell lymphoma after at least 1 systemic therapy in adults, and only if: they have stage IIB or higher mycosis fungoides, primary cutaneous anaplastic large cell lymphoma or Sézary syndrome and the company provides Brentuximab vedotin under a commercial agreement
Burosumab	Treatment of X-linked hypophosphatemia (XLH)	Recommended to treat X-linked hypophosphatemia (XLH) with radiographic evidence of bone disease in children 1 year of age and older and in young people with growing bones. Recommended only if company provides Burosumab under a commercial agreement
Cerliponase alpha	Type 2 neuronal ceroid lipofuscinosis (NCL2) or Batten's disease	Recommended as an option for the treatment of type 2 neuronal ceroid lipofuscinosis (NCL2), also known as tripeptidyl peptidase 1 (TPP1) deficiency, only if the conditions of the managed access contract are established
Eliglustat	Type 1 Gaucher Disease	Recommended for treatment of type 1 Gaucher disease, i.e., for long-term treatment in adults who are poor, intermediate or extensive cytochrome P4502D6 metabolizers. Eliglustat is only recommended when the company provides the agreed discount on the patient access scheme
Inotersen	Hereditary transthyretin amyloidosis in adults with stage 1 and 2 polyneuropathies	Recommended as an option for treating polyneuropathy in people with hereditary transthyretin-mediated amyloidosis. Recommended only if the company provides Inotersen under a commercial agreement
Migalastat	Fabry's disease	Recommended as an option for the treatment of Fabry disease in persons aged 16+ with a mutation based on the discount agreed via the patient access scheme and only if enzyme replacement therapy (ERT) is offered. With the discount provided in the patient access system, Migalastat has a lower total cost than ERT and potentially offers greater health benefits than ERT
Patisaran	Hereditary transthyretin amyloidosis in adults with stage 1 and 2 polyneuropathies	Recommended as an option for treating polyneuropathy in people with hereditary transthyretin-mediated amyloidosis. Recommended only if the company provides Patisaran under a commercial agreement
Strimvelis	Adenosine deaminase deficiency - severe combined immunodeficiency (ADA-SCID)	Recommended as a treatment option when no human leukocyte antigen-compatible cell donor is available
Voretigene neparvovec	Leber's congenital amaurosis	Recommended as an option for the treatment of RPE65-mediated inherited retinal dystrophies in people with vision loss caused by biallelic-confirmed inherited retinal dystrophy, confirmed mutations in RPE65 and who have sufficient viable retinal cells. Recommended only if the company supplies Voretigene neparvovec under a commercial agreement

Source: Prepared by the authors based on data from the NICE agency's digital platform.

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Discussion

The comparative analysis conducted in this study allowed us to identify that the two HTA agencies are evaluating several medicines. As shown in Charts 2 and 3, 24 different medications were demanded during the period studied at the agencies, which may depend on the regulatory aspects of authorization for these medicines to enter the market in each country. Regulation N° 141/2000 of the Council of the European Parliament introduced incentives in the countries of the European Union that helped the market approval of new therapies for rare diseases[21], which also occurred in Brazil, however, only in 2017, through the Resolution of the Collegiate Board of Directors n° 204 and n° 205, which expedited the authorization process for these medicines[22-23]. Notwithstanding this, the authorization to enter the market may not reflect more significant access to these medicines in health systems due to the difficulty in defining these medicines' attributes and value components through a classic or standard technological assessment[24]. In this sense, considering that most of these medicines are not provenly cost-effective, European HTA agencies started to share information in a network and create new national programs to provide standardization for the varying extension and scope of elements that may be considered in an HTA for rare diseases[25].

As evidenced by the analysis of the reports of the medicines Eculizumab, Nusinersen, and Elosulphase Alpha, evaluated through the European Union network matrix, the components described in their entirety by NICE were half (53.2%) of the elements recommended by the network model. On the other hand, 35.0% of the elements were fully considered by the Brazilian agency. According to Korge et al.[26], as an example, the researchers founded a 50% agreement between the European Union model (Core Model® 2.4) and the reports produced by the Genetics Council of the Luxembourg government. These results showed greater similarity with the NICE assessments and more significant discrepancy with the CONITEC agency. In this sense, we can reflect on the importance of information sharing and standardization in a structured network model. Among the main advantages of using a model is the possibility of smaller and less experienced agencies collaborating with other more experienced agencies on the short- and long-term consequences of applying a specific health technology and the scope of evidence used for final decision-making.

A study by different agencies in Europe and the Americas investigating the elements most frequently used and issued in an HTA assessment identified the domains of effectiveness, cost-effectiveness, safety, and quality of life as the prominent domains considered by representatives of the agencies in the respective countries[27]. The best-described aspects considered in the assessment of medicines for rare diseases in the NICE reports (Tables 1 and 2) corroborate the use of risk-sharing agreements or patient access schemes (confidential price discounts with the pharmaceutical industry) in all recommendations and the establishment of a highly specialized technology assessment program at NICE[14,28]. In this different setting, selected medicines are indicated by the government (up to three a year), which may have a range of formal elements and criteria considered as priorities in the agency's decision-making, reflecting the availability of alternative treatments for this population group. However, the decision still depends on the Committee's judgment and the undetermined amount of evidence the health system is willing to pay[29].

Several elements were not described in the reports of both agencies, or only partially described, in higher percentage and prevalence by the Brazilian agency (Tables 1 and 2). Noteworthy is that many of these elements are related to evidence of safety, effectiveness, and organizational aspects, which indicates a greater level of uncertainty for decision-making – which is intended to be evidence-based. Decision-makers often use intuition or heuristic phenomena to address domains of uncertainty, which has been reported in the literature as an essential tool in decision-making. An example of this is the 'affect heuristic' that can improve judgment efficiency by deriving risk and benefit assessments when considering perceptions and, consequently, considering only part of the attributes and not all of them[30].

The risk-sharing mechanisms or the managed entry of these medicines into health systems (some involving secret discounts) may express the level of uncertainty described in their reports. As of October 2018, NICE had 184 active agreements with various companies and, in all, 133 (72%) of these negotiations are simple discounts[31]. Nusinersen was the first medicine recommended through a risk-sharing agreement in Brazil[32].

Table 1. omparative analysis matrix of domains, components (elements) of the European ATS network model applied in NICE and CONITEC rare disease medicine reports.

Domains	Components (elements)	Eculizumab		Nusinersen		Elosulphase Alpha	
							
Health problem and current use of technology (18 questions - elements)	Health problem and target population	✓	✓	✓	✓	✓	✓
	Epidemiology	✓	✓	*	✓	*	*
	Regulatory status	✓	✓	✓	✓	✓	✓
	Alternative to technology	✓	✓	✓	✓	✓	X
Description and technical characteristics of the technology (15 questions - elements)	Technology review	✓	✓	✓	✓	✓	✓
	When was it developed and proposed indication	✓	✓	*	*	✓	*
	Who will use the technology, how and at what level of the health system	✓	✓	✓	✓	✓	*
	Materials, facilities, qualified personnel, equipment	X	*	*	*	X	*
	Training and necessary information	X	*	X	X	X	X
Security (11 questions - elements)	Direct and indirect damage to patients	✓	*	X	*	✓	*
	Damage risk reduction	✓	X	*	*	X	X
Clinical Effectiveness (12 questions - elements)	Health and quality of life benefit (QUALY)	✓	*	*	*	✓	*
	Effectiveness and safety	*	✓	*	*	✓	*
Cost and economic evaluation (11 questions - elements)	Identification and measurement of price, value and comparison of cost and technology outcomes based on value-based price judgment and priority setting across different healthcare technologies	*	*	*	*	*	*
	Use of resources, unit price, indirect cost, outcomes and consequences, and incremental cost-effectiveness	✓	✓	*	✓	✓	✓
Ethical analysis (20 questions - elements)	Social and moral prevalence, norms and relevant value of technology	✓	✓	*	*	*	*
	Ethical issue of technology and consequences of implementation and non-implementation	✓	*	*	*	X	*
	Identification of ethical and moral problems inherent in technology assessment	✓	*	*	✓	*	✓
Organizational aspects (15 questions - elements)	Technology dispensing model	*	*	*	*	*	*
	Process, resource, and management analysis	✓	X	✓	X	X	X
Social aspects (7 questions - elements)	Considerations, prior and post-implementation experiences	✓	✓	X	✓	✓	✓
	Where patients will use the technology (hospitals, primary system, and clinics)	*	✓	*	✓	✓	✓
	What are the main goals that people aim with technology	✓	*	✓	*	*	*
Legal aspects (17 questions - elements)	Basic patient rights such as autonomy, informed consent, privacy, and confidentiality	✓	✓	✓	✓	✓	*
	Legal requirements, authorization, guarantee, and market regulation	✓	X	X	X	✓	X

Captions: * partially described in the report; X not described in the report; ✓described in the report.

Source: Prepared by the authors from HTA Core Model Version 3.0.

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Table 2. Percentage of domains categorized from CONITEC and NICE reports.

Domains	Elements (n)	Described (%)		Not described (%)		Partially described (%)	
I	18	83.3%	83.3%	0.0%	8.3%	16.7%	8.3%
II	15	53.3%	40.0%	33.3%	13.3%	13.3%	46.7%
III	11	50.0%	0.0%	33.3%	33.3%	16.7%	66.7%
IV	12	50.0%	16.7%	0.0%	0.0%	50.0%	83.3%
V	11	33.3%	50.0%	0.0%	0.0%	66.7%	50.0%
VI	20	33.3%	33.3%	11.1%	0.0%	55.6%	66.7%
VII	15	33.3%	0.0%	16.7%	50.0%	50.0%	50.0%
VIII	7	50.0%	50.0%	0.0%	0.0%	50.0%	50.0%
IX	17	83.3%	33.3%	16.7%	50.0%	0.0%	16.7%
Total	126	67/126 (53.2%)	44/126 (35.0%)	18/126 (14.3%)	23/126 (18.0%)	41/126 (32.5%)	59/126 (47.0%)

Source: Authors' elaboration.

Similarly, other attempts and recommendations were previously implemented with the medicines evaluated in this study (Eculizumab and Elosulphase Alpha). In these cases, the incorporation Ordinances describe the condition that three-year usage data are evaluated to reconsider incorporation (managed entry). However, according to the results obtained from the matrix applied here, the elements relating to the organization of services and professionals for applying new treatments are poorly or not described in the agency's reports. In the Brazilian case, this result is especially troubling, as deficiencies recognized in specialized medium- and high-complexity health services point to a lack of necessary conditions for the effective monitoring of these treatments and the generation of reliable and unbiased real-life information to support the assessment of the results of the possible benefits of treatments. In this context, the incorporation recommendation reports should highlight these elements and induce the necessary investment in the related health services to a high investment in medicines under approval.

Garrison et al.[33] highlighted that some decisions on medicines show several uncertainties attributed to the judgment of the criteria used, which transcend the cost-effectiveness aspect as the only analysis component. This measure cannot be considered the only element in decision-making, and actually, the results presented here indicate that decisions are not entirely based on their proven cost-effectiveness. The analysis can be augmented by considering several potential value elements, such as disease severity value, financial risk protection insurance, the expectancy-value, and the knowledge value. Currently, certain agencies have incorporated some criteria and use them formally, as in NICE, which seeks to capture in the evaluation of these medicines the unmet clinical need, the innovation level, quality of life (report-based), and value-based price to achieve broader decision-making for these medicines[25,28].

A new tool is being proposed internationally to integrate relevant factors for HTA processes globally. The multiple-criteria decision analysis (MCDA) considers the classic concepts used in HTA (for example, those proposed by the European Union model), different values, and criteria (attributes) that can be used in practice in a standardized way[24,34]. While addressing the impact of a rarity in all considerations, such a mechanism leads to a balance between stakeholders when there is conflicting, vague, and even incomplete information during the decision process. According to Campolina et al., its use allows for the explicit consideration of the criteria that influence the decision, facilitates the monitoring and visualization of the process steps, enables assessing each contributing criterion in isolation and the aggregate to the decision's result, facilitating the discussion of divergent perspectives of interest groups, while increasing the understanding of the elaborated recommendations[35].

The transparent evaluation process and the clear criteria and parameters adopted – including the qualitative criteria and the explicit management of uncertainties – are fundamental conditions for health agencies and institutions

to have trust and legitimacy in society[36]. The development and application of mechanisms that can minimize the impact of uncertainties and conflicts of interest in the technology assessment process must be on the priority agenda of regulatory agencies.

Finally, this study has some limitations. One of them is that all analyses were performed from secondary sources publicly available on the agencies' websites, not including access to the original documents. The second limitation is the lack of participation in CONITEC or NICE public meetings during the evaluation of the respective medicines, which could improve the understanding of the phenomenon and the position of different stakeholders on the subject. Another limitation refers to the sample analyzed here. As it is still recent, the risk-sharing, conditional incorporation, or managed entry agreements were applied to a small number of incorporations in Brazil, and new analyses must be carried out to monitor the impact of these mechanisms on the incorporation processes.

Final considerations

The results suggest that HTA agencies (CONITEC and NICE) operate in a context of uncertainty in evaluating medicines for rare diseases, which is expressed in the lack of essential elements in the reports for incorporation of medicines by risk-sharing or conditioned incorporation agreements. This is due to the clinical, regulatory, economic, and social challenges of evaluating these medicines at different points in their life cycle. In the case of NICE, the agency showed higher agreement with the proposed assessment construction model, which may be related to sharing information in a network and creating a specific program that considers broader values in the evaluation of medicines for rare diseases. CONITEC showed a more significant number of domain elements classified as partially described and undescribed, especially in elements of organizational aspects and medication management within the health system. The generation of reliable and unbiased real-life data to support the assessment of the results of the possible benefits of treatments requires incorporation recommendation reports to highlight these elements and indicate the necessary investments in the services, not only in medications.

Similarly, Brazil currently has no defined procedure for creating new programs integrated into the HTA for evaluating emerging medicines for rare diseases. New HTA programs can improve the decision-making process regarding these medicines, ensuring the potential for asymmetric uncertainty. Such alternative programs and models would ensure a broader approach instead of the exclusive cost-effectiveness approach, which cannot guarantee asymmetry in all assessments. However, the question that still arises is whether these new decision-making programs and structures will be successful in practice and what is the accepted limit of uncertainty to set up an agreement with the pharmaceutical industry in a setting of increasingly higher and limitless prices. It is essential to question whether mergers based on commercial or conditional agreements can ultimately legitimize and normalize the uncertainties and lack of scientific evidence in this process.

A new setting for comprehensive care for these patients is required, which allows for defensible decision-making while preserving the legitimacy of the assessment of medicines for rare diseases and equitable access to innovative medicines.

Collaborations

We emphasize that G Vicente and SN Leite participated in the paper's design, planning, discussion, and final review. Furthermore, C Cunico and G Vicente contributed to the analysis of the results, discussion, and review of the writing of the manuscript.

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