

# A Brazilian cost-utility analysis of trabecular micro-bypass with iStent inject® for the treatment of open-angle glaucoma

Análise de custo-utilidade do implante trabecular iStent inject® para o tratamento do glaucoma de ângulo aberto no Brasil

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## How to cite:

Paletta Guedes RA, Souza CP, Dias LL, Murta L, Gravina DM, Chaoubah A. A Brazilian cost-utility analysis of trabecular micro-bypass with iStent inject® for the treatment of open-angle glaucoma. Rev Bras Oftalmol. 2022;81:e0049.

## doi:

<https://doi.org/10.37039/1982.8551.20220049>

## Keywords:

Glaucoma, open-angle; Glaucoma/surgery; MIGS; iStent inject®; Trabecular micro-bypass; Costs and cost analysis; Cost-benefit analysis

## Descritores:

Glaucoma de ângulo aberto; Glaucoma/cirurgia; MIGS; Injeção de iStent; Micro-bypass trabecular; Custos e análise de custo; Análise custo-benefício

## Received on:

Apr 27, 2022

## Accepted on:

Apr 27, 2022

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## Conflict of interest:

Ricardo Augusto Paletta Guedes:  
Consultant for Glaukos, SightSciences,  
OftaVision Health, Théa France, Allergan.  
All other authors: none.

## Financial support:

funding provided by Glaukos.

## Declaration of Helsinki:

The Declaration of Helsinki is not relevant to this study as it does not include human subjects.



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## ABSTRACT

**Purpose:** To evaluate the cost-utility of the iStent *inject*® for the treatment of mild-to-moderate open-angle glaucoma (OAG) within the Brazilian Unified Health System (SUS).

**Methods:** A Markov model was developed, in which the effectiveness outcome measure was the incremental cost-effectiveness ratio (ICER: R\$ / QALY quality-adjusted life-year). Direct medical costs were obtained from the SUS perspective. The base case comprised of a hypothetical cohort of patients with OAG using topical medication and being managed according to the Clinical Protocol and Therapeutic Guidelines (PCDT) and a real-world setting based on data from Datasus. The model's robustness through sensitivity analyses was tested.

**Results:** In the PCDT base case setting, the trabecular micro-bypass implant provided gains of 0.47 QALYs and an ICER of R\$7,996.66/QALY compared to treatment with topical medication. In the real-world setting based on data from Datasus, the trabecular micro-bypass implant, provided gains of 0.47 QALYs and an ICER of R\$4,485.68/QALY compared to treatment with topical medication. The results were robust to sensitivity analyses.

**Conclusion:** Incorporating iStent *inject*® to SUS provides an improvement in the patient's quality of life with an additional cost that warrants the benefit provided to patients. Results may be considered cost-effective compared to topical medication.

## RESUMO

**Objetivo:** Avaliar a relação custo-utilidade do iStent *inject*® para o tratamento do glaucoma de ângulo aberto leve a moderado no Sistema Único de Saúde.

**Métodos:** Foi desenvolvido um modelo de Markov, no qual a medida de resultado de efetividade foi a razão custo-efetividade incremental (razão de custo-efetividade incremental: R\$/ano de vida ajustado pela qualidade). Os custos médicos diretos foram obtidos por meio da perspectiva do Sistema Único de Saúde. O caso base foi composto de uma coorte hipotética de pacientes com glaucoma de ângulo aberto em uso de medicação tópica tratados de acordo com o Protocolo Clínico e Diretrizes Terapêuticas e um cenário do mundo real baseado em dados do Departamento de Informática do Sistema Único de Saúde. Foi testada a robustez do modelo por meio de análises de sensibilidade.

**Resultados:** No cenário base do Protocolo Clínico e Diretrizes Terapêuticas, o implante trabecular *micro-bypass* proporcionou ganhos de 0,47 ano de vida ajustado pela qualidade e razão de custo-efetividade incremental de R\$7.996,66/ano de vida ajustado pela qualidade em relação ao tratamento com medicação tópica. No cenário real baseado em dados do Departamento de Informática do Sistema Único de Saúde, o implante trabecular proporcionou ganhos de 0,47 ano de vida ajustado pela qualidade e razão de custo-efetividade incremental de R\$ 4.485,68/ano de vida ajustado pela qualidade em relação ao tratamento com medicação tópica. Os resultados foram robustos para análises de sensibilidade.

**Conclusão:** A incorporação do iStent *inject*® ao Sistema Único de Saúde proporciona melhora na qualidade de vida do paciente com um custo adicional que garante o benefício proporcionado a eles. Os resultados podem ser considerados custo-efetivos em comparação com a medicação tópica.

## INTRODUCTION

Glaucoma is a degenerative optic neuropathy, characterized by the loss of retinal ganglion cells and their axons, resulting in a loss of the visual field.<sup>(1)</sup> Glaucoma is considered the leading cause of irreversible blindness.<sup>(2,3)</sup> In 2013, the global prevalence of glaucoma and primary open-angle glaucoma (POAG) in patients aged 40 to 80 years were 3.54% and 3.05%, totaling 64.26 and 44.11 million reported cases, respectively. The prevalence of POAG was estimated to be 3.65% on the Latin American continent and the Caribbean (3.65%).<sup>(2)</sup>

Visual impairment and permanent blindness negatively impact the health-related quality of life (HRQoL) of patients with glaucoma. It occurs because, in addition to imposing physical limitations, there is a growing fear of developing permanent blindness and family affliction, and also of developing anxiety and depression.<sup>(4,5)</sup>

According to the Protocolo Clínico e Diretrizes Terapêuticas Glaucoma (PCDT) published in 2018,<sup>(6)</sup> the primary goal of glaucoma treatment is to stabilize disease through decreased intraocular pressure (IOP). The medications recommended by PCDT are topical eye drops and follow five main classes of drugs: beta-blockers, parasympathomimetics, alpha-adrenergic agonists, carbonic anhydrase inhibitors, and prostaglandin and prostamide analogues.<sup>(6)</sup> The treatments for glaucoma that are considered effective are those capable of reducing IOP in a sustainable, safe and cost-effective manner. Since glaucoma is progressive, treatment alternatives may be required to manage IOP throughout a patient lifetime.

Disease progression makes it necessary to use multiple topical drug products that, in the long-term, can cause several ocular AEs, such as dry eye syndrome, redness, burning, itching and blurred vision.<sup>(7)</sup> In addition, the long-term use of these drug products can cause changes in the ocular surface, leading to discomfort, tear film instability, conjunctival inflammation, and corneal surface impairment, leading to decreased success rates of future filtering surgeries, such as trabeculectomy.<sup>(7-9)</sup>

Due to the asymptomatic nature of glaucoma, adherence to treatment with topical drug products is considered unsatisfactory, with average persistence rates between 19% and 68% after 1 year of treatment.<sup>(10)</sup> While inadequate control of IOP leads to an increase in visual loss rates.<sup>(11)</sup> The complexity of the treatment and the fact that it is often self-administered has an important influence in adherence. It is known that approximately 20% of patients have dosing difficulties of topical medications, experiencing problems in controlling the number

of dispensed drops, among others. In addition, many patients with glaucoma may need more than one topical therapy, which also interferes with adherence.<sup>(12)</sup>

The use of surgical intervention is also mentioned in the PCDT for cases in which target IOP is not reached with topical treatment.<sup>(6)</sup> However, the benefits of this type of intervention are limited due to side effects and inadequate success rates.<sup>(13,14)</sup> While the gold standard of glaucoma surgery is trabeculectomy, it is associated with complications such as: hyperfiltration, atalamia, hypotonia, late infection, and excessive scarring.<sup>(15)</sup> The other surgical option currently available is laser trabeculoplasty, which despite having a favorable safety profile, similar to that of topical drug products (including early hypertensive peaks >5mmHg, uveitis, goniosynechiae formation and hyphema), its long-term effectiveness is low.<sup>(13,14)</sup>

In this setting, ab interno glaucoma surgeries, such as the iStent inject<sup>®</sup> trabecular micro-bypass, represent a new class of low-risk surgical treatments, which cause minor physiological and structural damage to patients with glaucoma who have failed treatment with topical drug products. Such procedures provide rapid postoperative recovery and can be performed in association with cataract surgeries, or as solo procedures (standalone).<sup>(16,17)</sup> This product has been registered with the Agência Nacional de Vigilância Sanitária (Anvisa) since 2016. It has been registered with the Food and Drug Administration (FDA) since 2018.<sup>(18,19)</sup>

The Sociedade Brasileira de Glaucoma (SBG), in its 2017 guideline, recommends the use of micro-invasive glaucoma surgery (MIGS) in patients with mild-to-moderate open-angle glaucoma (OAG) where traditional surgical treatment is not indicated.<sup>(15)</sup>

This analysis aimed to evaluate the cost-effectiveness of the standalone iStent<sup>®</sup> inject trabecular micro-bypass use in the treatment of adult patients with mild-to-moderate POAG requiring IOP reduction or who would benefit from the decrease in the number of drug products used for glaucoma and who have failed to use at least one topical drug product.

## METHODS

### Study design

A Markov model was developed, in which the effectiveness outcome measure was the incremental cost-effectiveness ratio (ICER: R\$/quality-adjusted life years – QALY) to evaluate the cost-effectiveness of iStent inject<sup>®</sup> trabecular micro-bypass implant standalone use in patients with mild-to-moderate POAG requiring IOP reduction or

who would benefit from a decrease in the number of drug products used for glaucoma and who failed to use at least one topical drug product.

A lifetime time horizon was adopted. A mean initial age of 63 years was estimated from the Departamento de Informática do Sistema Único de Saúde (Datasus) drug product database, based on the first entry of patients with the POAG International Classification of Diseases (ICD-10 H40.1), between August 2013 and March 2020. The perspective adopted was that of the Unified Health System (SUS), in which direct medical costs were taken into consideration, including the cost of the device, drug products, follow-up (medical appointment, tonometry, and other complementary exams), and procedures (trabeculectomy). An annual discount rate of 5% was applied to costs and outcomes, in accordance with the recommendations of the Methodological Guidelines for Economic Evaluating Studies in Health Technologies, published by the Ministry of Health ([https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes\\_metodologicas\\_diretriz\\_avaliacao\\_economica.pdf](https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_metodologicas_diretriz_avaliacao_economica.pdf)).

The PCDT recommends timolol as a first-line medical treatment, followed by dorzolamide, brinzolamide or brimonidine as second-line options and latanoprost, bimatoprost or travoprost as third-line options. Treatment can be carried out as monotherapy or a combination for first, second and third-line drug products.<sup>(2)</sup>

Although PCDT indicates timolol as a first-line drug product, in clinical practice this intervention is the least used as the first therapeutic option, with third-line drug products being the most used at the beginning of treatment. According to data from Datasus, of the patients who started treatment at SUS, only 16.24% used timolol as the first therapeutic option. Those who started treatment with second and third-line drug products represent 34.81% and 48.54%, respectively. Accounting for the difference between the PCDT recommendation and clinical practice, a second setting, called “real-world setting” considers treatment patterns actually used.

## Model design

An analytical decision model (Markov model), with monthly cycles, was developed to reproduce the life cycle of adult patients with mild or moderate POAG until their death, incorporating the progression of glaucoma in patients with disease in an eye.

The model structure and transition probability assumptions were based on a Canadian model developed by Patel et al, which uses an adaptation of the Hodapp-Parrish scale to track the progression of glaucoma severity between health status:<sup>(20, 21)</sup> mild (visual field damage of 0 up to -6dB); moderate (visual field damage of -6.01 up to -12dB); advanced (visual field damage of -12.01 up to -20dB); severe/Blindness (visual field damage lower than -20 dB).

The model is comprised of four mutually exclusionary health status as per glaucoma severity: mild, moderate, advanced or severe/blindness. Patients can migrate along health states in a single direction because visual field may worsen or remain constant, with visual field improvement not being possible. Death is an absorptive status and the patient may migrate to this from any health status.

Transition between POAG severity was based on the natural rate of visual field change of patients with untreated glaucoma, from the Early Manifest Glaucoma Trial (EMGT) study and IOP reduction caused by the treatment, from the RCT performed by Fea et al<sup>(11,17)</sup>. Since Fea et al. did not report glaucoma severity of patients enrolled in the study, it was assumed that patients starting were in the mild POAG state. In a sensitivity analysis, data used in the economic assessment by Patel et al were used, taking into consideration that 46.6% of patients start with mild glaucoma and 53.4% with moderate glaucoma.<sup>(21)</sup>

For the time to the next treatment, the progression definition of the EMGT study was considered, with progression being an intermediate status.<sup>(11)</sup> Up to five lines of treatment were taken into consideration in the model, with treatment sequence adopted in each setting being described in table 1. The model starts in the second treatment, after failure of the first treatment.

**Table 1.** Treatment sequence. Base case (*Protocolo Clínico e Diretrizes Terapêuticas Glaucoma*) and real-world setting

Comparison	1 <sup>st</sup> treatment	2 <sup>nd</sup> treatment	3 <sup>rd</sup> treatment	4 <sup>th</sup> treatment	5 <sup>th</sup> treatment	6 <sup>th</sup> treatment
Strategy 1	1 <sup>st</sup> line	1 <sup>st</sup> + 2 <sup>nd</sup> lines	1 <sup>st</sup> + 2 <sup>nd</sup> + 3 <sup>rd</sup> lines	Trabeculectomy	1 <sup>st</sup> line	1 <sup>st</sup> + 2 <sup>nd</sup> lines
Strategy 2	1 <sup>st</sup> line	iStent inject®	1 <sup>st</sup> line	1 <sup>st</sup> + 2 <sup>nd</sup> lines	1 <sup>st</sup> + 2 <sup>nd</sup> + 3 <sup>rd</sup> lines	Trabeculectomy
Real-world setting						
Comparison	1 <sup>st</sup> treatment	2 <sup>nd</sup> treatment	3 <sup>rd</sup> treatment	4 <sup>th</sup> treatment	5 <sup>th</sup> treatment	6 <sup>th</sup> treatment
Strategy 1	1 <sup>st</sup> line 2 <sup>nd</sup> line 3 <sup>rd</sup> line	1 <sup>st</sup> + 2 <sup>nd</sup> lines 2 <sup>nd</sup> + 3 <sup>rd</sup> lines 2 <sup>nd</sup> + 3 <sup>rd</sup> lines	1 <sup>st</sup> + 2 <sup>nd</sup> + 3 <sup>rd</sup> lines 2 <sup>nd</sup> + 2 <sup>nd</sup> + 3 <sup>rd</sup> lines 1 <sup>st</sup> + 2 <sup>nd</sup> + 3 <sup>rd</sup> lines	Trabeculectomy	1 <sup>st</sup> line 2 <sup>nd</sup> line 3 <sup>rd</sup> line	1 <sup>st</sup> + 2 <sup>nd</sup> lines 2 <sup>nd</sup> + 3 <sup>rd</sup> lines 2 <sup>nd</sup> + 3 <sup>rd</sup> lines
Strategy 2	1 <sup>st</sup> line 2 <sup>nd</sup> line 3 <sup>rd</sup> line	iStent inject®	1 <sup>st</sup> line 2 <sup>nd</sup> line 3 <sup>rd</sup> line	1 <sup>st</sup> + 2 <sup>nd</sup> lines 2 <sup>nd</sup> + 3 <sup>rd</sup> lines	2 <sup>nd</sup> + 2 <sup>nd</sup> + 3 <sup>rd</sup> lines 1 <sup>st</sup> + 2 <sup>nd</sup> + 3 <sup>rd</sup> lines 2 <sup>nd</sup> + 2 <sup>nd</sup> + 3 <sup>rd</sup> lines 1 <sup>st</sup> + 2 <sup>nd</sup> + 3 <sup>rd</sup> lines	Trabeculectomy

For mortality, data from the mortality table in 2018 published by the Instituto Brasileiro de Geografia e Estatística (IBGE) were taken into consideration, showing mortality data from the overall population for both sexes and divided by sex.<sup>(22)</sup> Data from studies of Fea et al<sup>(17)</sup> show that 44.27% of patients are women, i.e., 55.73% are men. This ratio of patients by sex was used to weigh mortality per sex and to obtain mortality for the overall population to be applied in the model. It is assumed that the presence of glaucoma does not change the risk of death.

### Intraocular pressure

The reduction of IOP was seen in the RCT conducted by Fea et al, where patients randomized for treatment presented a baseline IOP of 25.2mmHg (standard deviation – SD: 1.4mmHg) and 24.8mmHg (SD: 1.7mmHg) for the iStent inject<sup>®</sup> arm and medications, respectively. At the end of 12 months, the mean reduction of IOP was 12.2±2.5mmHg in the iStent inject<sup>®</sup> and 11.6±2.2mmHg in the drug group.<sup>(17)</sup>

The EMGT study showed a baseline IOP of 20.60 mmHg (95% confidence interval –95%CI – 16.50 – 24.70 mmHg), while in the study of Fea et al,<sup>(17)</sup> baseline IOP was approximately 25mmHg in both arms. Studies show that the higher the baseline IOP, a larger decrease in IOP is expected.<sup>(23)</sup> Thus, since visual field change adjustments used EMGT data as a basis, IOP reduction recorded in the study of Fea et al was adjusted as per EMGT baseline IOP.<sup>(11,17)</sup>

For patients on iStent inject<sup>®</sup> treatment, it was assumed that IOP reduction remains constant after one year of treatment. This assumption is based on the study by Lindstrom et al, that showed that the use of iStent inject<sup>®</sup> experienced a stable IOP reduction over four years of follow-up.<sup>(24)</sup> For patients on drug products, it was also taken into consideration that IOP reduction after one year of treatment remains constant.

For the arm treated with topical drug products, IOP reduction in the RCT may not mirror the reality, since this study uses stringent treatment protocols. As previously mentioned, due to the asymptomatic nature of glaucoma, compliance to treatment with topical drug products is deemed as poor.<sup>(10)</sup> Supporting this quote, Ribeiro et al performed a cross-sectional study to assess compliance to drug-induced treatment in 237 Brazilian patients diagnosed with glaucoma. The documented compliance was 54%.<sup>(25)</sup>

To reflect reality, it was assumed that IOP reduction is proportional to treatment compliance. For instance, taking into consideration a hypothetical IOP reduction

of 10mmHg and a treatment compliance of 54%, an actual IOP reduction of 5.4mmHg is expected. Since this a crude assumption, treatment compliance was assumed as 100% in a sensitivity analysis.

For trabeculectomy, Lichter et al<sup>(26)</sup> assessed surgery efficacy over 5 years. Patients undergoing surgery had a baseline IOP of 27.4mmHg, and after 5 years of follow-up, documented IOP was 15mmHg, representing an IOP reduction of 12.4mmHg.

### Changes in visual field

Glaucoma is an irreversible disease, and severity is determined by visual field damage progression. The rate of disease progression is partially determined by IOP, with IOP reduction being the single known manner to slow visual field damage. Transition between POAG severity measured by visual field change based on the natural rate of visual field change in untreated patients with glaucoma from EMGT study.<sup>(11)</sup> Early Manifest Glaucoma Trial estimated the hazard ratio (HR) for time to progression per increase unit in IOP as 1.13 (95%CI 1.07-1.19).<sup>(15)</sup> The reverse of 1.13 was used as the HR per unit of IOP reduction (i.e., 1/1.13=0.88). As per the EMGT, monthly visual field change was -0.05dB (SD=0.07dB) and -0.03dB (SD=0.05dB) for untreated and treated patients (p-value = 0.008), respectively, accounting for a decrease of 40% in visual field damage when treating glaucoma. Moreover, patients on treatment had an IOP decrease of 5.1mmHg (SD=3.40mmHg) within 3 months, while untreated patients had an IOP reduction within this same period.<sup>(11)</sup>

Using this information, a relationship was estimated between visual field damage and IOP reduction by Equation 3. For every 1 mmHg of pressure decrease, the visual field damage is decreased by 9.53%.

Thus, taking into consideration an IOP reduction of 9.65 mmHg, for the first month of the arm treated with iStent inject<sup>®</sup>, monthly visual field damage estimated was -0.0040dB.

Consistent with the methodology of the National Institute of Health and Care Excellence (NICE), switching probabilities were estimated as the reverse number of months required for the patient to switch from a health status to another, which was based on the adjusted efficacy of monthly visual field decrease.<sup>(27)</sup>

### Treatments costs

The costs of drug treatment were obtained from Autorizações de Procedimento de Alta Complexidade (APACs) described in table 2.

**Table 2.** Cost of drug-induced treatment.

Drug-induced treatment	Monthly cost	SIGTAP procedure
1 <sup>st</sup> line	BRL 12.44	03.03.05.006-3
2 <sup>nd</sup> line	BRL 52.92	03.03.05.007-1
3 <sup>rd</sup> line	BRL 85.33	03.03.05.008-0
1 <sup>st</sup> + 2 <sup>nd</sup> lines	BRL 65.36	03.03.05.015-2
1 <sup>st</sup> + 3 <sup>rd</sup> lines	BRL 97.77	03.03.05.017-9
2 <sup>nd</sup> + 3 <sup>rd</sup> lines	BRL 138.25	03.03.05.019-5
1 <sup>st</sup> + 2 <sup>nd</sup> + 3 <sup>rd</sup> lines	BRL 150.69	03.03.05.021-7

SIGTAP: Sistema de Gerenciamento da Tabela de Procedimentos.

For the iStent inject® the simPRO pricing (CP10) was referenced. For the cost of implanting the device, the value of APAC 04.05.05.013-5 (antiglaucomatous prosthesis implant) was considered. The cost of the trabeculectomy procedure was consulted in Datasus from April 2019 to March 2020. The cost of complications was defined by a microcosting and is shown in table 3.

**Table 3.** Cost of complications

Procedure	Management cost
Blebitis	BRL 36.74
Hyposphagma	BRL 324.52
Endophthalmitis	BRL 2,039.88
HypHEMA	BRL 37.57
Hypotonia	BRL 857.89
Stent obstruction	BRL 707.70
Filtering blister leakage	BRL 210.01
Blurred vision or vision disturbance	BRL 26.74
Discomfort	BRL 26.74
Intraocular inflammation	BRL 13.37
Vitreous detachment	BRL 92.64

For trabeculectomy, the procedure cost in Datasus was checked from April 2019 to March 2020. As per the search, the procedure cost was BRL 2,018.74, divided between hospital and outpatient costs of BRL 1,014.83 and BRL 1,003.91, respectively.

## RESULTS

Glaucoma surgery with standalone iStent inject® trabecular micro-bypass implant incorporated by SUS provided 0.47 incremental QALY, relative to the comparator and an ICER of BRL 7,996.66 per QALY. In the alternative real-world setting, based on data from Datasus, iStent inject® trabecular micro-bypass implant incorporated by SUS provided similar incremental QALY of 0.47 and an ICER of BRL 4,485,68 per QALY. The results are shown in table 4.

### Sensitivity analysis

#### Univariate sensitivity analysis

The results from the univariate sensitivity analysis are shown in figures 1A and 1B. In both settings, the factor that mostly impacted the results was treatment adherence with eye drops, followed by the discount rate and utility values.

**Table 4.** Cost-utility results. Base case (Protocolo Clínico e Diretrizes Terapêuticas Glaucoma) and real-world setting (Departamento de Informática do Sistema Único de Saúde)

Base case setting (PCDT)			
Endpoints	iStent inject®	Medications	Incremental
Total costs	BRL 12,327.43	BRL 8,564.02	BRL 3,763.41
iStent inject®	BRL 9,302.28	BRL 0.00	BRL 9,302.28
Trabeculectomy	BRL 84.46	BRL 606.51	-BRL 522.05
Medications	BRL 1,096.59	BRL 6,032.15	-BRL 4,935.56
Follow-up	BRL 1,819.19	BRL 1,807.29	BRL 11.91
Complications	BRL 24.91	BRL 118.07	-BRL 93.17
QALY	10.09	9.62	0.47
ICER per QALY gained			BRL 7,996.66
Real-world setting (Datasus)			
Total costs	BRL 13,606.28	BRL 11,520.39	BRL 2,085.89
iStent inject®	BRL 9,302.28	BRL 0.00	BRL 9,302.28
Trabeculectomy	BRL 84.46	BRL 606.51	-BRL 522.05
Medications	BRL 2,375.37	BRL 8,991.27	-BRL 6,615.90
Follow-up	BRL 1,819.19	BRL 1,807.29	BRL 11.91
Complications	BRL 24.98	BRL 115.32	-BRL 90.34
QALY	10.09	9.63	0.47
ICER per QALY gained			BRL 4,485.68

Source: [http://conitec.gov.br/images/Relatorios/2018/Relatorio\\_PCDT\\_Glaucoma.pdf](http://conitec.gov.br/images/Relatorios/2018/Relatorio_PCDT_Glaucoma.pdf)

PCDT: Protocolo Clínico e Diretrizes Terapêuticas Glaucoma; QALY: quality-adjusted life years; Datasus: Departamento de Informática do Sistema Único de Saúde; ICER: incremental cost-effectiveness ratio.

### Probabilistic sensitivity analysis

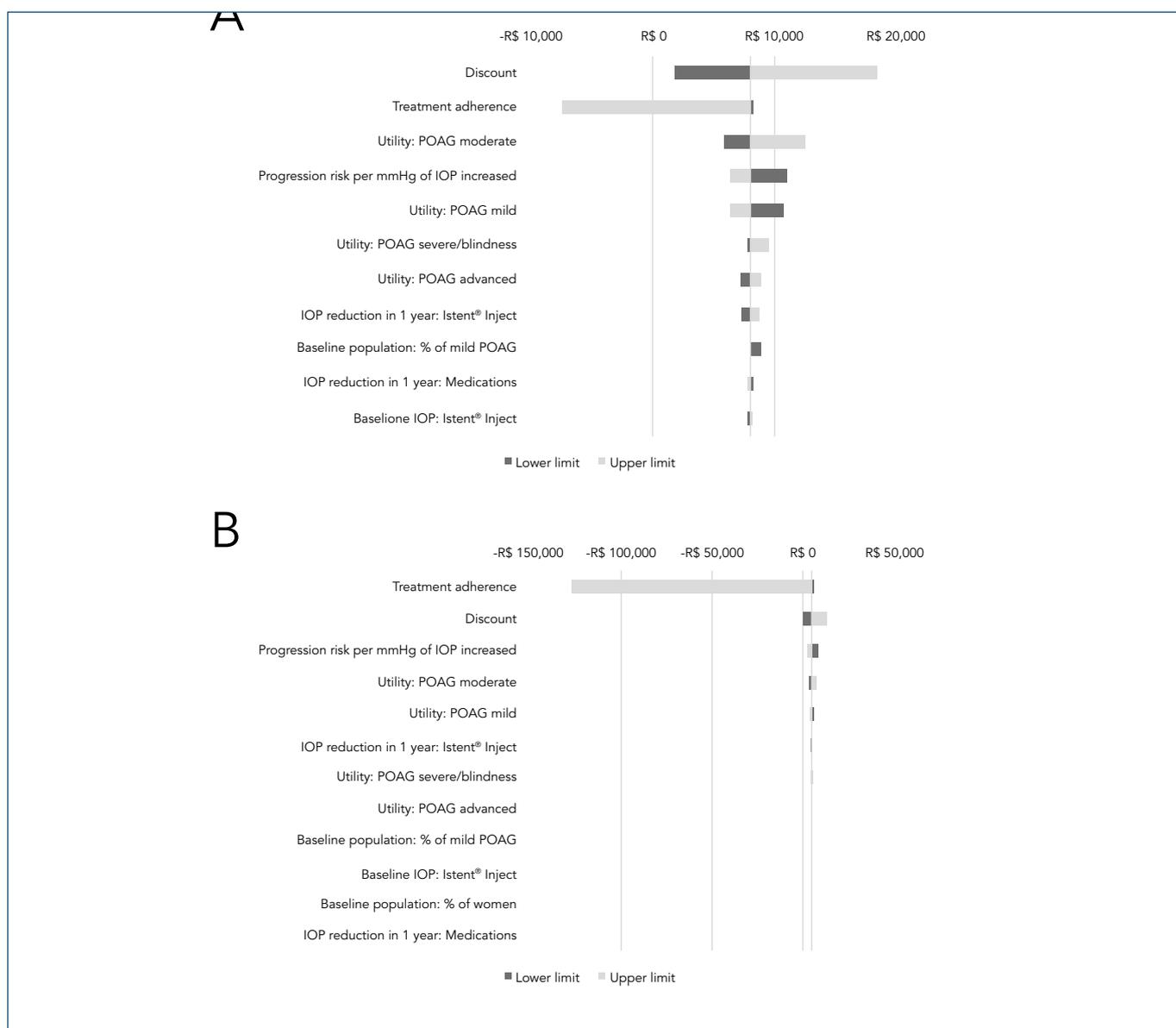
Figures 2A and 2B as follows shows the results of probabilistic sensitivity analysis for the base case setting (PCDT) and for the real-world setting (Datasus).

Probabilistic sensitivity analysis for both settings showed 68% of results in quadrant I, which translates into higher cost, however, with higher effectiveness; and 32% of results in quadrant II, which translates into higher cost, however, with lower effectiveness for patients. From these 23%, the higher concentration is very close to incremental effectiveness zero, which reflects that it is less likely that the device use is clinically worse for the patient. However, the 72% of quadrant I are distributed randomly among different incremental effectiveness, reaching results of up to 5.5 incremental quality-adjusted life years.

It is worth mentioning that the result distribution in the proposed setting is kept within a lower incremental cost range than the one seen in the base case setting, but in the same incremental effectiveness field, reinforcing the benefits of SUS incorporating angular antiglaucoma surgery with standalone iStent inject® trabecular micro-bypass implant.

## DISCUSSION

The economic analysis conducted was based on a cost-utility model to project effectiveness gains and costs related to the treatment. Results demonstrate a gain in QALYs with an increase in costs, although the incremental cost-effectiveness ratios are less than BRL 8,000.00. It



POAG: primary open-angle glaucoma; ICER: incremental cost-effectiveness ratio.

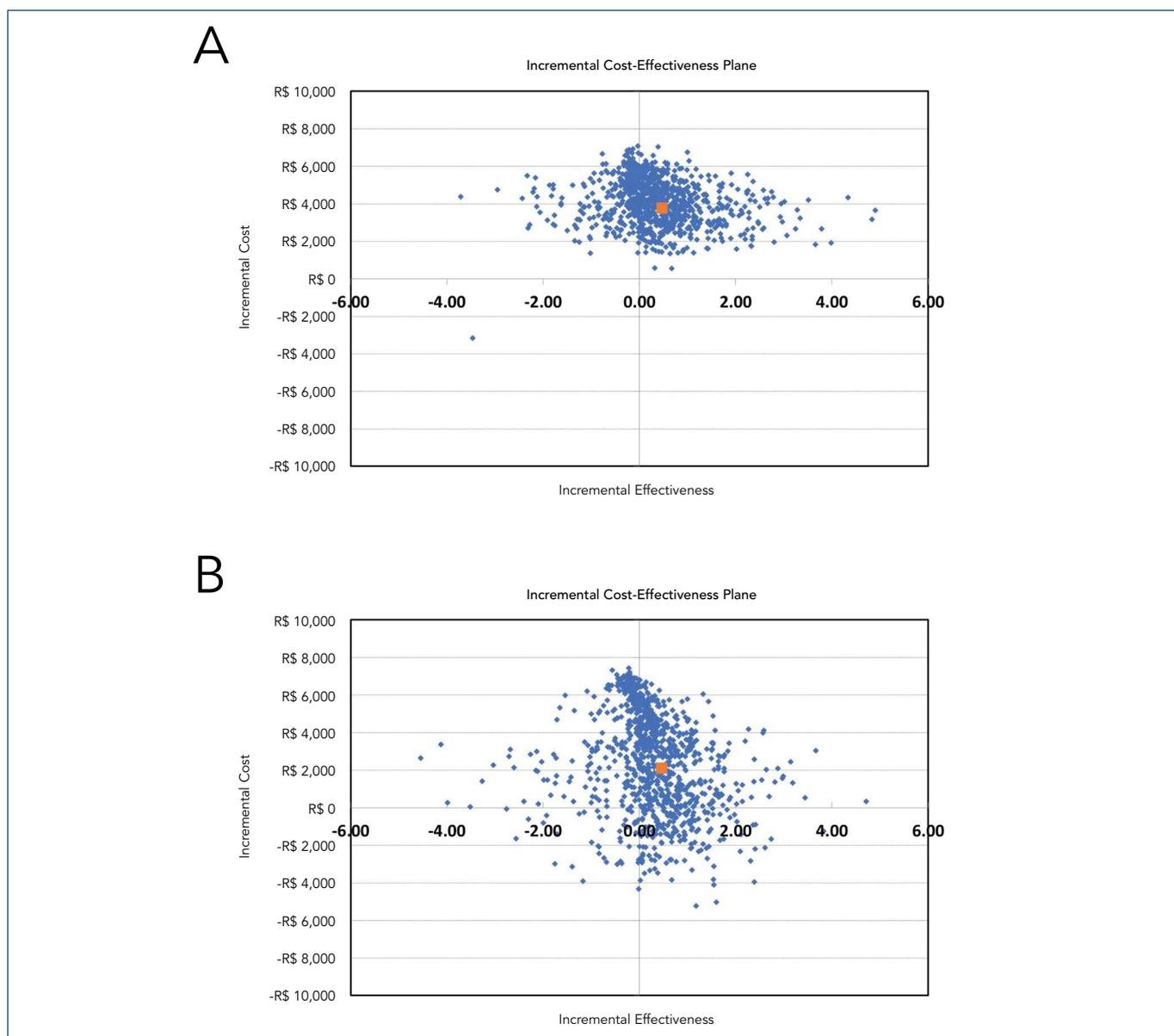
**Figure 1.** Univariate sensitivity analysis. Protocolo Clínico e Diretrizes Terapêuticas Glaucoma base case setting (A) and real-world setting (B).

is worth noting that the real-world setting showed similar benefits to the base case setting (0.47 incremental QALY) but with lower incremental cost (ICER of BRL 4,485.68 per QALY saved versus ICER of BRL 7,996.66 per QALY saved, respectively), enhancing the benefits of the SUS regime. Although no willingness to pay (WTP) threshold has been defined for Brazil, we may consider the World Health Organization's (WHO) one-to-three times Gross Domestic Product (GDP) per capita recommendation, where results fall under.<sup>(27)</sup> We may therefore conclude incorporating standalone iStent inject® trabecular micro-bypass implant surgery to SUS to be cost-effective compared to the use of eye drops, providing an improvement in the quality of life of patients with an additional cost that warrants

this benefit provided for patients. This conclusion was also supported by the probabilistic sensitivity analysis.

Our study results were similar to those of other standalone iStent technology cost-effectiveness studies in Canada and Columbia. Patel et al.<sup>(21)</sup> reported that iStent trabecular micro-bypass stent surgery (with two stents) as a standalone procedure dominated a comparator strategy of medication alone from the Canadian public payer perspective. Similarly, in a study conducted by Ordóñez et al.,<sup>(29)</sup> found iStent trabecular micro-bypass stent to be a cost-saving strategy in Colombia when compared to Selective Laser Trabeculoplasty (SLT).

The analysis has limitations to be considered when assessing applicability of results to clinical practice and



**Figure 2.** Probabilistic sensitivity analysis. Protocolo Clínico e Diretrizes Terapêuticas Glaucoma base case setting (A) and real-world setting (B).

funding decisions. First, medical device trials tend to be smaller than drug trials. It is known that clinical trials involving surgeries, frequently have smaller sample sizes than those involving drug treatments. Although, the sample size in the RCT performed by Fea et al.,<sup>(17)</sup> may be considered small, it was large enough to detect differences among groups for the primary endpoint. Another limitation relates to the follow-up time of 12 months. However, additional evidence with longer follow-up periods from non-randomized studies support maintenance of safety and efficacy assumptions in follow-up periods of up to four years.<sup>(23,30-32)</sup> Also, the burden of glaucoma medical and surgical treatment on a patient's quality of life is not captured in the model.

Finally, the perspective was that of a third-party payer, and not a societal one, as such, indirect costs and out-of-pocket direct costs incurred by the patient were not included.

## CONCLUSION

Evidence shown herein suggest that the incorporation of surgery with standalone iStent inject® trabecular micro-bypass implant by the Unified Health System is able to provide significant gains, once these procedures allow intraocular pressure control and allow a decrease of number of anti-hypertensive drug products used by patients with mild-to-moderate primary open-angle glaucoma.

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