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BUDGET IMPACT ANALYSIS OF MEDICINES: ESTIMATED VALUES VERSUS REAL-WORLD EVIDENCE AND THE IMPLICATIONS

SHORT TITLE

BIA: ESTIMATED VALUES VERSUS REAL-WORLD EVIDENCE AND THE IMPLICATIONS

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ABSTRACT

Objectives: Budget Impact Analyses (BIA) of medicines helps managers in promoting health systems' sustainability when assessing the role and value of new medicines. However, it is not clear whether BIAs typically underestimate or overestimate the impact on real-world budgets. This retroactive analysis seeks to compare estimated values obtained by a BIA and Real-World Evidence (RWE) to guide discussions. **Methods**: The estimated values were obtained through a BIA concerning the incorporation of adalimumab for the treatment of Rheumatoid Arthritis into the Brazilian Unified Health System (SUS) carried out retroactively and per international guidelines. RWE data was extracted from SUS computerized systems. We subsequently compared the number of treatments, costs, and Incremental Budget Impact (IBI). **Results** - The total number of treatments was underestimated by 10% (6,243) and the total expenditure was overestimated by 463% (US$ 4.7 billion). In five years, the total difference between the estimated values and real IBI reached US$ 1.1 billion. A current expenditure of US$ 1.0 was observed for every US$ 5.60 of estimated expenditure. **Conclusion** - The higher estimates from the BIA might cause decision makers to be more cautious in the introduction of the new drug to reduce the opportunity costs for other interventions.

1. BACKGROUND

Health Technology Assessments (HTA) are fundamental for managers of public or private health systems to review, update, and change clinical and therapeutic guidelines when new information including new technologies become available. This also includes potential areas of disinvestment [1-3]. Incorporating a new health technology into a healthcare system requires demonstrating their clinical benefits combined with their cost-effectiveness as well as the

economic feasibility. The economic feasibility with new medicines is becoming increasingly important with global spending on medicines likely to reach US$1.5 trillion by 2023 with approximately 50% of total expenditure on new specialty medicines, including those for chronic, complex, or rare diseases that require incorporating into healthcare systems including medicines for cancer and immune diseases [4]. The cost of new medicines in these areas have been growing in recent years, with often concerns with their value [5-9], which have resulted in calls for new models to better assess their value and funding [10]. Budget Impact Analysis (BIA) can help with decision making especially for new premium-priced technologies with increasing pressure on resources with estimates of the medium-term financial consequences of introducing or changing technology in a given healthcare system. In this sense, the BIA is the stage of an HTA that reveals whether a specific, safe, efficacious, effective, and efficient technology is economically accessible to a healthcare system, especially one that strives to attain or retain universal healthcare [11-16].

Good BIA guidelines have been developed over the past few years by HTA-linked institutions and systems in a number of countries including Australia, Canada, the United Kingdom, and Brazil [17,18,]. However, studies have shown concerns about the quality of a number of these analyses including conclusions [12,14,19-22]. This needs to be addressed. Concurrent with this, there is increasing realization that patients in clinical studies tend to be less co-morbid that those in routine clinical care [23,24]. Consequently, there is a need for Real-World Evidence (RWE) alongside the findings from randomized clinical trials to fully assess the role, value and budget impact of new technologies. RWE can be collected as part of outcome-based managed entry agreements especially with for instance new oncology medicines which are increasingly being launched early to address areas of unmet need as part of accelerated approvals with often considerable uncertainty [5, 25-28].

In view of this, we believe there is a need to compare estimated values and RWE to ascertain potential weaknesses in the approaches between the two methods and subsequently promote a greater degree of accuracy of BIAs to enhance their future utility. *Retroactively, we carried out a case study to evaluate the incorporation of adalimumab (ADA) in the Brazilian public system that helped in the treatment of patients with rheumatoid arthritis (RA) in 2006.* At that time, the estimated worldwide prevalence for RA was 1% of the population [29], affecting more than 1.3 million Brazilians [30]. *Between 2000 and 2007, the year following the incorporation of ADA, Ministry of Health of Brazil (MoHB) increased its spending on high-cost medicines by 106% [31].* The higher estimates from the BIA might cause decision makers to be more cautious in the introduction of the new drug to reduce the opportunity costs for other interventions. Consequently, we sought to undertake such a comparison. We believe our findings will have international relevance since the Brazilian guidelines are included in international BIA guidelines [11-14,18,32,33].

2. RESEARCH DESIGN AND METHODS

2.1 Study setting

The Brazilian Unified Health System (SUS) guarantees universal access and full coverage to all citizens. The financial resources for financing the system derive from taxes and levies [34] collected by the Federal Government, States, and Municipalities. Until 2011, HTAs were conducted by a sectoral commission of MoHB [35,36]. Following this, the National Commission for the Incorporation of Technologies in the SUS (CONITEC) [37,38] was created and assumed such responsibility.

The treatment of chronic diseases in Brazil is governed by specific clinical protocols and therapeutic guidelines (PCDT). Brazilian patients with chronic diseases can access free-of-charge approved medicines through an administrative process conducted by the SUS that verifies and authorizes the request for treatment considering the PCDTs. Patients receive their medication

monthly through regular reassessments in order to continuing to justify their use [39]. In this way, SUS can monitor through its computerized system utilization rates, physician prescribing and costs. Patients are subject to 100% co-payment for treatments outside of these protocols to conserve resources [40-42] unless their lawsuits are successful [43,44].

As mentioned, ADA is indicated for the treatment of active, moderate to severe RA in adult patients with an inadequate response to disease-modifying antirheumatic drugs. In 2006, ADA and etanercept (ETA) were incorporated for the treatment of RA [29] as an alternative to Infliximab (INF), until then the only biological medicine available [45]. Until 2010, the different States in Brazil were responsible for the entire process of purchase, storage, distribution, dispensing, and other expenses, but the MoHB reimbursed the drug costs. However, as of 2011 the MoHB assumed the responsibility for purchasing these drugs. We believe ADA's choice for the case study is justified due to the considerable financial consequences associated with its incorporation into SUS [44].

2.2 Study design

A retroactive BIA was performed between January 1, 2006, and December 31, 2010, considering SUS incorporation of ADA for RA treatment, comparing estimated values to RWE to guide future considerations.

2.2.1 Values determined with the modeled calculation of the budget impact before uptake was known

The estimated values were obtained using the SUS BIA Guidelines [17,46]. Calculations were retroactive to early 2006 when ADA had not yet been incorporated into SUS. Calculations employed data of that year from scientific studies, data provided by the MoHB, and information from the market. The analysis perspective adopted was that of the SUS, with a five-year time horizon (2006-2010). No mid-cycle adjustment was implemented. Three comparison settings

were established among the biological medicines used for RA: Benchmark setting (INF), the standardized treatment before 2006; Alternative setting A (INF+ADA+ETA) prioritizing INF; Alternative setting B (INF+ADA+ETA) prioritizing INF and ADA; Alternative setting C (INF+ADA+ETA) prioritizing ADA. The specific parameters and respective sources are described in Table 1.

Table 1. Parameters used for BIA of ADA, for RA in the SUS (2006 to 2010)

SETTINGS				
Settings composition	**INF 10 Mg**	**ADA 40 Mg**	**ETA 25 Mg**	**Sources**
(INF)	100%	0%	0%	Authors' choice based on: COWEN, 2009 [47]; JONSSON et al., 2008 [48]; COSTA et al., 2014 [49]; SILVA et al., 2014 [50]
A (INF+ADA+ETA)	70%	25%	5%	
B (INF+ADA+ETA)	50%	40%	10%	
C (INF+ADA+ETA)	32%	55%	13%	
ADA incorporation rate	**Model**	**Values for sensitivity analysis**		**Sources**
Year 1	5%	10%		Authors' choice based on: COWEN, 2009 [47]; JONSSON et al., 2008 [48]; COSTA et al., 2014 [49]; SILVA et al., 2014 [50]
Year 2	50%	25%		
Year 3	70%	55%		
Year 4	90%	80%		
Year 5	100%	100%		
POPULATION				
Definition of the population of interest	**Data**			**Sources**
Methods	Epidemiological			BRASIL, 2006 [29]; COSTA et al., 2014 [49]; SILVA et al., 2014 [50]
Brazilian population	187,336,137	100.00%		BRASIL, 2016 [51]
Eligible population	23,004,878	12.28%		FURST et al., 2003 [52]; WEINBLATT et al., 2003 [53]; KEYSTONE et al., 2004 [54]; VAN DE PUTTE et al., 2004 [55]
Disease prevalence	230,049	1.00%		van DE PUTTE et al., 2004 [55]; BRASIL, 2006 [29]
Restriction treatment DMARD-B SUS	23,005	10.00%		van de PUTTE et al., 2004 [55]; COSTA et al., 2014 [49]; GOMES, et al., 2016 [56]
Restricted access to drug SUS	11,502	50.00%		GUERRA JR et al., 2004 [57]; TASCA et al, 1999 [58]; CAHVES et al, 2005 [59]; PAHO, 2006 [60]
Increased judicialization demand	11,516	0.12%		BRASIL, 2012 [43]; FALCONETTI et al.; 2012 [44]
Disease dynamics - Factors that can change the population of interest				
% increased annual prevalence	Not applicable to RA			BRASIL, 2012 [17]
Mortality rate standard treatment	Not applicable to RA			
Mortality rate new treatment	Not applicable to RA			
COSTS				
Drugs	**INF 10 Mg**	**ADA 40 Mg**	**ETA 25 Mg**	**Sources**
Unit cost	US$ 2,016.64	US$ 2,282.86	US$ 1,423.45	BRASIL, 2016 [65]
Monthly Volume (Units)	4,50	2,17	8,67	BRASIL, 2006 [29]

Values for sensitivity analysis				
Lower cost of drug	US$ 1,845.86	US$ 2,111.78	US$ 754.37	BRASIL, 2016 [65]
Higher cost of drug	US$ 3,047.06	US$ 2,366.92	US$ 820.13	

INF: Infliximab; ADA: Adalimumab; ETA: Etanercept; DMARD-B: Disease-Modifying Antirheumatic Drugs - Biological; RA: Rheumatoid Arthritis; Mg: Milligrams; US$: US. American Dollars.

The market shares estimated for each biological medicine in each setting and the annual ADA incorporation rate were based on international market projections for the analyzed period recorded in reports from the pharmaceutical companies [47] and academic studies [48-50].

The total Brazilian population data, including age group compositions in 2006, was retrieved from the Brazilian Institute of Geography and Statistics (IBGE) [51]. The epidemiological method was adopted to calculate the population of interest, considering a prevalence of 1% of the total population [17]. The average age group of the population of interest was 52.7 years, the lowest found among the scientific studies published between 2003 and 2004 [52-55].

Three types of population restriction to the SUS were evaluated to identify the size of the population of interest: RA treatments with biologic medicines, access to medicines, and access to Primary Care Program (PHC). The first restriction refers to the number of RA patients treated by the SUS with biologic medicines. These studies [48,50,56] record data from 1996 facilitated by the MoHB (only 10% of RA patients used biological medicines). The second concerns access in the medicines availability dimension: the restriction rate adopted was 50%, based on published studies and other sources between 1998 and 2005 [57-60]. The third was based on the population parameter covered by the SUS' PHC and is justified by the understanding that citizens with no access to PHC do not have a diagnosis or medical prescription to access medicines. The coverage rate adopted was 55.9%, according to data from the MoHB for 2005 [61]. *We decided to keep only the first two restrictions because they are related to the population's access to biological medicines. After all, we are aware that the use of biological drugs to treat patients with immunological diseases, such as rheumatoid arthritis and other*

chronic diseases, has severely limited budgets in Central and Eastern European countries and even in Western European countries, despite some these are seen as high-income or close to high-income countries [62-64].

A potential judicial access demand rate was estimated from the number of lawsuits against the MoHB [43] and a study [44] on judicialization in Brazil published after 2006 but with data records available at the time. The mortality rate was not considered in population calculations since, as established by the guideline [17], in chronic diseases with low incidence and associated mortality, such as RA, the disease's dynamics barely influence the projected budget impact. Thus, the population remains stable over the five years as a result of the modeling.

The prices employed for the analyzed medicines were obtained by accessing MoHB's Health Price Database (BPS) [65] and referring to SUS purchases in the analyzed period. Each value for given medicines was derived from weighted averages (values and volume of items purchased). The administration schedules were established according to the standards of the time for INF [66], ADA [67] and ETA [68].

As indicated in the Brazilian guidelines, the model's uncertainties were assessed through undertaking sensitivity analysis, recalculating the spreadsheets, with changes in the following variables: ADA utilization rate, the population of interest, and medicine price as shown in Table 2.

Table 2. Incremental Budget Impact by comparing INF, ADA, ETA settings in the incorporation of ADA for RA into the SUS (2006 to 2010)

Budget Impact Analysis: ADA 40 mg AR treatment					
Analysis perspective: SUS-BR			**Reference setting:** 100% INF		
Time horizon: 5 years			**Setting A:** 70% INF + 25% ADA + 5% ETA		
Population size: 11,516			**Setting B:** 50% INF + 40% ADA + 10% ETA		
Incremental Impact: No avoided costs			**Setting C:** 32% INF +55% ADA + 13% ETA		
Setting A *vs.* Reference			**Setting B vs Setting A**		
Year	**USD Million**	**Difference (%)**	**Year**	**USD Million**	**Difference (%)**
2006	21.68	1.7	2006	38.40	3.0
2007	-45.80	-3.7	2007	-9.97	-0.8

2008	-75.79	-6.0	2008	-31.47	-2.7
2009	-105.78	-8.4	2009	-52.96	-4.6
2010	-120.77	-9.6	2010	-63.71	-5.6
In 5 years	**-326.45**	**-5.2**	**In 5 years**	**-119.71**	**-2.0**
Setting B *vs.* Reference			**Setting C vs Setting A**		
Year	**USD Million**	**Difference (%)**	**Year**	**USD Million**	**Difference (%)**
2006	60.08	4.8	2006	85.59	6.7
2007	-55.77	-4.4	2007	-19.45	-1.6
2008	-107.25	-8.6	2008	-66.14	-5.6
2009	-158.74	-12.7	2009	-112.83	-9.8
2010	-184.48	-14.7	2010	-136.17	-12.0
In 5 years	**-446.16**	**-7.1**	**In 5 years**	**-249.01**	**-4.2**
Setting C *vs.* Reference			**Setting C vs Setting B**		
Year	**USD Million**	**Difference (%)**	**Year**	**USD Million**	**Difference (%)**
2006	107.28	8.6	2006	47.20	3.6
2007	-65.25	-5.2	2007	-9.48	-0.8
2008	-141.93	-11.3	2008	-34.68	-3.0
2009	-218.61	-17.4	2009	-59.87	-5.5
2010	-256.95	-20.5	2010	-72.46	-6.8
In 5 years	**-575.46**	**-9.2**	**In 5 years**	**-129.29**	**-2.2**

Calculations performed by the Brazilian Health Technology Budget Impact Worksheet [46]
RA: Rheumatoid Arthritis; INF: Infliximab; ADA: Adalimumab; ETA: Etanercept

The BIA was validated from this study's outcome, which compared the outcomes of the estimated values and RWE. Indirect costs and discounts were not considered in the calculations in line with guidance on BIAs from a health authority perspective.

Inclusion criteria included patients treated by SUS, according to the parameters of the guideline in force at the time [45], with a population identified according to the following codes of the International Classification of Diseases (ICD-10): M05; M06. Exclusion criteria was according to use restrictions of the new intervention described in Table 1.

2.2.2 Values determined with the Real-World Evidence

MoHB administrative data were used to obtain RWE's outcomes, which referred to all records and payments of SUS hospital and outpatient procedures including medicines costs. A national cohort based on the population of patients undergoing RA treatment was built from January 2000 to December 2010, using a deterministic-probabilistic relationship technique, with more than 3.5 billion data records. This technique enabled the integration of the following databases

of the Brazilian public health system: Hospital Information System (SIH), Outpatient Information System (SIA), and Mortality Information System (SIM). The deterministic-probabilistic relationship was undertaken by linking data with a reliable, unique identifier (deterministic), and others by weighting the identifiers according to the degree of pairing certainty and precision (probabilistic) [69-75]. The possibility of a lack of success with this technique is 2% to 5% of the total data, which does not compromise the validity or quality of this study.

Inclusion criteria: Patients treated by SUS, according to parameters contained in the PCDT - Rheumatoid Arthritis [29] in force between 2006 and 2010, with a population identified under the following ICD-10 codes: M05.0; M05.1; M05.2; M05.3; M05.8; M06.0; M06.8; M08.0. There were no exclusion criteria.

2.3 Variables and sources

The annual data related to the following variables were calculated for each setting to obtain the estimated values outcomes: Number of patients; Treatment cost; Budget impact value.

Data related to the following variables were extracted from the data records contained in the SIH, SIA, and SIM databases to obtain the real-world outcomes: User profile (age, gender, start and end dates of treatment, and ICD 10); Treatment data and comorbidities (start and end dates of procedures, drug therapy, and procedural care line, and volumes and values spent on procedures and drugs). Gender, age category, the region of residence, diagnosis according to ICD-10 codes, the medication used and respective therapeutic class, and the calendar year were included. Variables were also used for events that occurred during follow-up. These included medication change, comorbidities, and death.

The medicines listed in the therapeutic regimens were categorized as Disease-Modifying Antirheumatic Drugs - Biological (DMARD-B), with distinction for INF, ADA, and ETA. Other medicines were also listed include other non-biological Disease-Modifying Antirheumatic Drugs

(DMARD-NB). Outpatient procedures included medications, laboratory tests, and diagnostic procedures. Outpatient and hospital procedures costs were based on the values recorded in the SIH and SIA databases. Drug costs were determined by the price recorded by the Brazilian government during the period analyzed [76].

2.4 Monetary values

We did not use any discounts during our calculations. This is because international guidelines and authors recommend not using discounts in BIA calculations since it is up to the budget holder to know the financial impact of the BIA comparing at the same time the values obtained, the available budget and the purchasing power [11,14,15]. Consequently, excluding any types of monetary adjustment, interest, or monetary value restatement.

All monetary amounts were converted to US$ adjusted by the Purchasing Power Parity (PPP) according to figures provided by The World Bank by calendar year [77]. The following exchange rates were considered: 1 US$ = 1,0986 BRL (2006) = 1,1391 BRL (2007) = 1,2153 BRL (2008) = 1,2944 BRL (2009) = 1,3863 BRL (2010).

2.5 Criteria employed to compare the outcomes

The following indicators were compared to compare the estimated values and RWE outcomes related to incorporating ADA by the SUS in the RA treatment: Number of treatments; Treatment cost; Budget impact value. The most advantageous outcomes for the SUS were adopted from the estimated values . In other words, the outcomes of the setting that indicated the lowest budget impact.

Real-life data were analyzed using a unique numeric identifier which keeps patients anonymous. The methodology for calculating RWEs was approved by the Research Ethics Committee of the Federal University of Minas Gerais under ETIC 0069.0.203.000-11.

3. RESULTS

3.1 Outcomes of the budget impact estimated values calculation

In five years, scenarios C (32% INF + 55% ADA + 13% ETA), in comparison with the others, presented more advantageous results, from the perspective of the public health system, with savings of 9.2% (US $ 575.46 million) in relation to the reference scenario (100% INF).In the most advantageous setting, the total population attended in the analyzed period would be 57,581 patients, equally divided between the years. The following apportionment was seen between the three biological treatments: INF (46.5%), ADA (34.7%), and ETA (18.9%) (Table 4). In financial terms, SUS total expenditure in the analyzed period would be US$ 5.69 billion (Table 4).

Sensitivity analysis performed with varying ADA usage rates of the population of interest and medicines values showed consistent outcomes since setting C remained the most advantageous alternative despite significant variation in financial values.

3.2 Outcomes recorded by real-world evidence (RWE)

Between 2006 and 2010, RWE registered a total of 111,343 people treated for RA treatment, with all lines of care and medication, mostly women (80.6%). A total of 17,390 (15.6%) treatments used DMARD-B drugs *and that started treatment with*: INF (5.4%); ADA (6.05%); ETA (4.1%). The mean expenditure per treatment with biological medication was US$ 8,199.40 (INF); US$ 9,647.86 (ADA); US$ 11,798.61 (ETA). On the other hand, 87,789 (78.05%) treatments were performed only with non-biological DMARDs (DMARD-NB), at an average cost of US$ 3,005.89. The 46-55 years' age group recorded the highest number of treated patients (30,103, 27.0%), and 2007 recorded the highest number of patients at the onset of treatment (26,184, 23.5%) (Table 3).

RWE also allowed knowing the number of procedures including adjuvant treatments performed in SUS in patients with RA and their respective costs. The procedures were classified considering that the same patient may have had occurrences in more than one class.

Total expenses in the period analyzed were US$ 1.20 billion. Medicines were the highest expenditure item accounting for at five years a total of US$ 1.13 billion (94.4%): DMARD-B (US$ 1.01 billion, 84,5%); DMARD-NB (US$ 116.17 million, 9,6%); others (USD 2.30 million, 0.3%). After these, clinical procedures cost a total of US$ 30.21 million (2.5%) over the 5 years, surgical procedures US$ 26.21 million (2.2%), diagnosis cost US$ 7.22 million (0.6%), transplant cost US$ 2.99 million (0.2%), and other costs a total of US$ 0.85 million (0.1%). Total expenditure over the 5-year period was US$ 1.20 billion.

As established by the Brazilian guidelines, model uncertainties were assessed by undertaking sensitivity analyses, recalculating the spreadsheet with changes in the utilization rate of ADA, the population of interest, and drug prices according to parameters described in the BIA guideline of the SUS. The outcomes indicate consistency, given that setting C remained the most advantageous for SUS despite the significant variation in financial values.

3.3 Comparing treatment costs

Number of treatments - In the most advantageous setting of the estimated version, the total number of treatments with DMARD-B was 57,581, with 19,952 for ADA, against RWE, which totaled 63,824, with 26,414 for ADA (Table 4).

Treatment costs - In the most advantageous setting of the estimated values, the estimated total expenditure for the period analyzed for RA treatments with DMARD-B was US$ 5.69 billion, of which US$ 1.85 billion for ADA, against a real-world total of US$ 1.01 billion and US$ 465.55 million for ADA. The total cost estimate was overestimated by 463.3%, corresponding to US$ 4.69 billion (Table 4).

Budget impact value - RWE also allowed knowing the total expenditure of RA treatments with DMARD-B in the SUS in 2005. Consequently, we calculated the incremental Budget impact (IBI) and the differences, in absolute numbers, between real and estimated values. This accumulated US$ 1,175.69 million in the analyzed period (Table 5).

3.4 Accuracy of the findings

We verified the representativeness of the estimated values against the real outcomes to identify the outcomes' degree of accuracy. In the analyzed period, we observed a variation from 1,268% (overestimated) to 53% (underestimated) in the number of treatments, and from 13,005% (overestimated) to 152% for expenses, with variation in the per capita form between 858% and 417% (Table 5).

4. DISCUSSION

The outcomes from BIA support managers' decision-making within health systems coverage [11,13] regarding the accessibility of patients to a specific technology given likely budget restrictions especially within universal healthcare systems. BIAs also establish a budget plan for incorporation and provide a basis for promoting increased funding for new technologies into health care system when justified [12]. However, similar to the study by Snider et al. (2019), this retroactive study shows that there can be significant differences between BIAs derived with estimated values versus RWE BIAs despite being built in line with the leading international guidelines [78].

The population of interest is one of the essential variables for a robust BIA calculation, and it is necessary to provide an accurate estimate of the number of people [13]. The reimbursement method (measured demand) or the epidemiological model (with variables of prevalence, incidence, restrictions, and additional demands) can be used for the calculation, but the latter tends to overestimate the budget impact [11,13,16,29]. Our study overestimated more than 6,000 treatments during the period, mainly for the first years. In the first year alone, the expected number of treatments was 11,516 versus 842 actually performed. Consequently, for BIAs to be meaningful to managers, it is crucial to accurately estimate the transition of patients to the new treatment and observe the dynamic elements, which modify the size of the population of interest [29].

Among the factors that must be considered when undertaking BIAs are the patient's lack of knowledge about the availability of the new technology where pertinent, the patient's convenience in continuing the ongoing treatment, the possibility of not adapting to the new treatment, the logistics chain that involves the purchase, distribution, storage, professional training, and medication dispensing, and the number of treatments already available to patients. In addition, available finances with the potential for restricting usage where there are concerns [23,79]. The transition between treatments must be considered, especially in treating patients with chronic diseases where the replacement of a medication can compromise adherence to therapy [80].

The therapeutic package's direct costs must be considered in a BIA. This includes the cost of the analyzed technology and any directly associated costs including the use of adjuvant treatments for adverse events [11,13,16,17]. Similar to the population of interest, cost is one of the essential variables for any BIA calculation. Despite other economic assessments of health technologies comparatively analyzing two or more excluding technologies (health outcomes or their costs), BIA includes populations, the drug market, and cost data from the manager's perspective [17]. This is important especially in countries with universal healthcare systems and limited budgets.

Since the estimate of the budget impact is linked to the population of interest and costs, any inadequacy in calculating these variables implies a significant difference in the estimates. In this sense, when comparing the outcomes of this study, a considerable difference was observed between the financial outcomes achieved with the estimated values in the face of reality. ADA values were overestimated by 298%, reaching a difference of US$ 1.4 billion and overall costs biologicals were overestimated by 463% reaching US$ 4.7 billion. This major difference was caused mainly by two factors. Wrong population estimate: a transition between treatments, discontinuity due to change of medication or loss of patients was not considered. The estimate of the cost of treatment was the second factor: variations in drug prices over the years of the

analyzed period were not considered. Although the estimated total number of treatments in the period was less than the real one, the first two years registered numbers much higher than the real ones. This resulted in an estimated treatment expense higher than the real one. However, this difference tends to be even more significant, as the costs associated with treatment were not computed in the estimated values.

We believe this study is among the first to compare BIA outcomes with real-world data. Geenen et al. (2019) pointed out that in a BIA carried out to substantiate decisions on access to 10 cancer drugs in the Netherlands, the estimated value was € 140.7 million, while only € 82.1 million was actually spent [81]. Aiming to compare estimated values by pharmaceutical companies when evaluating the costs of recommended medicines in Wales, Keeping et al. (2019) reported that the total expenditure was overestimated by 41% to 62% over three years [82]. Similar, or even more significant deviations, have been reported by Broder et al. (2017) [83], Iwanczuk et al. (2015) [84], Cha et al. (2013) [85], and Sooksriwong & Chanjaruporn (2011) [86]. This is a concern as health system managers often rely on BIAs to determine drug coverage policy and its effect on their financial outcomes [78]. However, this study like others recorded significant differences between theory and practice. An accumulated difference of more than US$ 1.1 billion was observed at the end of the analyzed period. Disregarding the first year, since it is the most critical year to incorporate the new technology, the difference would be above US$ 1.0 billion, recording an annual overestimated average of US$ 267 million. To this end, coupled with ever increasing prices for new medicines, we are beginning to see countries develop robust models to better manage their entry [23,79,87]. This includes improved epidemiological models to better predict likely patient numbers for new medicines based on available data [23,87]. One such model has been introduced in Sweden starting with Horizon Scanning and preliminary budget impact of new medicines up to three years before launch, and carried on post-launch, including an assessment of outcomes in practice as well as an assessment of prescribing against agreed guidance [28,87-89]. As part of this, the Regions in Sweden also undertake annual

forecasts of likely drug expenditure including medicines that are likely to lose their patents and release valuable resources coupled with new medicines, their likely costs and likely patient numbers. Accuracy is enhanced by robust systems to monitor patient numbers and care [90].

We are aware that BIA studies have two limitations. These include different calculation methods – with or without the inclusion of certain variables or inputs – and selecting the population of interest. Concerning the BIA estimated model, the difficulties in obtaining and choosing data that faithfully reproduce local systems are also limitations. Specifically, for this study, the lack of inclusion of non-biological drugs can be identified as a limitation. However, as seen their costs were relatively small compared with the overall costs for the DMARDs-biologicals. The main limitation of RWE BIAs includes the availability of accurate epidemiological and treatment data. In addition, the model considered the duration of treatment for each patient over the 12 months, each year, not considering discontinuities, and this can interfere with the total annual cost. This is a limitation of the study, as well as a limitation of the BIA guideline.

5. CONCLUSION

Our study showed that estimates of the number of treatments and costs in the BIA were significantly higher than those recorded in the real world, totaling a difference of more than 6 thousand treatments and more than US$ 4.7 billion in five years. The estimated values expectation of stability in the number of treatments was the aspect that generated the greatest distortion between theory and reality, either by the number of patients or by its reflection in costs. The guideline does not consider an adequate transition, mainly for a health system in developing countries. The situation is aggravated by the fact that the guideline does not consider disease dynamics and the factors that can change the population of interest. In this sense, the guidelines should consider, especially in the first year, in the transition between technologies, both logistical and technical aspects that directly influence the number of treatments. This is in

addition to the suspected utilization rate of the incorporated drug and the market share of the various medicines.

Public systems and developing countries need to consider an increase in the number of treatments due to address key areas of unmet need. The outcomes presented here support methodological advances and point to the need for adjustments to the Brazilian BIA Guidelines and, consequently, other systems, to improve decision making especially if increased resources are needed. We will be following this up in the future.

KEY ISSUES

- Pharmaceutical companies seek to maximize their profits. On the other hand, (public and private) health systems look for ways to meet infinite demands within finite resources without moving away from the quality of care as well as incentivizing companies to develop new medicines to address areas of unmet need.

- BIAs seek to facilitate decisions by managers of public and private health systems. However, publications indicate that BIA studies are still not achieving their desired effect compromised by concerns with a number of published analyses.

- This study shows that BIAs must improve their acceptability, relevance and robustness despite being carried out according to the parameters established by international guidelines.

- Our findings also suggest the need to review the Brazilian BIA Guidelines and consequently that of other countries, incorporating advances in methodologies, to enhance their future utility. This includes a greater role for real-world evidence.

COMPLIANCE WITH ETHICS GUIDELINES

RWE were analyzed using a unique numeric identifier, which hinders distinguishing patients. The methodology that allowed knowing the RWEs was approved by the Research Ethics Committee of the Federal University of Minas Gerais under ETIC 0069.0.203.000-11

CONSENT FOR PUBLICATION

Not applicable.

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To users of the health system.

DECLARATION OF INTEREST

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

GEOLOCATION INFORMATION

Brazil

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AUTHOR CONTRIBUTIONS

Study design and governance: DRF; AAGJ. Write-up and ongoing critical review of the article: DRF; BBG; AAGJ. Materials/analysis tools: DRF; RGP; AAGJ. Ongoing study review and feedback regarding design, data collection, analysis and critical review of the manuscript: DRF; JAT; ENS; BBG; RGP; EIGA; FFA; AAGJ. All authors had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 3. RWE: Demographic and clinical characteristics and average costs of patients' RA and associated diseases treated through the SUS (2006 to 2010)

Parameter	N (%)	Average annual cost per patient US$ (SD)
Cohort	111,343 (100.00)	4,089.83 (1,031.07)
Gender		
Male	21,543 (19.35)	5,322.72 (1,622.36)
Female	89,800 (80.65)	3,801.87 (917.69)
Age at the onset of treatment, years, mean +-SD	49.09 (+-15.50)	-
Male	46.06 (+-16.79)	-
Female	49.82 (+-15.09)	-
Age range at the onset of treatment, years		
0-17 years	3,589 (3.22)	4,548.58 (1,395.30)
18-25 years	5,150 (4.63)	4,541.38 (1,077.35)
26-35 years	12,264 (11.01)	4,568.39 (1,217.04)
36-45 years	20,831 (18.71)	4,426.04 (1,101.11)
46-55 years	30,103 (27.04)	4,182.58 (1,058.77)
56-65 years	23,852 (21.42)	3,811.72 (973.35)
> 65 years	15,554 (13.97)	3,112.15 (823.05)
Residence Region, beginning of the cohort		
Southeast	52,223 (46.90)	4,620.84 (1,227.42)
South	16,707 (15.00)	3,424.73 (950.83)
Northeast	21,978 (19.74)	2,766.98 (536.08)
North	3,044 (2.73)	3,381.07 (697.75)
Midwest	5,650 (5.07)	5,463.97 (1,441.01)
Without identification	11,741 (10.54)	4,001.04 (986.68)
Primary diagnosis, onset of treatment		
Felty's Syndrome	39,059 (35.08)	3,789.48 (838.07)
Other serum-positive rheumatoid arthritis	31,326 (28.13)	4,171.88 (1,195.13)
Serum-negative rheumatoid arthritis	21,717 (19.50)	4,400.33 (1,227.21)
Other specified rheumatoid arthritis	9,603 (8.62)	4,145.65 (1,377.21)
Rheumatoid arthritis with involvement of other organs	4,365 (3.92)	4,078.89 (902.86)
Juvenile rheumatoid arthritis	2,846 (2.56)	4,965.54 (1,574.29)
Lung rheumatoid disease	1,725 (1.55)	3,465.17 (833.05)
Rheumatoid vasculitis	702 (0.63)	2,671.23 (486.74)
Pharmacological group, onset of treatment		
DMARD-S	87,789 (78.85)	3,005.89 (871.62)
DMARD-B	17,390 (15.62)	9,707.38 (4,492.64)
Immunosuppressant	4,434 (3.98)	2,501.86 (548.53)
DMARD-B+DMARD-S	968 (0.87)	9,480.25 (4,427.56)
DMARD-S+Immunosuppressant	710 (0.64)	2,469.67 (534.78)
DMARD-B+Immunosuppressant	42 (0.04)	10,554.05 (4,875.87)
Other pharmacological groups	10 (0.01)	7,978.78 (7,000.91)
Drug, onset of treatment		
Leflunomide	49,953 (44.86)	3,666.93 (1,116.80)
Hydroxychloroquine	14,004 (12.58)	1,152.75 (334.12)
Adalimumab	6,731 (6.05)	9,647.86 (5,727.36)
Chloroquine	6,730 (6.04)	1,076.36 (342.31)
Infliximab	6,061 (5.44)	8,199.40 (2,472.89)

Sulfasalazine	5,305 (4.76)	2,820.12 (861.06)
Methotrexate	4,857 (4.36)	2,280.22 (595.26)
Etanercept	4,590 (4.12)	11,798.61 (6,971.28)
Other drugs	13,112 (11.78)	3,435.25 (781.50)
Year of entry in the cohort, onset of treatment		
2006	17,946 (16.12)	3,948.35 (1,478.25)
2007	26,184 (23.52)	4,486.67 (1,322.98)
2008	24,726 (22.21)	4,677.18 (1,351.96)
2009	20,441 (18.36)	4,833.44 (1,492.39)
2010	22,046 (19.80)	4,389.99 (1,319.91)
Group CID10 – Deaths		
Ischemic heart disease	415 (9.30)	3,530.98 (1,036.94)
Inflammatory polyarthropathies	350 (7.85)	4,046.05 (1,867.32)
Cerebrovascular diseases	299 (6.70)	3,361.31 (607.62)
Influenza and pneumonia	284 (6.37)	3,403.92 (1,025.34)
Other heart diseases	251 (5.63)	3,062.23 (1,033.50)
Diabetes mellitus	191 (4.28)	3,278.83 (688.54)
Other groups CID10 – Death	2,670 (59.87)	3,601.72 (780.91)

DMARD: Disease-Modifying Antirheumatic Drugs (Simple or Biological)

Table 4. Annual number and value of estimated patients and RWE of ADA for RA in the SUS (2006 to 2010)

Year	INF			ADA			ETA			Total	
	n	US$ million	%	n	US$ million	%	n	US$ million	%	n	US$ million
Estimated values - Scenario C: more advantageous											
2006	7,964	941.43	69.2	317	37.44	2.8	3,235	382.46	28.1	11,516	1,361.32
2007	5,937	612.89	51.6	3,167	326.92	27.5	2,412	248.99	20.9	11,516	1,188.79
2008	5,036	486.37	43.7	4,434	428.16	38.5	2,046	197.59	17.8	11,516	1,112.12
2009	4,136	371.84	35.9	5,701	512.54	49.5	1,68	151.06	14.6	11,516	1,035.44
2010	3,685	319.07	32.0	6,334	548.40	55.0	1,497	129.62	13.0	11,516	997.10
Total	**26.759**	**2,731.59**	**46.5**	**19,952**	**1,853.46**	**34.7**	**10,871**	**1,109.71**	**18.9**	**57,581**	**5,694.77**
RWE											
2006	806	10.22	95.7	36	0.17	4.3	0	0.00	0.0	842	10.39
2007	3,642	43.75	57.6	1,632	20.25	25.8	1,054	13.65	16.7	6,328	77.65
2008	5,128	65.85	38.4	5,155	79.48	38.6	3,063	55.91	23.0	13,346	201.25
2009	5,181	59.52	27.6	8,225	154.41	43.8	5,356	112.37	28.5	18,762	326.31
2010	5,278	51.78	21.5	11,366	211.24	46.3	7,902	132.41	32.2	24,546	395.43
Total	**20,035**	**231.13**	**31.4**	**26,414**	**465.55**	**41.4**	**17,375**	**314.35**	**27.2**	**63,824**	**1,011.03**

RWE: Real-World Evidence; DMARD: Disease-modifying Antirheumatic Drugs (Biological); INF: Infliximab; ADA: Adalimumab; ETA: Etanercept

Table 5. Incremental Budget Impact (IBI) and annual representation real *vs.* estimated values of ADA for RA in SUS (2006 to 2010)

	2005	2006	2007	2008	2009	2010	Total
Incremental Budget Impact - DMARD-B (US$ million)							
Costs RWE	11.01	10.39	77.65	201.25	326.31	395.43	-
IBI - RWE		-0.63	67.26	123.60	125.05	69.13	-
IBI – Estimated		107.28	-65.25	-141.93	-218.61	-256.95	-
Absolute difference RWE vs. estimated		**107.91**	**132.51**	**265.53**	**343.66**	**326.08**	**1,175.69**
Annual representation - DMARD-B							
Treatments (n)							
Theory		11,516	11,516	11,516	11,516	11,516	57,581
Real		842	6,328	13,346	18,762	24,546	63,824
Representativeness		**1,268%**	**82%**	**-14%**	**-39%**	**-53%**	**-10%**
Total expenditure (US$ million)							
Theory		1,361.32	1,188.79	1,112.12	1,035.44	997.10	5,694.77
Real		10.39	77.65	201.25	326.31	395.43	1,011.03
Representativeness		**13,005%**	**1,431%**	**453%**	**217%**	**152%**	**463%**
Representativeness per capita		**858%**	**741%**	**540%**	**417%**	**437%**	**524%**

IBI: Incremental Budget Impact; RWE: Real-World Evidence; DMARD-B: Disease-Modifying Antirheumatic Drugs (Biological)