Jornal de Assistência Farmacêutica e Farmacoeconomia
v.9, n.3, jul. 2024.
Original Article

Budgetary Impact of Advanced Therapy Products in the Unified Health System

Impacto Orçamentário dos Produtos de Terapias Avançadas no Sistema Único de Saúde

Denizar Vianna Araujo[1]; Camile Giaretta Sachetti[2]; Antonio Carlos Campos de Carvalho[3]; Gesner Oliveira[4]; Luccas Saqueto[4]; André Pellizzaro[5]; Antonio Macedo[6]; João Pedro Mussi[7]; Maria Paula Heck[8]; Jéssica Portal Maia[9]

[1] Faculdade de Ciências Médicas da Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brasil.
[2] Fundação Oswaldo Cruz, Brasília, Distrito Federal, Brasil.
[3] Universidade Federal do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brasil.
[4] Fundação Getúlio Vargas, São Paulo, São Paulo, Brasil.
[5] Faculdade de Economia, Administração, Contabilidade e Atuária, Universidade de São Paulo, São Paulo, São Paulo, Brasil.
[6] Faculdade de Economia, Administração, Contabilidade, Universidade de São Paulo, Ribeirão Preto, São Paulo, Brasil.
[7] Faculdade de Administração, Economia e Contabilidade da Universidade de Brasília (FACE/UnB), Brasília, Distrito Federal, Brasil.
[8] Centro Universitário do Distrito Federal, Brasília, Distrito Federal, Brasil.
[9] Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brasil.

Corresponding Author: Universidade do Estado do Rio de Janeiro, Centro Biomédico, Clínica Médica. Boulevard 28 de setembro nº 77 - 3º andar - sala 329, Vila Isabel, 20551030, Rio de Janeiro, RJ, Brasil.
E-mail: denizar@uerj.br

Receipt date: 03/18/2024

Publication date: 05/11/2024

ABSTRACT

We sought to map the main advanced therapy products approved by reference health agencies to assess the potential impact of incorporation into the Unified Health System. To this end, we defined the price by the methodology applied by CMED for products with molecules new and therapeutic gains and the demand was based on the incidence of diseases, following population growth. The impact estimations resulted between R$16.6 and R$53.0 billion for the five years after incorporation scenarios, providing relevant subsidies for decision-making agents.

Keywords: Advanced therapies, budget impact, CMED, SUS

RESUMO

Buscou-se mapear os principais produtos de terapia avançada aprovados por agências sanitárias de referência para avaliar o potencial impacto da incorporação no Sistema Único de Saúde. Para isso, definiu-se o preço a partir da metodologia de precificação aplicada pela CMED para produtos com moléculas novas e ganho terapêutico e a demanda a partir da incidência das doenças, seguindo o crescimento populacional. Como resultado, estimou-se, para os cinco anos após cenários de incorporação, impactos entre R$16,6 e R$53,0 bilhões, proporcionando subsídios relevantes para os agentes tomadores de decisão.

Palavras-chave: Farmacoeconomia. Análise de Impacto Orçamentário. Produto de Terapias avançadas. Análise de Incorporação de Medicamentos.

JEL Classification: H51, I18

Introduction

The objective of this article is to estimate the budgetary impact of the incorporation of Advanced Therapy Products (ATPs) in the SUS over a 5-year interval. To this end, different scenarios of disease incidence and the degree of insertion of these therapies after their incorporation were considered.

Advanced Therapy Products (ATPs) are pharmaceutical products in a special category of new drugs or biologics that includes the advanced cell therapy product, the tissue engineered product, and the gene therapy product for the purpose of regulating, repairing, replacing, adding, deleting, or editing a genetic sequence or modifying the expression of a gene, according to the National Health Surveillance Agency (Anvisa, 2021).[1,a] Currently, ATPs represent one of the fastest growing areas, offering alternatives for diseases that lack treatment or effective therapeutic options.[2] Despite the great advance in scientific knowledge with positive repercussions on morbidity and mortality outcomes, these are products of complex manufacturing, which require highly specialized equipment, processes and manufacturing skills, limited availability of clinical data on efficacy and safety, logistics and the need to organize health care infrastructure.[3,4]

Viral vector-based cell and gene therapies have achieved promising clinical results for the treatment of a variety of diseases. T-cell therapies expressing the chimeric antigen receptor (CAR) have produced relevant results in the treatment of hematological malignancies, such as lymphomas, leukemias, and myelomas, achieving excellent response rates and disease-progression-free survival when compared to traditional chemotherapy.[5,6,7,8] In addition, other gene therapies have demonstrated efficacy in the treatment of genetic diseases offering the prospect of a cure for serious conditions.

However, the greatest challenge to be overcome for access to these therapies is related to the high costs of treatment.[9,10] On the one hand, the industry justifies such a price level under the promise of delivering value in health[11], combined with the high costs of development, manufacturing, and quality control. On the other hand, there is global concern about the impact of ATPs on the sustainability of health systems, especially for those with universal access such as the Unified Health System (SUS). Thus, governments face the challenge of balancing the financial sustainability of health systems with the promotion of innovation and the development of new therapies.[12]

The pressure for access to ATPs, whether through incorporation or judicialization, is growing in Brazil. Considering the potential increase in registrations of ATPs by Anvisa in the coming years, it is necessary to estimate the impact of these products for the planning of specific public policies. The entry process has a period of up to 905 days (approximately 2.4 years) for approval of registration by Anvisa, pricing by the Drug Market Regulation Chamber (CMED) and incorporation by the National Commission for the Incorporation of Technologies in SUS (CONITEC).[a]

Budget Impact Analysis (BIA) can be defined as the assessment of the financial consequences arising from the adoption of a new health technology, within a given health scenario with finite resources.[13,14] Such analysis is recurrently required by public agents for reimbursement analyses.[15] In this case, the costs of the new intervention itself are included, costs of co-interventions, movement of resources associated with the therapeutic options in use, and possible reallocation of resources to cases in which the inclusion of a new technology may result in savings for the health system.

However, due to the complexity of applying this method to the variety of technologies included, this study was limited to estimating the budgetary impact based on the forecast of prices and potential demand in five years after entry into the SUS list. The pricing followed the methodology established by article 5 of RDC CMED No. 2/2004, assuming the classification of TPAs as new molecules with therapeutic gain (Category 1), which provides that "for new products classified in Category I, the Factory Price – FP proposed by the company may not be higher than the lowest PF practiced for the same product in the countries listed in item VII of paragraph 2 of article 4, adding the taxes levied, as the case may be".

The basket of countries indicated in item VII, §2, art. 4th includes Australia, Canada, Spain, the Uni-

ted States of America, France, Greece, Italy, New Zealand, Portugal and the country of origin of the product. Therefore, we sought to map the products registered with the respective health agencies.

The demand estimate, in turn, was carried out based on the survey of the therapeutic indication of each product and its incidence, with growth following the IBGE's expectation of population variation. To measure the impact, different scenarios of disease incidence and speed of incorporation of these therapies into the SUS were considered, with potential costs brought to present value.

Data source and assumptions

The data mapping strategy aimed to answer which are the TPAs that can enter Brazil in the next 5 years. To this end, it was assumed that products already registered with other health authorities have a greater potential for entry into the national territory. Thus, in order to enable the replication of the pricing methodology defined by CMED (2004), the products registered with the European Medicine Agency (EMA) of the European Union, the Food and Drug Administration (FDA) of the United States, Anvisa from Brazil, Australia, New Zealand and Canada (without registration) were surveyed. Although not explicitly foreseen, Japan's Pharmaceuticals and Medical Devices (PMDA) has also been included due to the country's relevance in the development of new TPAs. As a result, the mapping carried out in August 2023 totaled 90 approved TPAs.

Due to the limited resources to analyze all the products identified, a prioritization criterion was adopted based on the relevance of new technologies for oncohematological treatments and rare diseases, as indicated by the experts consulted. The process resulted in the filtering of the products that fit according to their purpose, totaling 15 TPAs for rare diseases and onco-hematological diseases (Table 1).

For the mapping of international prices of the selected TPAs, the sources indicated by CMED Communiqué No. 09/2014 for the USA, Spain, France, Italy, Greece, Australia and New Zealand were used. In addition, complementary unofficial alternatives were used for cases in which information was not identified in the original lists. However, in the cases of Canada and New Zealand, price information was not located, so they were not included in the database. The mapping of prices practiced in Japan was also added, due to their relevance in the scenario of development of the TPAs (Table 2).

The definition of the lowest international price was applied only to cases that do not have registration and defined price in Brazil. The monetary conversion of the price used the average of the 60-day exchange rates, between 08/14/2023 and 11/09/2023, relative to the currencies USD, CAD, EUR, AUD, NZD, JPY, available for all currencies at sales prices in Quotations and Bulletins of the Central Bank of Brazil.[p]

Table 1. PTAs with active registrations by jurisdiction*

ID	PTA	Class	Subclass	FDA[b]	EMA[c]	Anvisa[d]	PDMA[e]	Australia[f]	New Zeland[g]
1	Elevidys	Advanced therapy	Rares diseases	1	0	0	0	0	0
2	Libmeldy	Advanced therapy	Rares diseases	0	1	0	0	0	0
3	Luxturna	Advanced therapy	Rares diseases	1	1	1	0	1	1
4	Rethymic	Advanced therapy	Rares diseases	1	0	0	0	0	0
5	Strimvelis	Advanced therapy	Rares diseases	0	1	0	0	0	0
6	Upstaza	Advanced therapy	Rares diseases	0	1	0	0	0	0
7	Vyjuvek	Advanced therapy	Rares diseases	1	0	0	0	0	0
8	Zolgensma	Advanced therapy	Rares diseases	1	1	1	1	1	1
9	Zynteglo	Advanced therapy	Rares diseases	1	1	0	0	0	0
10	Abecma	Advanced therapy	Hematology	1	1	0	1	0	0
11	Breyanzi	Advanced therapy	Hematology	1	1	0	1	0	0
12	Carvykti	Advanced therapy	Hematology	1	1	1	1	1	0
13	Kymriah	Advanced therapy	Hematology	1	1	1	1	1	0
14	Tecartus	Advanced therapy	Hematology	1	1	0	0	1	0
15	Yescarta	Advanced therapy	Hematology	1	1	1	1	1	0
Total number of approved records				**12**	**12**	**5**	**6**	**6**	**2**

Source: Prepared by the author
*Cases with active registration were marked with (1) and those without registration, with (0).

Then, from the set of selected TPAs, the respective therapeutic indication was sought in order to identify which diseases or conditions are indicative of these products, thus defining the eligible population as an indication of potential demand. Chart 1 summarizes the results of therapeutic indication.

It was not possible to access a historical series of the total number of individuals diagnosed with the above conditions. There is also limited information on the total number of cases for the diseases listed in Brazil. Thus, it was decided to estimate the eligible population by applying the constant incidence and variation of demand proportional to the projection of Brazilian population growth.

Table 2. International prices of the analyzed TPAs (converted to local currency – in reais)

APT	Brazil[o]	USA[n]	Spain[m]	France[l]	Greece[k]	Italy[j]	Australia[i]	Japan[h]	Country	Value
Elevidys		15.682.021,33							USA	15.682.021,33
Libmeldy						15.285.387,92			Italy	15.285.387,92
Luxturna	2.155.753,34	1.554.652,62	1.834.246,55	1.541.830,43	1.834.246,55	1.913.996,40	3.832.546,00		Brazil	2.155.753,34
Rethymic		13.309.056,68							USA	13.309.056,68
Strimvelis			1.887.413,12			3.158.094,06			Spain	1.887.413,12
Upstaza				15.949.970,00	15.949.970,00	15.949.970,00			France	15.949.970,00
Vyjuvek		90.772,49							USA	90.772,49
Zolgensma	7.600.207,96	10.564.555,19	10.340.897,22		10.340.897,22	11.458.057,84	8.073.174,70		Brazil	7.600.207,96
Zynteglo		10.480.948,94			8.373.734,25				Greece	8.373.734,25
Abecma		2.066.145,71						1.102.998,63	Japan	1.102.998,63
Breyanzi		2.020.833,34							USA	2.020.833,34
Carvykti	2.539.036,07	2.290.244,93							Brazil	2.539.036,07
Kymriah	1.568.166,09	1.951.566,54	1.701.330,13		1.547.234,92	1.701.330,13	1.909.885,42		Brazil	1.568.166,09
Tecartus		2.047.166,99			1.780.016,65	1.913.996,40	1.660.769,93		Australia	1.660.769,93
Yescarta	1.762.452,86		1.738.546,73		1.559.109,57	1.738.546,73	1.596.894,17		Brazil	1.762.452,86

Chart 1. Mapping of the pharmaceutical indication of each TPA

ID	APT	Therapeutic indication
1	Elevidys	Duchenne muscular dystrophy.
2	Libmeldy	Children with metachromatic leukodystrophy (MLD).
3	Luxturna	Hereditary retinal dystrophy associated with biallelic mutations in the RPE-65 gene.
4	Rethymic	Immune reconstitutior in pediatric patients with congenital athymia.
5	Strimvelis	Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCI D).
6	Upstaza	Human aromatic L-amino acid decarboxylase (AADC) deficiency.
7	Vyjuvek	Vyjuvek epidermolysis bullopsa was approved by the FDA to treat wounds in individuals with DEB, aged 6 months or older, who have mutations in the COL7A1 gene.
8	Zolgensma	Treatment of pediatric patients under 2 yeas of age with spinal muscular atrophy with biallelic mutations in the survival motor neuron 1 (SMN1) gene.
9	Zynteglo	Treatment of patients with beta-thalassemia, aged 12 years and older, who require regular blood transfusions
10	Abecma	Relapsed or refractory multiple myeloma after four or more lines of treament.
11	Breyanzi	Diffuse large B-cell lymphoma (DLBCL); Primary mediastinal large B-cell lymphoma (PMBCL); Follicular lymphoma grade 3B (FL3B).
12	Carvykti	Adults with relapsed or refractory multiple myeloma who have received at least three therapies.
13	Kymriah	Acute B-cell lymphoblastic leukemia in the second relapse (or later) or refractory, relapsed or refractory large B-cell lymphoma after two or more combinations of systemic treatment.
14	Tecartus	Adults with mantle cell lymphoma (MCL).
15	Yescarta	Relapsed or refractory large B-cell lymphoma after two or more combinations of systemic treament.

Source: Prepared by the author

The estimated incidence (Chart 2) may be affected by underreporting or inaccurate diagnoses, leading to a variation in the incidence rate of the diseases. We chose to maintain a constant incidence, equivalent to the last recorded in relation to population increase, as a conservative premise. This choice is based on the assumption that the rate in question is the most effective for correcting underreporting and misdiagnosis, assuming that the current reporting system and diagnostic processes are superior to those of the past. This approach was adopted to minimize further fluctuations in the budget impact.

As an alternative to measuring the incidence of rare diseases, the main source used was the Orphanet website.[16] Although it does not use data from Brazil, it is a reference in the analysis of rare diseases with data provided by 41 countries. This was the best source available, after exhausting attempts to access this data by competent and official Brazilian agencies. In cases of unavailability of information in Orphanet, other specific websites for the disease and/or scientific articles were used if possible. In the case of Luxturna, whose indicated disease is not found in Orphanet, the information published by Conitec Report No. 664/2021 was used.[17]

The same scenario of uncertainty occurred for onco-hematological diseases, as the TPAs analyzed are for third-line use. This means that a hematological cancer patient needs to go through first- and second-line treatments without satisfactory effects and have survived to the point of receiving indication of these products. Therefore, for this group, it was decided to use the values of patients eligible for this treatment today in Brazil, provided by a panel of experts representing the main reference institutions in Brazil for the treatment of onco-hematological diseases. The following experts were consulted:

• Dr. Angelo Maiolino[z], PhD, Coordinator of Hematology at Oncology Americas - RJ, Associate Professor of Hematology UFRJ.

• Dr. Antônio Carlos Campos de Carvalho[aa], PhD, Full Professor UFRJ.

• Dra. Camile Sachetti[bb], PhD, Technologist at the Oswaldo Cruz Foundation.

• Dr. Denizar Vianna[cc], PhD, Full Professor UERJ.

• Dr. Martin Hernan Bonamino[dd], PhD, Researcher at the National Cancer Institute and Specialist at the Oswaldo Cruz Foundation.

The data obtained for the incidence of diseases in the population can be found in ranges of variation or in absolute values. For example, for diseases indicated for TPA Zolgensma, the incidence varies between 1 in 10,000 to 1 in 25,000 live births. In cases where the source does not indicate variation in incidence, a range of ±5% was applied for the minimum and maximum values. Therefore, to accommodate these cases, the projection of the eligible population for the Brazilian health system was established in 3 different scenarios: conservative (lower incidence), moderate (medium incidence) and aggressive (higher incidence).

Chart 2. Mapping the incidence of each TPA

ID	APT	Incidence*	Source
1	Elevidys	1 in 3,500 to 1 in 9,300 male live births per year.	Orphanet[q]
2	Libmeldy	1 in 100,000 live births per year.	Orchard Therapeutics[r]
3	Luxturna	Estimated eligible population between 41 and 50 patients per year.	Report nº 664/2021 Conitec[s]
4	Rethymic	1 in 1,000,000 live births per year.	Orphanet[t]
5	Strimvelis	1-9 in 1,000,000 of the population per year.	Orphanet[u]
6	Upstaza	<1 in 1,000,000 of the population per year.	Orphanet[v]
7	Vyjuvek	1.35 in 1,000,000 live births per year.	Orphanet[w]
8	Zolgensma	1 in 10,000 to 1 in 25,000 live births per year.	Orphanet[x]
9	Zynteglo**	1in 100,000 ive births worldwide per year.	Orphanet[y]
10	Abecma	Estimated eligible population of 320 patients per year.	Panel of experts
11	Breyanzi	Estimated eligible population of 284 patients per year.	
12	Carvykti	Estimated eligible population of 320 patients per year.	
13	Kymriah	Estimated eligible population of 126 patients per year.	
14	Tecartus	Estimated eligible population of 83 patients per year.	
15	Yescarta	Estimated eligible population of 284 patients per year.	

Source: Prepapred by the authors.
*For Luxturna and hematologic tests, the number of cases of the diseases was reported.
** Brazil accounts for approximately 2.5% of the words population.

The projection of Brazilian population growth was made available by the Brazilian Institute of Geography and Statistics (IBGE) from the 2022 Census, estimated at 0.52%[cc] per year. This projection was also applied to the total number of live births in 2022 published by DataSUS[ff]. From the application of the incidences found on the total of each year, the eligible population totaled from 1,595 to 2,200 patients per year, depending on the scenario adopted (Table 3).

Future annual adjustments were estimated based on the projection of the Extended National Consumer Price Index (IPCA). To this end, the estimates of the latest Focus report released on the date of this study (03/11/2024) by the Central Bank of Brazil (BCB)[gg], which provides the median of expectations until 2027, were adopted. For 2028 and 2029, the current inflation projection set at 3.5% was used.

Budget Impact Modeling

The methodology used to calculate the budget impact used two main components, the price and the demand for TPA.

The initial price of commercialization of the product in Brazil was estimated according to the lowest price found for the advanced therapy product *j* in the countries of the basket in which it is commercialized. This methodology for pricing follows the determination of CMED and was carried out in the research incorporating both the websites used by the agency and websites for studies in the sector. The definition used for prices follows:

$$preço_{j0} = \begin{cases} preço_{Brasil}, & se\ registrado\ pela\ Anvisa \\ \min_{c}\{u_c \times preço_{cj}\}, & caso\ contrário \end{cases}$$

$$preço_{jt} = preço_{j0} \times inflação_t.$$

Where:

- c = USA, Spain, France, Greece, Italy, Australia, Japan;
- $j = 1,..., 15$;
- $price_{j0}$ is the current price of therapy *j* for Brazil (t = 0);
- $price_{cj}$ is the current price of therapy *j* for country *c* that has commercialization of this therapy;
- u_c is the country's exchange rate to national currency (BRL), equal to the monthly average of the 60 days prior to the study (08/14/2023 to 11/09/2023);
- $price_{jt}$ it is the estimate of the price in the year;
- $inflation_t$ refers to the annual price adjustment. In this study, the IPCA will be a *proxy* for the VPP (Percentage Variation in Price).[hh]

The demand for advanced therapy was calculated according to the incidence of the disease in the eligible population. Thus, assuming that the incidence remained constant in the period analyzed, the rates *aj* , βj were the same in all years, which means that the incidence of the disease and the composition of the categories of the eligible population of the diseases varied only by the proportion of the population growth projection. The demand for *j* therapy was defined in *t* year by

$$demanda_{jt} = \begin{cases} população_t \times \alpha_j \times \beta_j, & sej = 1, \dots, 9 \\ incidência_t, & sej = 10, \dots, 15 \end{cases}$$

Table 3. Projection of the total population, live births, eligible population and IPCA

Variável		2024	2025	2026	2027	2028	2029
População IBGE		205.198.287	206.265.318	207.337.898	208.416.055	209.499.818	210.589.218
Nascidos vivos		2.573.634	2.587.017	2.600.469	2.613.991	2.627.584	2.641.248
Projeção IPCA		3,91%	3,50%	3,50%	3,50%	3,50%	3,50%
População elegível	**Conservador**	1.595	1.603	1.611	1.620	1.628	1.637
	Moderado	1.782	1.791	1.800	1.810	1.819	1.829
	Agressivo	2.143	2.154	2.166	2.177	2.188	2.200

Source: IBGE, DataSUS, and Focus Report

In which,

- $population_t$ represents the total population of Brazil projected by IBGE.
- a_j is the proportion of rare and feasible disease incidence to receive therapy j of the eligible population.
- β_{jt} is the proportion of the eligible and feasible rare disease population to receive j therapy in year t over the total population.
- $incidence_t$ corresponds to the incidence of available hematological disease, adjusted for year t according to the population growth projection forecast by the IBGE for the period.

The TPAs were grouped according to similar characteristics. It was denoted as the budgetary impact of advanced therapy products in period t, defined by:

$$impacto_t = \sum_j demanda_{jt} \times preço_{jt}$$

The impact projection follows specific characteristics for each variable. Net present value is an economic-financial analysis tool capable of determining the present value of a discounted money flow at a discount rate. When there is a discount rate that makes this discounted flow equal to zero, we call it the internal rate of return. For budget impact analyses, adjustments for inflation and discount rates are not routinely recommended.[13] Considering the short time horizon and the fact that the result of the BIA corresponds to the present value used in the manager's budget estimates, it is important to highlight that the budget represents a financial amount spent in the present. This is not adjusted for inflation, nor affected by discounts.

To calculate the net present value of the impact, the Methodological Guideline of the Ministry of Health was used, which determines a standard recommendation for the discount rate of 5% per year, also established by Valentim and Prado (2008).[18] Using the rate of 0% in the analysis of sensitivity and absence of inflation, the budgetary impact would increase by 4.11%.

However, for the Brazilian reality, the CMED establishes the annual readjustment of drug prices, considering the inflation of the previous year. Therefore, it is necessary to estimate a net present value adjusted for inflation to more accurately reflect economic fluctuations.

Due to the uncertainties in the speed of incorporation of technologies into the SUS, three possible cases were assumed: (i) immediate incorporation of all the TPAs analyzed: it is considered that there is already an immediate budgetary impact due to the high judicialization of this market with a period analyzed between 2024 and 2028; (ii) incorporation of all TPAs analyzed after one year: considering the scenario that all products surveyed will apply for registration in January 2025, after one year of analysis between the application for registration and incorporation into the health system (between 2025 and 2029); and (iii) staggered incorporation of the TPAs analyzed after one year: assuming that the incorporations will not be requested and approved at the same time, for simplification purposes, a progressive increase of 20% in costs and eligible population per year was considered, totaling 100% of the potential revenue of the products at the end of the 5 years analyzed (between 2025 and 2029).

For each case of incorporation mentioned, the different incidence patterns (conservative, moderate and aggressive) were applied, in order to reduce expensive variabilities and uncertainties inherent to the assumptions adopted. These considerations resulted in the formulation of nine distinct scenarios, each characterized by its own projections and implications. The results of these analyses will be presented in the subsequent section.

Results

The combination of the three hypotheses related to the speed of incorporation with the demand parameters resulting from the variation in incidence results in nine possible scenarios. Table 4 summarizes the total impact of each scenario as a result of the Net Present Value (NPV) considering an Internal Rate of Return (IRR) of 5% for five years after the merger, according to the assumptions summarized. The five years following the merger were considered, between 2024 and 2028 for case (i) and between 2025 and 2029 for the others.

Table 4. Incidence Flow in the SUS (in billions)

Scenario	Case i – immediate Incorporation of all TPAs	Case ii – Incorporation of all TPAs after on year of analysis	Case iii – Gradual incorporation of TPAs after one year of analysis
Conservative	R$28,3	R$28,1	**R$16,7**
Moderate	R$35,5	R$35,1	R$20,9
Aggressive	**R$53,2**	R$52,7	R$31,4

Source: Prepapred by the authors.

The greatest impact was achieved in the scenario of higher demand, with immediate inflow, resulting in R$53.2 billion for the entire period observed. In addition, the minimum estimated impact reached R$ 16.7 billion, considering a staggered entry of products in the five years following approval.

The SUS budget of R$ 161.2 billion for expenses executed in 2023[ii], added to the PPA 2024-2027 forecast on health budget actions[ji] of R$ 816.75 billion, totaled an estimated R$ 977.98 billion for five years (2023-2027). Compared to the scenarios previously presented at this level, it is expected that there will be an increase of between 1.7% and 5.4% on the total budget foreseen for the health sector in five years.

For the scenarios of immediate incorporation (i) and full entry after one year of analysis (ii), the disaggregated impacts per year ranged from approximately R$6 billion to 14 billion (Chart 1 and Chart 2). In relation to case (iii), the costs of acquiring the TPAs in the first year were estimated between R$ 1.2 and R$ 2.4 billion (Graph 3).

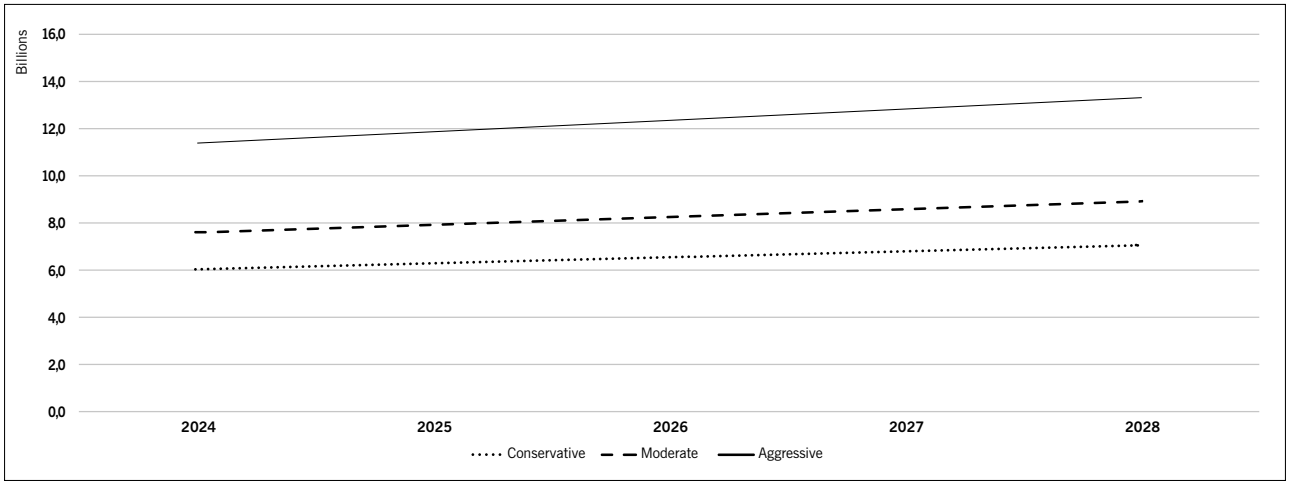
The results presented allowed us to measure the potential impact of the incorporation of new advanced therapy products in the SUS. Thus, it is intended to contribute to the analysis process of government decision-making agents, by bringing greater emphasis to one of the main components of the cost of treatment of these diseases.

Discussion

Although Brazil has implemented a TPA regulation system since 2018, currently, five products have already been priced by CMED, demonstrating their viability for commercialization. However, of these, only one was incorporated into the Unified Health System (SUS) on the recommendation of CONITEC.

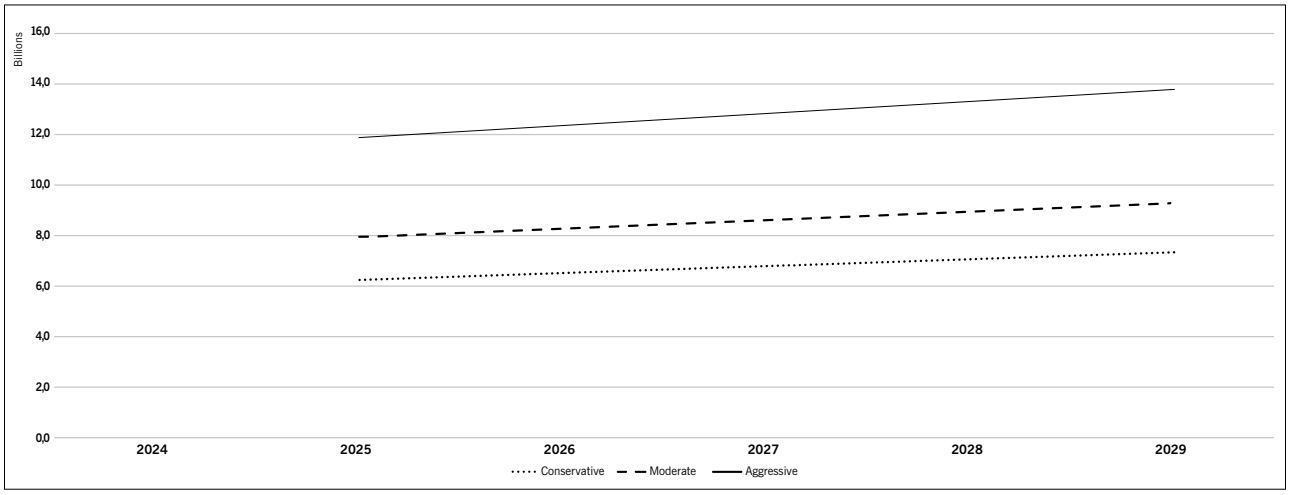
Given this scenario, it is necessary to evaluate and innovate on the available financing models. Some examples are contractual agreements, such as risk sharing between payers and developers of the technologies; price negotiation; creation of a specific fund for high-cost medicines; value-based payment models; policies to encourage R&D; subsidies; and international purchasing consortia.

Graph 1. Predicted annual impact for each Case scenario (i) – 2024 to 2028



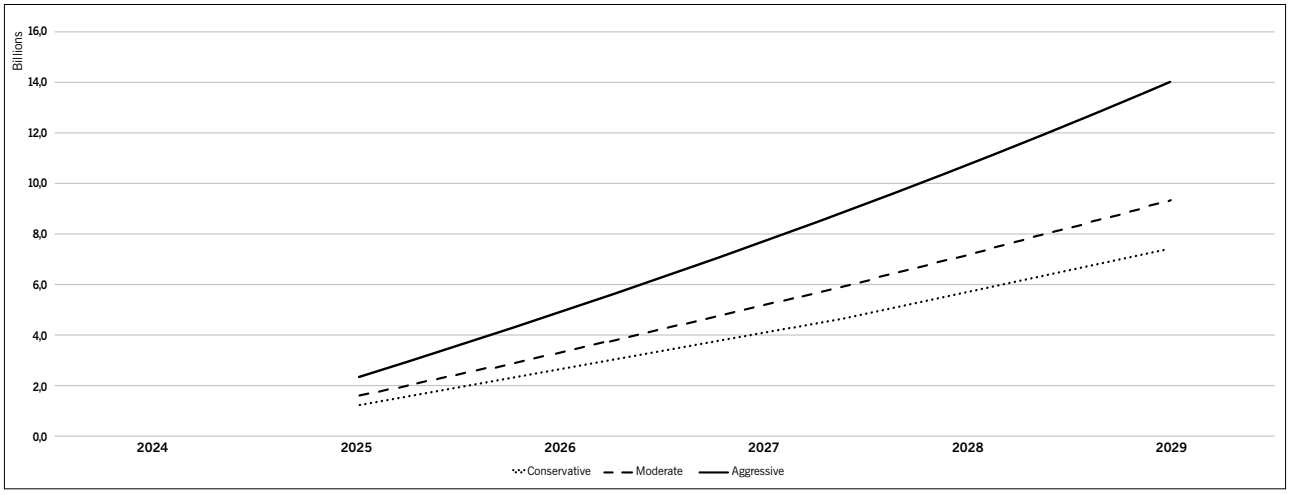
Source: Prepared by the authors

Graph 2. Predicted annual impact for each Case scenario (ii) – 2025 to 2029



Source: Prepared by the authors

Graph 3. Predicted annual impact for each scenario of Case (iii) – 2025 to 2029



Source: Prepared by the authors

There are already risk-sharing agreements between international health systems and TPA manufacturers, but in Brazil, this practice is still incipient.[19,20] The first gene therapy incorporated into the SUS for Spinal Muscular Atrophy (SMA) linked the payment for the clinical performance of the treatment, resulting in the need for patient monitoring to collect data on the treatment.[21,22]

Co-financing mechanisms can use public or philanthropic sources as a means to attract private sector investment.[23] Also under discussion is the approach of blended finance as a strategy to mobilise additional finance, involving different combinations of stakeholders, such as public-public and/or public-private participation.[24]

The establishment of national policies and the strengthening of SUS strategic capacity can contribute to mitigating technological dependence and putting into effect the principles of universality, equity, and integrality of health care.[25] In Brazil, there are two specific policies for the promotion of the Economic-Industrial Health Complex (CEIS) that can promote technological development and local production: the National Strategy for the Development of the CEIS26 and the New Industry Brazil – Plan for Neoindustrialization.[27]

Measuring the impact of these new high-cost technologies also allows us to assess and compare the feasibility of available financing strategies. Thus, the main objective is to provide subsidies to optimi-

ze the resources available in the health sector, in order to provide greater access and quality in the care provided to society.

Conclusion

This study presented, in an unprecedented way, the potential budgetary impact on the SUS of the incorporation of a small sample of TPAs already on the market in the international scenario, focused on rare and onco-hematological diseases. Over five years, the estimated impact ranged from R$16.7 billion to R$53.2 billion, depending on the different assumptions about the speed of incorporation and the incidence. This result reveals a significant commitment of the annual budget of the SUS to only 15 TPAs, indicating its relevance in discussions about the sustainability of the sector.

The scenario of immediate incorporation was based on the constitutional right to health, which provides that the SUS will pay for several non-incorporated treatments to guarantee the right to universal health. An example of this is Zolgensma; when the Ministry of Health financed at least 75 treatments through lawsuits, at a cost of 12 million reais per dose, totaling R$ 715.7 million before it was incorporated into the SUS.[28] However, it is understood that the scenario of entry within one year of analysis is more likely, given that the incidence applied to the entire population does not consider the potential barriers applicable to the population eligible for access to these products.

The impacts measured in this study have several limitations. Initially, it was not possible to obtain a historical series of the number of individuals diagnosed with the conditions mentioned in Brazil. It is noteworthy that several official and scientific sources were accessed, however, divergences were found. In addition, the repressed demand corresponding to the prevalence of the diseases in question was not taken into account.

Regarding prices, the possibility of new unmapped or entry incorporations of products listed in other countries of the analyzed basket is highlighted, which may alter the parameter of the lowest international price selected. Exchange rate variations can also affect the cost in national currency.

It is important to emphasize that the budget impact estimate presented does not measure the other direct and indirect costs involved in the treatment of the patient for each specified disease. Linked to the price of the product, the guidelines for economic evaluation in health establish the need to detail the costs incurred by the decision-maker, separated by type (medical-hospital direct, non-medical-hospital direct, indirect and intangible).[29] Therapies with CAR-T cells, for example, add to the price of the technology the costs of hospitalization, procedures, other inputs, and factors, such as care for the occurrence of adverse events.[30,31]

Although these are preliminary results, it is understood that the maturation of advanced products in the international sphere can have high repercussions in Brazil. Therefore, the evidence found reinforces the relevance of monitoring this market to ensure the balance between the quality of health care and the sustainability of the sector.

Author contributions
DVA: conception and design of the study and writing of the manuscript; CGS: Conception and design of the study, data collection and writing of the manuscript; ACCC: study design and manuscript review; GO: validation of the economic analysis and writing of the manuscript; LS: manuscript review; AP: impact analysis and financial modeling; AM: projections for pricing and incidence and writing of the manuscript; JPM: analysis and development for pricing and advocacy and writing of the manuscript; PHP: data collection; JPM: methodological design for pricing and incidence and writing of the manuscript.

Conflicts of interest
The authors declare no conflicts of interest.
Responsible Editor
Lindemberg Assunção-Costa.

References

1. Gomes KLG, Silva RE, Silva Junior JB, Novaes MRCG. Comparison of new Brazilian legislation for the approval of advanced therapy medicinal products with existing systems in the USA, European Union and Japan. Cytotherapy. 2022; 24(5): 557–66.
2. Goula A, Gkioka V, Michalopoulos E, Katsimpoulas M, Noutsias M, Sarri EF et al. Advanced

Therapy Medicinal Products Challenges and Perspectives in Regenerative Medicine. J Clin Med Res. 2020; 12(12): 780–6.
3. Moody J, Milligan WD, St Onge M, Goonewardene A, Rivers P. Cell and gene therapy: a snapshot of investor perspectives. Cytotherapy. 202; 23(3): 256–60.
4. Iglesias-Lopez C, Agustí A, Vallano A, Obach M. Methodological Characteristics of Clinical Trials Supporting the Marketing Authorisation of Advanced Therapies in the European Union. Frontiers in Pharmacology. Frontiers Media S.A. 2021; 12.
5. Chavez JC, Bachmeier C, Kharfan-Dabaja MA. CAR T-cell therapy for B-cell lymphomas: clinical trial results of available products. Ther Adv Hematol. 2019; 10: 1–20.
6. Mohyuddin Gr, Rooney A, Balmaceda N, Aziz M, Sborov DW, McClune B et al. Chimeric antigen receptor T-cell therapy in multiple myeloma: A systematic review and meta-analysis of 950 patients. Blood Adv. 2021; 5(4): 1097–101.
7. Yu WL, Hua ZC. Chimeric Antigen Receptor T-cell (CAR T) therapy for hematologic and solid malignancies: Efficacy and safety-A systematic review with meta-Analysis. Cancers (Basel). 2019; 11(47): 1–27.
8. Teoh PJ, Chng WJ. CAR T-cell therapy in multiple myeloma: more room for improvement. Blood Cancer J. 2021; 11(84): 1–18.
9. Brennan TA, Wilson JM. The special case of gene therapy pricing. Nat Biotechnol. 2014; 32(9): 874–6.
10. Dowdalls J. $1-million price tag set for Glyberagene therapy. Nat Biotechnol. 2015; 33.
11. Gonçalves, E. Value-based pricing for advanced therapy medicinal products: emerging affordability solutions. Eur J Health Econ. 2022; 23(2): 155-163.
12. Who. World Health Organization Regional Office for Europe. Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research [Internet]. 2015. Available from: http://www.euro.who.int/pubrequest- [accessed in February 13, 2024]
13. Brazil. Ministry of Health. Methodological Guidelines: Economic Evaluation Guideline. Secretariat of Science, Technology and Strategic Inputs. Department of Science and Technology (2nd ed.). 2014.
14. Leelahavarong P. Budget Impact Analysis. Journal of Medical Association of Thailand. 97 (Suppl. 5): S65-S71. 2014.
15. Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins C, Nuijten M et al. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices – budget impact analysis. Value in Health 2007; 10: 336-47.
16. Orphadata Science. Orpha.net, 2023. The portal for rare diseases and orphan drugs. Available from: ttps://www.orpha.net/consor/cgi-bin/Disease_Search.php?data_id=13913&lng=en- [acessed in November 10, 2023].
17. Conitec. Recommendation Report No. 664: Voretigene neparvovec for biallelic RPE65 mutation-mediated hereditary retinal dystrophy, September 2021. Brasília, DF.
18. Valentim J, Prado M. Social Discount Rates. 2008. Available from: http://dx.doi.org/10.2139/ssrn.1113323- [accessed in November 10, 2023].
19. Vianna D, Sachetti CG, Boaventura P. Risk Sharing Agreement: a pilot project in the Brazilian Unified Health System. J Bras Econ Saúde. 2022; 14(Suppl.1): 101–7.
20. Zampirolli Dias C, Godman B, Gargano LP, Azevedo PS, Garcia MM, Souza Cazarim M et al. Integrative Review of Managed Entry Agreements: Chances and Limitations. Pharmacoeconomics. 2020; 38(11): 1165–85.
21. Brazil. Conitec. MS and Novartis sign commitment for the development of a risk-sharing agreement for SMA. Available from: https://www.gov.br/conitec/pt-br/assuntos/noticias/2022/dezembro/ms-e-novartis-firmam-compromisso-para-elaboracao-do-acordo-de-compartilhamento-de-risco-para-ame. [accessed in February 25, 2024].
22. Guimarães R. New challenges in health technology assessment (HTA): the case of Zolgensma. Ciência e Saúde Coletiva. 2023; 28(7): 1881–9.
23. Mc Guire F, Vijayasingham L, Vassall A, Small R, Webb D, Guthrie T et al. Financing intersectoral action for health: A systematic review

of co-financing models. Global Health. 2019; 15(1).
24. OECD Development Co-operation Directorate. The OECD DAC. Blended Finance Guidance. 2021. Available from: https://www.oecd-ilibrary.org/development/the-oecd-dac-blended-finance-guidance_ded656b4-en - [accessed in February 13, 2024]..
25. Gadelha CAG, Braga PSC. Health and innovation: economic dynamics and Welfare State in Brazil. Cad Saúde Publica. 2016; 32 (Sup 2: e00150115): 1–13.
26. Brazil. Planalto. Available from: https://www.gov.br/planalto/pt-br/acompanhe-o-planalto/noticias/2023/09/presidente-lanca-nova-estrategia-nacional-para-o-complexo-economico-industrial-da-saude- [accessed in February 25, 2024].
27. Máximo W. Understand the Nova Indústria Brasil program. Agência Brasil. 01/22/24. Available from: https://agenciabrasil.ebc.com.br/economia/noticia/2024-01/entenda-o-programa-nova-industria-brasil- [accessed in February 25, 2024].
28. Pereira V. Judicialization of Health: Availability of Zolgensma® Gene Therapy through the Unified Health System for Patients with Spinal Muscular Atrophy. Dissertation of the Professional Master's Program in Public Administration at the Brazilian Institute of Education, Development, and Research (IDP). 2022.
29. Brazil. Ministry of Health. Methodological Guidelines: Economic Evaluation Guideline. Secretariat of Science, Technology, and Strategic Inputs. Department of Science and Technology (2nd ed.). 2014.
30. Choi G, Shin G, Bae SJ. Price and Prejudice? The Value of Chimeric Antigen Receptor (CAR) T-Cell Therapy. International Journal of Environmental Research and Public Health. MDPI. 2022; 19.
31. Lyman GH, Nguyen A, Snyder S, Gitlin M, Chung KC. Economic Evaluation of Chimeric Antigen Receptor T-Cell Therapy by Site of Care among Patients with Relapsed or Refractory Large B-Cell Lymphoma. JAMA Netw Open. 2020.