Preventing glaucoma progression using the trabecular micro-bypass implant iStent inject®. A cost-effectiveness analysis

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ABSTRACT

Objective: To assess the economic impact of reducing glaucoma progression by using the trabecular micro-bypass implant, iStent inject®, in the Reference Centers for glaucoma treatment within the Brazilian Public Unified Health System (SUS).

Methods: In a cost-effectiveness analysis, a Markov model was developed, and the costs were obtained from the SUS perspective (medical direct costs). Effectiveness was measured in progression-free life-years. The time horizon was the mean life expectancy of the Brazilian population. The model parameters were obtained through a review and a critical analysis of the literature. The base case comprised a hypothetical cohort of patients with open-angle glaucoma, using anti-glaucoma eye drops and followed up at Reference Centers of SUS. We tested whether the incorporation of iStent inject® as an alternative second-line therapy would be cost-effective. The outcome measure was the incremental cost-effectiveness ratio (R$/progression-free life-years). We tested the robustness of the model by univariate and probabilistic sensitivity analyses.

Results: The use of iStent inject® led to decreased progression rate of glaucoma, evidenced by the amount of progression-free life-years obtained with each treatment strategy (7.82 progression-free life-years with iStent inject® versus 6.33 progression-free life-years with medical treatment), thereby improving glaucoma control. There was also a reduction in future costs associated with eye drops, filtering surgeries, and treatment complications. Incremental cost-effectiveness ratio ranged from R$6,429.30 to R$7,550.97/progression-free life-years. The model proved to be robust in the sensitivity analyses.

Conclusion: This analysis showed that iStent inject®, when used after the failure of the first-line therapy, is able to reduce the rate of glaucoma progression at an acceptable cost.

RESUMO

Objetivo: Avaliar o impacto econômico da redução da progressão do glaucoma pelo uso do implante de by-pass trabecular iStent inject® no ambiente dos Centros de Referência para tratamento do Sistema Único de Saúde (SUS).

Métodos: Em uma análise de custo-efetividade, elaborou-se um modelo de Markov, cujos custos foram obtidos a partir da perspectiva do SUS financiador (custos médicos diretos). A efetividade foi medida em anos de vida livres de progressão. O horizonte temporal foi a expectativa de vida média da população brasileira. Os parâmetros do modelo foram obtidos pela revisão e pela análise crítica da literatura. O caso base foi composto de uma coorte hipotética de portadores de glaucoma de ângulo aberto em uso de colírios antiglaucomatosos e em acompanhamento nos Centros de Referência do SUS. Testou-se se a incorporação do iStent inject® como alternativa à segunda linha de tratamento seria custo-efetiva. A medida de desfecho foi a razão de custo-efetividade incremental (R$/anos de vida livres de progressão). A robustez do modelo foi testada por meio de análises de sensibilidade univariada e probabilística.

Resultados: A utilização do iStent inject® proporcionou uma diminuição da velocidade de progressão do glaucoma, evidenciada pela quantidade de anos de vida livres de progressão obtida com cada estratégia de tratamento (7,82 anos de vida livres de progressão com iStent inject® versus 6,33 anos de vida livres de progressão com tratamento com colírios), melhorando, dessa forma, o controle do glaucoma. Houve ainda redução nos custos futuros associados aos colírios, às cirurgias filtrantes e às complicações do tratamento. A razão de custo-efetividade incremental variou de R$6.429,30 a R$7.550,97/anos de vida livres de progressão. O modelo mostrou-se robusto nas análises de sensibilidade.

Conclusão: O iStent inject®, quando usado após a falha do primeiro medicamento, é capaz de reduzir a taxa de progressão do glaucoma a um custo aceitável.
INTRODUCTION

The only treatment proven to be efficient in glaucoma is the adequate control of intraocular pressure (IOP), aiming to slow or stop the progression of visual loss.\(^1\)

The pressure reduction required to control glaucoma depends on disease stage, among other factors. In general, the more advanced the glaucoma is, the greater the need to reduce the IOP, and, consequently, the more aggressive the treatment should be.\(^2\) Therefore, reducing glaucoma progression is easier in the initial phases.

The therapeutic options for open-angle glaucoma (OAG), the most common type, include medical treatment (eye drops), laser trabeculoplasty, and surgery.\(^3,4\) The classical algorithm for glaucoma treatment consists of using eye drops as primary therapy. The guidelines of specialized societies recommend the initial usage of one eye drop. Additional eye drops are employed (usually up to three eye drops per patient) as needed (when IOP required to control the disease is not reached).\(^5\) The literature shows the average amount of eye drops required to control the disease increases with the glaucoma stage.\(^6\) Moreover, it is known that the amount of resources and costs related to glaucoma care tends to grow with disease progression.\(^6\)

Eye drops are the basis of OAG treatment; however, several limitations make this therapy not ideal. Most patients continue to progress despite access to the drugs,\(^5\) and some causes could be identified, such as low compliance (it may achieve approximately 50% after one year); non-negligible prevalence of local and systemic adverse events; and potential toxicity for eye tissues (ocular surface and trabecular meshwork).\(^6-8\)

Laser trabeculoplasty is indicated as an alternative to eye drop treatment.\(^9,10\) The pressure results are comparable to clinical treatment, however, there is a progressive loss of efficacy, which can lead to a failure rate of 80% after three years.\(^10\)

Conventional filtering surgeries for glaucoma have a high success rate; nonetheless, the risk of complications is high, making this therapeutic alternative indicated for cases refractory to eye drops and laser.\(^11,12\)

New micro-invasive glaucoma surgeries (MIGS) have been recently developed with the purpose of increasing safety of the procedure and allowing an earlier indication.\(^13,14\) Among MIGS, trabecular bypass implants, such as iStent inject\(^*\) (Glaukos Inc. San Clemente, CA, USA) stand out. This technique has long-term efficacy and safety confirmed in the literature, leading to an adequate control of IOP and drastically reducing the need for eye drops in most patients.\(^15-17\) Studies showed surgical success is related to the glaucoma stage. The earlier the implant iStent inject\(^*\) is placed, the greater the chance of reducing IOP, with no need to add adjuvant hypotensive eye drops.\(^18,19\)

Since this is a new device, it generates costs for health systems. On the other hand, by reducing the need for eye drops, there is a trend towards decreased costs associated with glaucoma care in the future. The impact of incorporating trabecular implants in health systems is still incipient,\(^20\) and there is no evidence of it in the Brazilian Public Unified Health System (SUS).

The objective of this study was to perform a cost-effectiveness analysis of the use of the trabecular bypass implant iStent inject\(^*\), as an alternative to the second-line therapy at the SUS Reference Centers for glaucoma treatment.

METHODS

A cost-effectiveness analysis was performed with the target population, comprising adult patients with primary open angle glaucoma (POAG) in mild to moderate stage, who were not appropriately controlled with one antiglaucoma eye drop, and treated at SUS’s Reference Centers for glaucoma treatment.

The study adopted the payer’s perspective (SUS as a service payer), in which the direct medical costs (cost of drugs, tests, materials, and procedures) were considered. The time horizon of average life expectancy (lifetime) of the Brazilian population was considered.

The intervention consisted of a surgical procedure using implant iStent inject\(^*\) in patients with initial to moderate POAG, enrolled in the SUS glaucoma program, who failed in first-line treatment (use of one hypotensive eye drop). The comparator for this analysis was the usual treatment performed at SUS Glaucoma Reference Sites, based on the Clinical Protocol and Therapeutic Guidelines (CPTG), which consists of therapy with combined drugs.\(^21\)

An annual discount rate of 5% was applied to cost and effectiveness outcomes, in accordance with the recommendations of the Methodological Guidelines for Economic Evaluation of Health Technology Studies, published by the Brazilian Ministry of Health.

The clinical outcome considered was progression-free life-years (PFLY), evaluating the time up to occurrence of disease progression. This outcome is highly relevant from both clinical and economic point of view, since glaucoma progression induces significant functional loss (visual deficiency), besides increasing glaucoma-related costs. Economic outcomes were the direct medical costs.
Treatment strategies were compared using the incremental cost-effectiveness ratio (ICER), defined by difference in cost divided by difference in effectiveness.

An analytical decision model (Markov model), with annual cycles, was developed with the objective of reproducing the life cycle of adult patients with initial or moderate OAG until their death.

Patients started on the model after failure of the first treatment, and were submitted to the second treatment option chosen according to the study setting. Two scenarios have been investigated. The base case compared iStent inject® with the combination of timolol and second-line drugs, according to the SUS CPTG recommendation. The alternative case, which we called the real-world setting, compared iStent inject® with the distribution of all therapeutic options that appeared on the SUS database (DATASUS) as used by patients after first-line treatment failure; this reflects what patients have used as treatment in the real world (source: https://datasus.saude.gov.br/informacoes-de-saude-tabnet/).

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-Anderson criteria to track the progression of glaucoma severity between health status, which are mutually exclusive, as follows: mild (visual field damage of 0 up to -6 dB); moderate (visual field damage of -6.01 up to -12 dB); advanced (visual field damage of -12.01 up to -20 dB); and severe/blindness (visual field damage greater than -20 dB). (22)

Patients may progress, usually towards a single direction; i.e., the 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 OAG severity levels was based on the natural rate of visual field change of patients with untreated glaucoma, of the Early Manifest Glaucoma Trial (EMGT), and IOP decrease resulting from treatment, of the randomized clinical trial (RCT) performed by Fea et al. (23, 24).

Since the RCT by Fea et al. has not described severity levels of glaucoma, these patients were assumed as starting at mild OAG status. In a sensitivity analysis, data from the economic evaluation by Patel et al. were used, taking into consideration that 46.6% of patients started with mild glaucoma and 53.4% with moderate glaucoma. (22,24)

For the time to the next treatment, the definition of progression used was from the EMGT, with progression being an intermediate status. (23)

Up to five therapeutic lines were considered in the model, and the treatment sequence adopted in each setting is described in Table 1. It is important to point out the table also shows the first treatment, but the model started in the second therapy, after the failure of the first.

The mortality rate was obtained from the mortality table of 2018, published by the Brazilian Institute of Geography and Statistics (IBGE), showing data of the general population for both sexes or divided by sex. It is worth mentioning that, when considering mortality of the general population, it is assumed the presence of glaucoma does not change the risk of death.

Intraocular pressure reduction was searched in the RCT by Fea et al., where patients randomized to treatment showed a baseline IOP of 25.2 mmHg (standard deviation – SD of 1.4 mmHg) and 24.8 mmHg (SD of 1.7 mmHg) for iStent inject® and drug arms, respectively. After 12 months, the mean reduction of IOP was 12.2±2.5 mmHg in the group of iStent inject®, and 11.6±2.2 mmHg in the group of drugs. (23)

Early Manifest Glaucoma Trial showed a baseline IOP of 20.6 mmHg (95% confidence interval – 95% CI 4.1 mmHg), while in the study by Fea et al., it was approximately 25 mmHg in both arms. Studies showed the higher the baseline IOP, the greater the expected decrease in IOP. 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. (24, 25)

Table 1. Treatment sequence in base case (Clinical Protocol and Therapeutic Guidelines) and alternative case (real world)

| Base case (CPTG) | 1st treatment | 2nd treatment | 3rd treatment | 4th treatment | 5th treatment | 6th treatment |
|------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Strategy 1       | 1st line      | 1st + 2nd lines | 1st + 2nd + 3rd lines | Trabeculectomy | 1st line      | 1st + 2nd lines |
| Strategy 2       | 1st line      | iStent inject® | 1st line      | 1st + 2nd lines | 1st + 2nd + 3rd lines | Trabeculectomy |

| Alternative case (real world) | 1st treatment | 2nd treatment | 3rd treatment | 4th treatment | 5th treatment | 6th treatment |
|-------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Strategy 1                   | 13.4% 1st line | 13.4% 1st + 2nd lines | 13.4% 1st + 2nd + 3rd lines | Trabeculectomy | 13.4% 1st line | 13.4% 1st + 2nd lines |
| 32.3% 2nd line               | 32.3% 2nd + 3rd lines | 32.3% 2nd + 2nd + 3rd lines | 32.3% 2nd + 2nd + 3rd lines | 54.4% 3rd line | 54.4% 3rd line | 54.4% 3rd line |
| 54.4% 3rd line               | 54.4% 3rd + 4th lines | 54.4% 3rd + 3rd lines | 54.4% 3rd + 2nd lines | 54.4% 3rd + 2nd lines | 54.4% 3rd + 2nd lines | 54.4% 3rd + 2nd lines |
| Strategy 2                   | 13.4% 1st line | iStent inject® | 13.4% 1st line | 13.4% 1st + 2nd lines | 13.4% 1st + 2nd lines | Trabeculectomy |
| 32.3% 2nd line               | 32.3% 2nd + 3rd lines | 32.3% 2nd + 2nd + 3rd lines | 32.3% 2nd + 2nd + 3rd lines | 54.4% 3rd line | 54.4% 3rd line | 54.4% 3rd line |
| 54.4% 3rd line               | 54.4% 3rd + 4th lines | 54.4% 3rd + 3rd lines | 54.4% 3rd + 2nd lines | 54.4% 3rd + 2nd lines | 54.4% 3rd + 2nd lines | 54.4% 3rd + 2nd lines |

Table 1: Treatment sequence in base case (Clinical Protocol and Therapeutic Guidelines) and alternative case (real world)

Strategy 1: usual treatment based on CPTG of the SUS glaucoma program (base case) or the proportion of each treatment line, obtained from real data from DATASUS (alternative case).

CPTG: Clinical Protocol and Therapeutic Guidelines.
First, IOP relative reduction was estimated by dividing decreased IOP by baseline IOP. Then, the result was multiplied by baseline IOP from the treated arm of EMGT study.

For patients on iStent inject®, it was presumed that IOP reduction remained constant after one year of treatment. This assumption is based on the study by Lindstrom et al., which showed the use of iStent inject® led to a stable IOP reduction over four years of follow-up.\(^{[26]}\)

For patients on drugs, it was also considered IOP reduction after one year of treatment remained constant.

For the arm treated with topical medications, IOP reduction in the RCT may not reflect the reality, since this type of study uses stringent treatment protocols. As previously mentioned, due to the asymptomatic nature of glaucoma, compliance to treatment with topical eye drops is deemed as poor.\(^{[27,28]}\)

Supporting this quote, Ribeiro et al. performed a cross-sectional study to assess compliance to medical treatment in 237 Brazilian patients diagnosed as glaucoma, and the documented compliance was 54%.\(^{[8]}\)

To reflect the reality, it was assumed IOP reduction is proportional to treatment compliance. For instance, taking into account a hypothetical IOP reduction by 10 mmHg and treatment compliance of 54%, an actual IOP reduction of 5.4 mmHg is expected. Since this assumption is weak, treatment compliance was deemed as 100% in a sensitivity analysis.

It is pointed out IOP reduction assumptions for iStent inject® for periods longer than one year, and IOP reduction adjustment as per compliance to medical treatment are applied given that IOP reduction was adjusted to baseline from EMGT study, instead of raw data of Fea et al.\(^{[24]}\)

For trabeculectomy, Lichter et al. assessed efficacy of surgery over 5 years.\(^{[29]}\)

Patients undergoing surgery showed a baseline IOP of 27.4 mmHg, and after 5-year follow-up, the documented IOP was 15 mmHg, thus representing an IOP drop by 12.4 mmHg. When the proposal above was applied, an adjusted IOP reduction of 9.32 mmHg was reached, and such drop was deemed as constant over time.

The rate of disease progression is mostly determined by IOP, and IOP reduction is the only known measure to slow down visual field defect.

Transition between OAG severity measured by alterations in visual field was based on the natural rate such changes in untreated patients with glaucoma, from the EMGT study. For every one mmHg of pressure decrease, the visual field damage is decreased by 9.53%. Thus, considering an IOP reduction of 9.65 mmHg, monthly visual field damage estimated was -0.0040dB for the first month of the arm treated with iStent inject®.

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 move from a health status to another. This was based on the adjusted efficacy of monthly decrease in visual field.

The Kaplan-Meier survival curve for time to progression in the control group was scanned to generate data simulated at patient level, and using algorithm R of Guyot et al.\(^{[29]}\)

Next, the best adjustment parametric curve was identified as the distribution with the lowest Akaike information criterion (AIC). Based on these criteria, log-normal distribution was identified as the best adjustment curve.

EMGT estimated the hazard ratio (HR) for time to progression per increase unit in IOP as 1.13 (95%CI 1.07-1.19).\(^{[23]}\) The reverse of 1.13 was used as the HR per unit of IOP reduction (i.e., 1/1.13=0.88).

For cost of medical treatment, we considered the Authorization for High Complexity Procedures (APAC) costs related to glaucoma treatment. For iStent inject®, the simPRO (www.simpro.com.br) price was considered. For the cost of implanting the device, the APAC value of 04.05.05.013-5 (implant of antiglaucoma prosthesis) was considered. For trabeculectomy, the procedure cost in DATASUS was checked from April 2019 to March 2020. The cost of complications was defined by micro-costing.

We tested the model robustness through univariate and probabilistic sensitivity analysis. In the latter, all analysis parameters varied according to proper distribution for each item. Probabilistic sensitivity analysis was estimated with 1,000 iterations. The willingness-to-pay threshold of R$ 94,761 per PFLY was used, which is equivalent to three times the GDP per national capita, in 2017.

The statistical analysis was performed using the software Microsoft Excel (Microsoft In., 2019, USA).

**RESULTS**

The parameters used to build the Markov model are presented in Tables 2 and 3. Table 2 shows the values of different medical resources and their costs to SUS. Table 3 displays the micro-costing of complications of procedures and treatments used in this study.

The progression curves of the different strategies of POAG treatment, as well as the progression curve of patients without treatment (extracted from EMGT data), are shown in Figure 1.
Preventing glaucoma progression using the trabecular micro-bypass implant iStent inject®

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Table 2. Resources and their associated unit costs applied to Markov’s economic evaluation model

| Resources                                | Code (SUS)* | Unit value (R$) |
|------------------------------------------|-------------|-----------------|
| Initial appointment + ancillary tests    | 03.01.01.01.02 | 57.74           |
| Follow-up visit                          | 03.03.05.001.2 | 17.74           |
| Medication (first line)                  | 03.03.05.006.3 | 12.44           |
| Medication (second line)                 | 03.03.05.007.1 | 52.92           |
| Medication (third line)                  | 03.03.05.008.0 | 85.33           |
| Medication (first + second lines)        | 03.03.05.015.2 | 65.36           |
| Medication (second + third lines)        | 03.03.05.017.9 | 97.77           |
| Medication (first + third lines)         | 03.03.05.019.5 | 138.25          |
| iStent inject†                           | 04.05.05.013.5 | 16,831.83       |
| Trabeculectomy                           |             | 2,018.74        |

*SUS list of procedures, Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS (accessed on Jan 22, 2021). Available from: http://sigtap.datasus.gov.br/tabela-unificada/app/sec/inicio.jsp

Table 3. Micro-costing of complications associated with treatment in both arms of the economic evaluation model

| Complication                        | Management cost (R$) |
|-------------------------------------|----------------------|
| Blebitis                            | 36.74                |
| Hypophagama                         | 324.52               |
| Endophthalmitis                     | 2,039.88             |
| Hyphema                             | 37.57                |
| Hypotonia                           | 857.89               |
| Stent obstruction                   | 707.70               |
| Filtering blister leakage           | 210.01               |
| Blurred vision or vision disturbance | 26.74                |
| Discomfort                          | 26.74                |
| Intraocular inflammation            | 13.37                |
| Vitreous detachment                 | 92.64                |

Table 4. Costs, effectiveness, and incremental cost-effectiveness ratios for each setting studied (Clinical Protocol and Therapeutic Guidelines and real-world setting)

| Setting                  | Endpoint      | iStent inject® | Drug products | Incremental cost-effectiveness ratio (per PFLY gained) |
|--------------------------|---------------|----------------|---------------|-----------------------------------------------------|
| Base case (CPTG)         | Total costs   | R$19,856.98    | R$8,564.02    | R$11,292.96                                         |
| iStent inject®           | R$16,831.83   | R$0.00         | R$16,831.83   |                                                     |
| Trabeculectomy           | R$84.46       | R$606.51       | -R$522.05     |                                                     |
| Drugs                    | R$1,096.59    | R$6,032.15     | -R$4,935.56   |                                                     |
| Follow-up                | R$3,819.19    | R$1,807.29     | R$11.91       |                                                     |
| Complications            | R$24.91       | R$118.07       | -R$93.17      |                                                     |
| PFLY                     | 7.82          | 6.33           | 1.50          |                                                     |
| Alternative case (real world) | Total costs   | R$21,135.83    | R$11,520.39   | R$9,615.44                                         |
| iStent inject®           | R$16,831.83   | R$0.00         | R$16,831.83   |                                                     |
| Trabeculectomy           | R$84.46       | R$606.51       | -R$522.05     |                                                     |
| Drugs                    | R$2,375.37    | R$8,991.27     | -R$6,615.90   |                                                     |
| Follow-up                | R$3,819.19    | R$1,807.29     | R$11.91       |                                                     |
| Complications            | R$24.98       | R$115.32       | -R$90.34      |                                                     |
| PFLY                     | 7.82          | 6.33           | 1.50          |                                                     |
| ICER (per PFLY gained)   |               | R$7,550.97     | R$6,429.30    |                                                     |

CPTG: Clinical Protocol and Therapeutic Guidelines; ICER: incremental cost-effectiveness ratio; PFLY: progression-free life-years.

Figure 1. Progression curves of visual field loss in individuals with open-angle glaucoma, according to treatment strategy used.

The cost results for each strategy of OAG treatment, gains in PFLY, and ICER are presented in Table 4.

The results of the Tornado diagram of univariate sensitivity analysis demonstrated, in both settings, the factor that most impacted results was compliance to treatment with eye drops, followed by the discount rate, and the quality of life-related data.

The univariate analysis for the unit value of device iStent inject† is shown in Figure 2. Even considering the table price of the device, i.e., the maximum marketed price, it is noted the ICER remains well below the willingness-to-pay threshold of one-fold the Brazilian per capita GDP. The unit value of iStent inject† that would make the procedure present a strong dominance ranged between R$6,000.00 and R$8,000.00, depending on the setting evaluated.

Figure 2. Univariate sensitivity analysis of device value (iStent inject†): base case (A) and alternative case (B).
The probabilistic sensitivity analysis for the base case showed 68% of results in quadrant I, which translates into higher cost, but higher effectiveness; and 31% of results in quadrant II, translating into higher cost and lower effectiveness for patients. Out of the 31%, the higher concentration is very close to incremental effectiveness zero, which reflects the use of the device it is less likely to be clinically worse for patients. However, the 68% of quadrant I are randomly distributed among incremental effectiveness, reaching results of up to 5.32 incremental quality-adjusted life years.

The probabilistic sensitivity analysis for the alternative setting demonstrated a similar interpretation to that of the base setting.

**DISCUSSION**

The results of this analysis showed the use of iStent inject® as an alternative therapy to the second-line drug treatment of OAG, at the Glaucoma Reference Sites of SUS, could significantly reduce the progression rate of visual field loss, increasing PFLY by approximately 1.5 years (7.8 PFLY with iStent inject® versus 6.3 PFLY with usual treatment).

The decrease in progression rate results from more efficient control of IOP. Studies showed the strict control of IOP is the most important measure to control OAG progress. The fact of incorporating the iStent inject® as an alternative to medications benefits patients, by decreasing dependence on long-term and continuous use of eye drops. This progression rate decrease has already been demonstrated in other studies, in which the trabecular bypass device was used combined with cataract surgery.

In Brazil, an important public health policy provides free access to medications for individuals with OAG treated at the Glaucoma Reference Sites of SUS. In this sense, treatment persistence – the capacity of patients maintaining long-term treatment, is partially solved, since there is no cost barrier to get the eye drops.

However, treatment compliance plays an important role in therapeutic failure. Compliance is related to individual factors and treatment. In general, compliance to antiglaucoma eye drops is lower in the following settings: male sex, good visual acuity, young patients (<50 years), elderly patients (>80 years), previous disease on the eye surface, anxiety, quantity of drugs and daily drops, greater treatment complexity (storing the vial in the fridge, for example), and drug adverse effects.

After 12 months, Ribeiro et al. found a compliance rate to eye drops of 54% at the Glaucoma Reference Sites of SUS. This shows the real difficulty in maintaining topical treatment for glaucoma, even when the cost barrier is removed. This fact has two important repercussions: the patient has an inadequate treatment, and the disease progresses despite access to treatment; on the other hand, the government pays a significant amount to make on the drugs available, but the expected effect is not attained, leading to waste of public funds.

The implementation of iStent inject® generates an additional initial cost; however, this cost is diluted over time. In chronic diseases requiring treatment throughout the patient’s life, the costs should consider the long-term horizon, as described in the present study. Although there are no studies assessing the clinical effects of iStent inject® on life expectancy, there is evidence indicating the real possibility of a long-lasting effect. The RCT conducted by Fea et al. assessed the results one year after the procedure, but Lindstrom et al. presented a long-lasting effect for up to 4 years of follow-up.

In the analysis of direct medical costs, the cost of iStent inject® is approximately R$16,500.00. In the long-term model, it yields savings in the use of drugs (approximately R$5,000.00 to R$6,500.00 per patient, depending on the setting used). It also yields savings in both costs of future filtering surgeries (trabeculectomies) and of future complications. By reducing the glaucoma progression rate with implementation of iStent inject®, fewer patients will require more aggressive treatments, such as filtering surgeries. The frequency of undesired effects of such treatments and the associated costs also decrease, since patients require less eye drops and filtering surgeries.

The ICER reflects the cost per benefit reached by a specific technology. In this analysis, the PFLY ranged from R$6,500.00 to R$7,500.00, which is well below the willingness-to-pay threshold of one-fold Brazilian per capita GDP (R$34,533.00). This can be considered as a low cost given the advantages of the device. The benefit of effectively controlling glaucoma progression is much more than just reducing the amount of eye drops and of more invasive procedures. Although not addressed in this analysis, there is a future trend to decrease the number of visually-impaired individuals due to glaucoma. The impact on cutting non-medical direct costs is also relevant, in addition to future reduction of indirect costs.

It is important to note the unit value of the device has a significant impact on ICER. The reference value used in this analysis is the maximum price list. However, this value is hardly ever used in real life, and the marketing price is usually below the list value. In the univariate sensitivity
analysis of the device value, it was observed that reductions in device unit value have a major impact on improving the economic efficiency of the procedure, in which reductions by 50% can make the procedure under analysis have a strong dominance; i.e., it is cheaper and more effective than the reference treatment with drugs.

Several studies have already assessed the cost-effectiveness ratio of trabecular bypass implants. In Brazil, Guedes et al. assessed the impact of incorporating the first-generation iStent combined with cataract surgery, at the Brazilian private health system. These authors found out that ICER was R$5,491.99/PFLY, concluding the additional cost would be acceptable considering the amount of clinical benefit attained. In Canada, Patel et al. observed despite having higher initial costs, the incorporation of trabecular bypass devices (iStent inject) led to significant gains in quality of life. The period required for devices to be cost-effective (strong dominance) was 3.7 years.

In the USA, Berdahl et al. studied the costs associated with two treatment strategies: implant of trabecular bypass devices versus drugs, and versus laser trabeculectomy. The findings showed trabecular devices may require less resources, and reduce the future annual costs related to glaucoma treatment. The difference was greater when the comparison was made with the drug treatment arm.

As observed in several studies in different health systems worldwide, as well as in the present analysis, there is a real trend to reduce future glaucoma treatment costs when trabecular devices be incorporated as alternatives to the usual eye drop therapy.

In economic studies based on models and assumptions, the quantification of uncertainty in results and the identification of variables that most affect this uncertainty are substantial. According to the results of sensitivity analysis, this model of economic evaluation can be considered robust.

Some limitations should be considered when analyzing these results. This study used scarce literature as source of data. The model did not stratify patients according to risk factors for progression, such as race, corneal thickness and biomechanics, family history of blindness, perfusion pressure, among others. Like any model-based study, the results are influenced by data availability in literature and the adoption of assumptions.

CONCLUSION
The economic cost-effectiveness analysis in different scenarios showed that iStent inject®, when used after failure of the first-line drug at Glaucoma Reference Sites of SUS, can reduce glaucoma progression rate over the average life expectancy of the Brazilian population. This is performed at an affordable price, thus reducing future costs associated with eye drops, filtering surgeries, and complications.

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