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Modeling Complex Treatment Strategies: Construction and Validation of a Discrete Event Simulation Model for Glaucoma

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ABSTRACT

Objective: Discrete event simulation (DES) modeling has several advantages over simpler modeling techniques in health economics, such as increased flexibility and the ability to model complex systems. Nevertheless, these benefits may come at the cost of reduced transparency, which may compromise the model's face validity and credibility. We aimed to produce a transparent report on the construction and validation of a DES model using a recently developed model of ocular hypertension and glaucoma.

Methods: Current evidence of associations between prognostic factors and disease progression in ocular hypertension and glaucoma was translated into DES model elements. The model was extended to simulate treatment decisions and effects. Utility and costs were linked to disease status and treatment, and clinical and health economic outcomes were defined. The model was validated at several levels. The soundness of design and the plausibility of input estimates were evaluated in interdisciplinary meetings (face validity). Individual patients were traced throughout the simulation under a multitude of model settings to debug the model, and the model was run with a variety of extreme scenarios to compare the outcomes with prior expectations (internal validity). Finally, several intermediate (clinical) outcomes of the model were compared with those observed in experimental or observational studies (external validity) and the feasibility of evaluating hypothetical treatment strategies was tested.

Results: The model performed well in all validity tests. Analyses of hypothetical treatment strategies took about 30 minutes per cohort and lead to plausible health–economic outcomes.

Conclusion: There is added value of DES models in complex treatment strategies such as glaucoma. Achieving transparency in model structure and outcomes may require some effort in reporting and validating the model, but it is feasible.

Keywords: discrete event simulation, disease-progression model, modeling, ocular hypertension, primary open-angle glaucoma, validation.

Introduction

The application of discrete event simulation (DES) modeling in health economic decision analyses has been growing steadily in recent years [1]. This may be partly ascribable to the advances in computing technology, which enables faster Monte Carlo simulations, but undoubtedly also to some of the appealing advantages of DES in terms of flexibility and the ability to model complex systems [1–4]. Such increased complexity of a model can enhance the accuracy of the outcomes, but may come at the cost of a loss in transparency and therewith face validity and credibility [1,2]. This is a problem since a lack of understanding of a model and trust in its outcomes may limit the degree to which information generated by the model is considered by the target audience. It is therefore important to not only maximize transparency, but also to convincingly validate a model and its outcomes [5]. With this article we aim to contribute to the literature regarding the construction, validation and reporting of DES models in complex treatment strategies, drawing from our experience with a recently developed health economic DES model to simulate disease progression in glaucoma patients.

Glaucoma is an ocular condition involving the slow but gradual and irreversible loss of retinal nerve fibers, leading to visual field loss and possibly blindness. The etiology of glaucoma is unknown, but the most important known risk factor for its occurrence is an elevated intra-ocular pressure (IOP). As long as the IOP is elevated without signs of retinal nerve fiber loss, the condition is termed ocular hypertension (OHT). Nevertheless, when nerve fiber loss occurs at a level that causes optic nerve cupping and/or visual field loss, the condition is termed primary open-angle glaucoma (POAG). The transition from OHT to POAG is termed "conversion." If nerve fiber loss continues (progression), the visual field deteriorates and a patient may progress to blindness. Treatment of glaucoma is directed at lowering the IOP to slow down the neurodegenerative process [6,7]. Since glaucoma is a chronic condition, patients are usually monitored and treated lifelong from the moment of diagnosis. Treatment guidelines for glaucoma have been formulated based on evidence from clinical trials, but several issues in these guidelines remain unspecified due to a lack of evidence [8,9]. For example, it is unclear how often patients need to be evaluated for progression, and how low the target pressure should be to prevent further progression.

The information necessary to resolve these issues cannot be generated by clinical trials, because the follow-up period needed to establish differences in relevant outcomes (i.e., vision impairment or blindness) is long, and by the time the results are available they may no longer be relevant. Moreover, until the results of clinical trials are available, treatment decisions still need to be made today. A large number of trials would be necessary to investigate all relevant combinations of treatment strategy characteristics (initiation, monitoring frequency, type of intervention, target pressure, etc.) yielding a massive need for study subjects,

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and for obvious ethical reasons it is not possible to investigate the effect of withholding treatment. Finally, the study protocols would be inflexible to future treatment options and insights from scientific research in the pathogenesis of glaucoma. Therefore, rather than obtaining new evidence, we have used a modeling approach to synthesize all currently available evidence regarding glaucoma disease progression and the effects of treatment. The resulting health economic disease progression model will be employed to generate predictions of the (cost) effectiveness of a wide range of treatment strategies for OHT and POAG patients. We have used the DES model structure because it was expected to provide important advantages over other modeling techniques in the context of glaucoma and our research objectives. In this article we intend to: 1) justify the choice for a DES model; 2) describe how disease progression and treatment effects in glaucoma were translated into the structure of a DES model; and 3) present the results of the model validation.

Methods

Justifying the Chosen Model Structure

One of the first steps in decision analytic modeling is to choose the most appropriate model structure. The choice for any particular model type must be based on the decision problem(s), the theory of the health condition being modeled, and on additional desired features such as flexibility or user-friendliness [10–12]. Various model types represent various levels of complexity, and the chosen model structure should only be complex enough to meet its intended purpose [5]. Modeling glaucoma and its treatment calls for a relatively complex model structure because of (among others) the following reasons [13]. Glaucoma is a chronic condition that requires lifetime monitoring and treatment, so a decision analytic model should facilitate a lifetime horizon of disease progression and treatment. Within this lifetime a number of treatment options are available, such as watchful waiting, medication, laser treatment (LT), or surgery, and a concurrent or sequential combination thereof. Even within medicinal treatment over 56,000 combinations of agents and dosages are possible [14]. A decision analytic model of glaucoma therefore needs to compare treatment *strategies* rather than single treatment options. In addition, a treatment strategy is not only defined by the way treatments are ordered or combined, but also by the circumstances that call for a treatment change. After all, in clinical practice a great number of factors may be considered in the decision to alter the existing glaucoma treatment, such as age, disease history, treatment history, current clinical status, the efficacy and tolerability of previous therapies, and the outcomes of diagnostic tests. Therefore, in order to evaluate different treatment strategies in the glaucoma decision analytic model, the model must be able to discern all the factors that are deemed relevant for the treatment strategy. In addition, the model must take account of all factors that are relevant for the costs and outcomes. Lastly, glaucoma disease progression is not characterized by clearly discernable disease states, but rather represents a sliding scale of anatomical and functional disease manifestations [15].

The most common model types used in decision analytic modeling are (in increasing order of complexity) decision trees, Markov models and DES models [2–4]. Several authors have recently reviewed model structures and offered a guide on choosing the most appropriate method [16–19]. Given the requirements described in the previous paragraph, we needed an individual sampling model based on either a Markov or a DES model structure. The main limitations of Markov models precluded its applicability in our research. First, in view of the multifaceted nature of glaucoma treatment and the fact that Markov health states are mutually exclusive (i.e., a patient can only be in one health state at the time), the necessary amount of health states and transition probabilities would be enormous. For example, simplifying the disease status to four levels (OHT, mild POAG, severe POAG, and blind) and the number of treatments to 10 (no treatment, 7 types of (combinations of) medications, and 2 invasive procedures) would already yield 40 health states and up to 1600 transition probabilities. Second, the cycle time in a Markov model is fixed, whereas we wanted to explicitly evaluate the effects of altering the frequency of ophthalmologist consultations on cost-effectiveness outcomes. Third, a Markov model has no memory with regard to the treatment history of a patient, whereas the treatment options of a glaucoma patient depend on his exposure to and experience with previous treatments. Also the effectiveness of some treatments may vary depending on past exposure to other treatments. The structure of a DES model enabled us to overcome these issues, and has the additional advantage that a "finished" model allows for relatively easy adjustments to future research questions, new treatment options, or new scientific evidence.

Building Blocks of Discrete Event Model

The typical elements of a DES model are: entities, attributes, events, relationships, and outcomes. In order to simulate glaucoma and its treatment with a DES model, we have "conceptualized" our knowledge of the underlying pathogenetic and therapeutic processes in terms of these DES model elements. In order to facilitate the identification of model elements in the remainder of this article, we have used the notation described in Table 1. The entity in the model is a patient (further referred to in the masculine form). Attributes are characteristics that refer to the patient or his better eye. Attributes can either be fixed throughout the simulation (e.g., sex), or change in time (e.g., age). Events represent relevant moments in time. At an event the attributes of the entity are re-evaluated and adjusted. In our model, time-progression is event-based, which means that the model "jumps" from one event to the next (please see the Supporting Information Appendix S1 for this article at http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i4_vanGestel.asp). The timing of future events may be conditional upon the new values of the attributes. This issue will be discussed more elaborately when we explain how the attributes managing future events ($\langle$time-to-xxx$\rangle_A$) were calculated in the model. Relationships are the model elements that link entities, attributes, events, and outcomes together with mathematical and/or logical terms. Outcomes are the model element that aggregate information needed to draw conclusions from the simulations. An outcome is expressed by a relationship involving any of the model elements or a combination of elements. Examples of outcomes are 1) $\langle$average IOP$\rangle_O$, which is an outcome based on an attribute; 2) $\langle$occurrence of conversion$\rangle_O$, which is an outcome

Table 1 Notation of model elements

Specific model elements are referred to with their name in angle brackets $\langle\ \rangle$.
The subscript indicates the type of model element:
A for an attribute $\langle\ \rangle_A$
E for an event $\langle\ \rangle_E$
O for an outcome $\langle\ \rangle_O$
For example: $\langle$Age$\rangle_A$ signifies that the referred model element is an attribute with the name "Age" and $\langle$Visit$\rangle_E$ signifies that the referred model element is an event called "Visit."

based on an event; 3) ⟨age at conversion⟩$_O$, which is an outcome based on both an attribute and an event; and 4) ⟨discounted lifetime costs⟩$_O$, which is an outcome based on attributes (e.g., ⟨medication⟩$_A$), events (e.g., ⟨visit⟩$_E$), discount rates, and time.

Various methods exist to transfer a DES model concept into a running model, ranging from pure programming languages to dedicated software packages [20]. We have used Excel spreadsheets (Microsoft Excel 2000, Microsoft Corporation, Redmond, WA) to simulate the individual patient, and added Visual Basic macros (Microsoft Visual Basic 6.0, Microsoft Corporation) to create a heterogeneous population of simulated patients.

Conceptualizing Glaucoma and Its Treatment

We have conceptualized glaucoma and its treatment from a clinical perspective. This means that we have not necessarily simulated the actual pathogenetic processes themselves, but rather how they manifest themselves in clinical practice. In the model, OHT and POAG represent two distinct disease states (please see the Supporting Information Appendix S1. Conversion is modeled as an event upon which the disease state changes from OHT to POAG. Visual field damage is a proxy for glaucoma severity and is expressed as mean deviation (MD) ranging from 0 (no damage) to −35 (severe damage) decibel (dB) [21]. Below a certain MD threshold, patients are considered blind. Progression is modeled by means of an intrinsic rate at which the visual field decreases annually. The effect of treatment is that it lowers IOP, which in turn affects the conversion risk and the progression rate in the model.

The set of attributes, events, and relationships that simulate this natural disease progression of an individual patient is discussed in the next paragraph. Additional model elements were added to the disease progression model to simulate treatment decisions and effects. These are discussed in subsequent paragraphs. An overview of the most important events, attributes, and relationships in the model is presented in Table 2. Details on model elements and parameter estimates are provided in the Supporting Information Appendix S1.

Simulation of Natural Disease Progression

At the start of a simulation (T_0) a set of baseline attributes is determined for the patient and his better eye, including ⟨Age⟩$_A$, ⟨Gender⟩$_A$, ⟨IOP⟩$_A$, and ⟨Risk profile⟩$_A$. The ⟨Risk profile⟩$_A$ represents a set of factors (other than age and gender) quantifying the relative risk of conversion in the patient relative to the average patient [22]. The baseline ⟨disease status⟩$_A$ is set by the user to either OHT or POAG. The values of the other baseline attributes are randomly drawn from distributions. The specifications of these distributions can be adjusted to generate specific patient populations, like a high risk OHT population or a young POAG population. To establish which event occurs next, the model uses special attributes (time-to-xxx) that set the time interval to each possible future event. The intervals are compared, and the smallest value determines which event occurs next and when. The model then jumps to that event and recalculates all attributes, including all time-to-xxx attributes.

If the baseline ⟨disease state⟩$_A$ of the simulated patient is OHT, two events may occur in the future: ⟨conversion⟩$_E$ and ⟨death⟩$_E$. Time-to-death is calculated by subtracting the current ⟨Age⟩$_A$ from ⟨age at death⟩$_A$. The latter is determined at baseline by a random draw from a distribution of life-expectancies [23]. Time-to-conversion is based on ⟨risk profile⟩$_A$, ⟨Age⟩$_A$, and ⟨IOP⟩$_A$ at the time of the event. The determination of ⟨time-to-conversion⟩$_A$ occurs via a new random draw from a distribution at each event (please see the Supporting Information Appendix S1. The distribution itself is redefined at each event to adjust it to the current values of ⟨Age⟩$_A$ and ⟨IOP⟩$_A$. At higher values for age and IOP, the chance to draw a small value for time-to-conversion is higher, the chance that this value is the smallest time-to-event value is higher, and so the likelihood of conversion occurring is higher.

The distribution of time-to-conversion is based on a survival function (Eq. 1) that is customized to the individual patient at the specific event. The latter is established by calculating the individual's current hazard *(h_i)* from the average hazard of conversion observed in OHT-populations, hazard ratios for age and IOP as reported in literature, and the hazard ratio of other risk factors given by ⟨Risk profile⟩$_A$ (Eq. 2).

$$P = 1 - S = 1 - e^{-h_i \cdot t} \tag{1}$$

$$h_i = HR_i \cdot h = e^{\ln(HR_{Age}) \cdot \left(\frac{\langle Age \rangle_A - Age_{av}}{10} \right)} \cdot e^{\ln(HR_{IOP}) \cdot (\langle IOP \rangle_A - IOP_{av})} \cdot HR_{other_i} \cdot h \tag{2}$$

where P = cumulative probability of conversion.
S = conversion free survival.
h_i = current hazard rate of individual i at current event.
t = time.
h = hazard rate in reference OHT population.
HR_i = total hazard ratio of individual i at current event.
HR_{age} = hazard ratio of age (per 10 years older).
HR_{IOP} = hazard ratio of IOP (per mmHg higher).
$\langle Age \rangle_A$ = age of individual i at current event.
Age_{av} = average age of reference OHT population.
$\langle IOP \rangle_A$ = IOP of individual i at current event.
IOP_{av} = average IOP in the reference OHT population (mmHg).
HR_{other} = hazard ratio of other risk factors.

With the resulting hazard h_i, Eq. 1 can be completed to generate an updated cumulative distribution of time-to-conversion for individual *i*. A random draw from the thus created distribution provides the value for ⟨time-to-conversion⟩$_A$ at the current event. Incidentally, as the time-to-conversion distribution is only updated during events, large time intervals between events would induce flawed risk estimations because the risk from increasing age between events would not be accounted for. A separate event (⟨update⟩$_E$) was introduced in the model to solve this problem.

Table 2 Overview of the most important attributes and relationships in the model

Attributes	Relationships	Updated at all events?
Age	Age = F(Age$_0$, time)	Yes
Gender		No
IOP	IOP$_u$ = F(IOP$_0$, surgery, time) IOP$_i$ = F(IOP$_u$, effect (%))	Yes
Disease status		Only at "conversion"
MD	MD = F(MD$_0$, MDR, time)	Yes
MDR	MDR = F(MDR$_0$, IOP)	Yes
Treatment type		Only at "visit"
Medication		Only at "visit"
E (%)	E = F(medication, E$_0$)	Yes
SEs	SE = F(medication, SE$_0$)	Yes
Time-to-next-event	Time-to-death = F(Age, gender) Time-to-conversion = F(IOP, Age, Risk$_0$) Time-to-visit = F(treatment type, visit number) IOP$_{target}$ = F(disease status, progression)	Yes

$_0$, baseline; E, effect; F(x), function of x; IOP$_i$, current intraocular pressure; IOP$_u$, IOP without medication or LT effect; MD, mean deviation; MDR, mean deviation rate; SE, side effect.

The interval between updates was fixed to ensure a regular update of the patient attributes, regardless of the frequency of the other events.

When disease state changes to POAG, two additional attributes become relevant: MD ($\langle MD \rangle_A$) and MD rate ($\langle MDR \rangle_A$). MD (dB) represents the disease severity of the POAG patient, and MDR (dB/year) represents the speed of progression. As mentioned previously, a higher IOP is a risk factor for progression, so we needed to define another relationship in the model to create the link between these two factors. For each patient a fixed value for $\langle MDR_{ref} \rangle_A$ is drawn from a distribution based on the average MDR in a POAG population [24]. This attribute represents the MDR if the patient had a risk profile and IOP similar to the average in the referent POAG population. During the simulation, the actual value of $\langle MDR \rangle_A$ is calculated according to Eq. 3, using the fixed $\langle MDR_{ref} \rangle_A$, the current $\langle IOP \rangle_A$, and an additional attribute ($\langle$progression risk$\rangle_A$) that represents an aggregation of other risk factors for progression.

$$MDR = MDR_{ref} \cdot HR_i = MDR_{ref} \cdot e^{\ln(HR_{IOP}) \cdot (\langle IOP \rangle_A - IOP_{av})} \cdot HR_{other},$$
$$\langle IOP \rangle_A \geq IOP_{no\ progression}$$
$$MDR = 0, \quad \langle IOP \rangle_A < IOP_{no\ progression} \tag{3}$$

where MDR = mean Deviation Rate of individual i at current event.

MDR_{ref} = mean Deviation Rate of individual i if IOP and HR_{other} were as the average in the reference POAG population.

HR_i = total hazard ratio of individual i at current event.

HR_{IOP} = hazard ratio of IOP (per 1 mmHg higher than average IOP in the reference POAG population).

HR_{other} = hazard ratio of other risk factors ($\langle$progression risk$\rangle_A$).

$\langle IOP \rangle_A$ = IOP at current event (mmHg).

IOP_{av} = average IOP (mmHg) in the reference POAG population (15.5 mmHg).

$IOP_{no\ progression}$ = IOP threshold for disease progression.

Simulation of Treated Disease Progression

The previous paragraphs have described how the *natural* disease progression of glaucoma was translated into a DES model structure. With an additional set of events, attributes, and relationships, this model was extended to simulate the *treated* course of disease. Before elaborating on these additional model elements, we will briefly discuss what typically constitutes "treatment" in OHT and POAG management. Watchful waiting is the least intensive form of treatment, and consists of regular consultations with the ophthalmologist to monitor IOP, optic disc, and visual field but without active intervention. In terms of active interventions, there are three different methods to reduce IOP: medication (eye drops), LT, and surgery. The pressure reducing effect of medication and LT is proportional to the IOP before treatment, whereas the IOP level after surgery is independent on the presurgical IOP. Treatment guidelines advice to start treatment for OHT and POAG with medication(s) and to proceed to laser and/or surgery if maximally tolerated medication is not sufficiently effective [8,9]. A scheme of this treatment flow is provided in the Supporting Information Appendix S1.

The only new event that was added to the model to simulate treatment was $\langle visit \rangle_E$. The associated attribute $\langle$time-to-visit$\rangle_A$ was defined by means of a look-up table specifying the interval to the next $\langle visit \rangle_E$, depending on treatment type and the number of visits since the last treatment change (please see the Supporting Information Appendix S1.

Attributes

A considerable amount of attributes was added to the model to simulate treatment and its effects. Some attributes do not represent any physical characteristic of the patient but rather aid the model to keep track of treatment history. Other new attributes represent the information an ophthalmologist has available to inform his/her treatment decisions. For example, the model always uses the real MD value to simulate disease progression and calculate utilities, but it uses a second MD attribute (representing the MD as measured) to inform treatment decisions. The latter can be influenced by settings in the treatment strategy such as the frequency or the sensitivity of visual field testing (which enables the evaluation of such aspects of treatment), whereas the progression of the real MD is not affected by such treatment settings.

The effect of medication and LT are simulated as a relative pressure lowering (%) of the IOP. The effect of surgery is simulated by resetting the IOP. Two sets of attributes were therefore created in the model. The first calculates an IOP ($\langle IOP_u \rangle_A$), that indicates how high the IOP would be in the absence of medication or LT treatment. If a patient has not undergone surgery, the IOP_u is similar to the baseline IOP with a small annual increase. When surgery occurs, IOP_u is reset. The second set of attributes calculates the total pressure lowering effect (in %) of all currently prescribed medications and previously performed LT treatment that act upon the IOP_u. The combination of IOP_u and the total pressure lowering effect yields the actual IOP of the patient ($\langle IOP \rangle_A$). Four different types of medication are used: β-blockers, prostaglandin analogues, carbonic-anhydrase inhibitors, and α_2-adrenergic agonists. There are two types or surgery: trabeculectomy and tube implantation. The effect of all types of medication and LT, and the specific value of the new IOP_u after surgery in the simulated patient are randomly drawn for each individual patient and are determined at baseline. In addition, randomly drawn attributes define whether the patient has contraindications or will experience side-effects with each type of medication.

The simulation of treatment decisions and effects was more elaborate in the model than described above (please see the Supporting Information Appendix S1). Briefly, the model allowed for the combination of medications, LT, and surgery and used additional sets of effect estimates to calculate the aggregate effect of the combination therapies. Also, the model accounted for a gradual loss of effect after LT treatment, and for three different types of response to surgery: no response, a temporary response, and a lifelong response.

Relationships

One of the most appealing features of DES modeling is its ability to mimic complex and individual treatment decisions, and what is more, to enable adjustments in the complete treatment strategy from one analysis to the next through minor alterations in the model. In the glaucoma model, this was achieved by defining a specific set of relationships that represent the "decision rules." The decision rules are logical relationships, and are composed for the most part of "if–then" statements based on the treatment flowcharts. An example is presented in Figure 1, which shows how a series of if–then relationships leads to a new value of $\langle treatment \rangle_A$. Within the decision rules, the values of patient attributes are compared with benchmark values such as the target IOP or the minimal effectiveness required to continue a

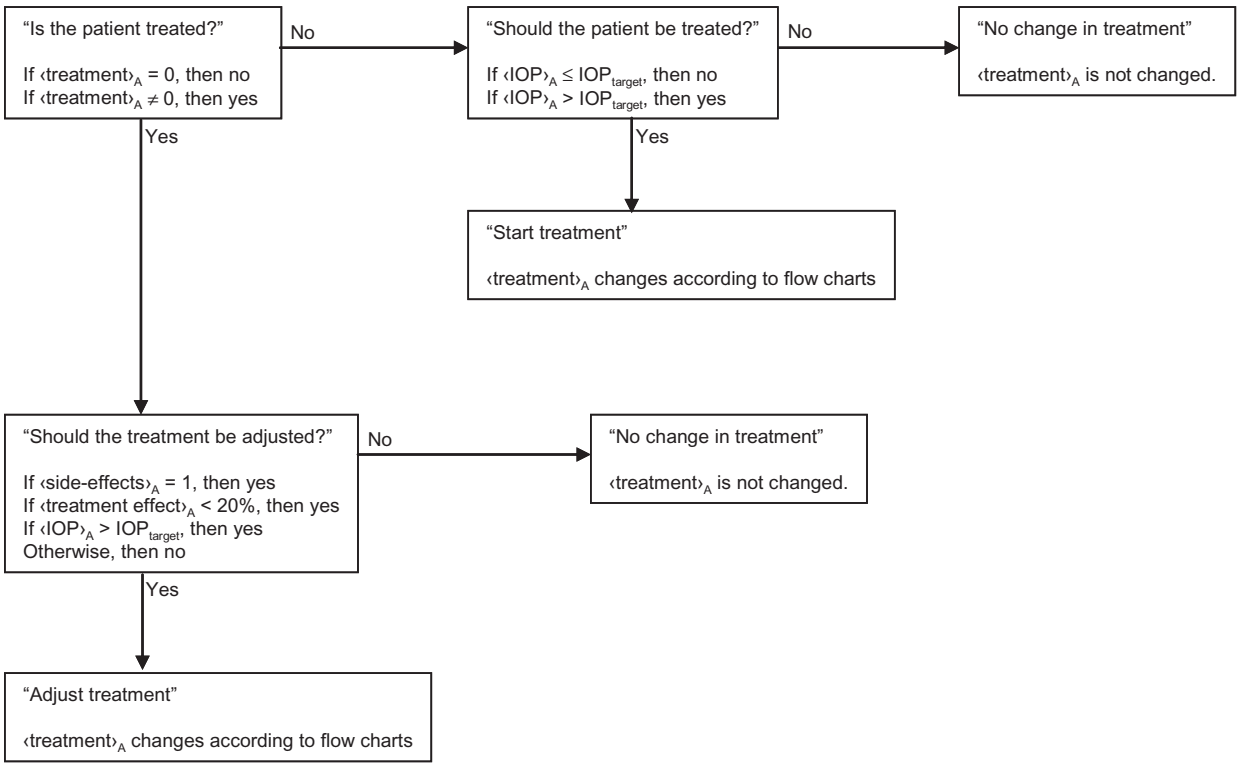

Figure 1 Examples of logical relationships that collectively create a decision regarding the simulated patient's future treatment.

single medication. The benchmark values of a treatment strategy are specified before a cohort of patients is simulated, and so is the order of the medication types. Adjustments in a treatment strategy can be made by simply changing the value of these benchmarks.

Outcomes

The flexibility of a DES model allows for the collection of basically all types of outcomes that may be of interest to the targeted audience. In the glaucoma model for example, the main outcomes that were collected from the simulation of an individual's disease progression were 1) whether conversion occurred; 2) whether the eye progressed to blindness; 3) the number of life-years adjusted for the VFQ –25 score (see below); 4) the number of life-years adjusted for utility; and 5) the total costs associated with the disease and its treatment. The outcomes had a societal perspective and took a discounting factor into account [25]. Future effects were discounted with 1.5% per year, and future costs were discounted with 4% per year according to Dutch guidelines for pharmacoeconomic research [26]. Blindness was defined as an MD lower than –25 dB in the simulated eye. The Visual Functioning Questionnaire (VFQ-25) is a vision specific health-related quality of life questionnaire [27]. The life-years adjusted for VFQ-25 score were calculated by multiplying the length of the time intervals between events with the VFQ-25 score during those time intervals. The VFQ-score was calculated based on the MD, the presence of side effects, and the presence of cataract, and was transformed from the original 0–100 scale to a 0–1 scale (Eq. 4) [28]. The quality-adjusted life-years (QALYs) were calculated in a similar fashion, multiplying the time intervals between events with utility based on the Health Utilities Index (Eq. 5). The costs associated with treatment and impaired vision were calculated by linking the occurrence of treatment and the patient's MD respectively to resource costs. The derivation of all utility and cost estimates is described in the Supporting Information Appendix S1.

$$Score_{VFQ-25} = 0.94 + 0.016 \cdot MD - 0.1 \cdot SE - 0.092 \cdot Cataract \quad (4)$$

$$Utility_{HUI3} = 0.88 + 0.01 \cdot MD - 0.1 \cdot SE - 0.059 \cdot Cataract \quad (5)$$

where MD = mean deviation.
SE = presence of side-effects, 0 = no, 1 = yes.
$Cataract$ = presence of cataract, 0 = no, 1 = yes.

Validation

The disease progression model for OHT and POAG was developed with a high level of attention for quality, validity, and transparency. Guidelines for model development must remain quite general due to the large variety in models, and there is not a specific checklist to assess the quality of a DES model [11,12,29,30]. Nevertheless, we have regarded the good practice guidelines for decision analytic modeling by Philips et al. as a minimal set of requirements during the development of the model [11]. In these guidelines, three dimensions of quality are distinguished: structure, data, and consistency. The dimension of structure refers to the definition of the decision problem, the objective and scope of the model, justification of the model type, structural assumptions, and the translation of the disease to the model structure. These issues are important for "face validity," which is discussed in more detail below. The dimension of data refers to the transparency and justification of all activities involving the

identification, analysis, and incorporation of data. Transparency in this dimension requires more text space than a journal article can provide, so issues regarding data have been included in the Supporting Information Appendix S1. Another aspect within the dimension of data is the assessment of four types of uncertainty (methodological, parameter, structural, and heterogeneity). The assessment of all four types of uncertainty is feasible with a DES model, but uncertainty analyses must be made in the context of a specific decision analysis and cannot be reported here for the model as a whole. The dimension of consistency refers to the internal and external consistency of the model, and is described in more detail below.

The face validity of a model refers to the soundness of the design and the plausibility of the input estimates as perceived by experts in the field. There should be a general feeling that all relevant events and attributes are considered in the model, and that the defined relationships are correct. Face validity was guarded throughout the development process by continuous consultation with glaucoma experts, epidemiologists, and health technology assessment experts. The development of the model concept and the establishment of the quantitative parameter estimates were discussed in frequent multidisciplinary meetings with the abovementioned experts. During these meetings no information was provided on the outcomes of the simulations to prevent bias toward desirable outcomes. The model design was presented to an independent panel of Dutch glaucoma experts in November 2007 to seek feedback. An extensive report about the model design and outcomes was evaluated by independent reviewers for The Netherlands organization for health research and development (ZonMW), and has been approved in February 2009.

The internal validity of the model refers to the consistency between the theoretic model design and the product that is eventually used to run the simulations. The internal validity of the model was evaluated in several ways. The model was programmed in Microsoft Excel spreadsheets, enabling the programmer (A.v.G) to review all attributes during all events in the complete disease and treatment history of an individual patient. A visual excerpt of such an overview, showing the most important attributes, is presented in Figure 2. A detailed review of events and attributes was conducted for a large number of patients with specific characteristics and treatment strategy settings, to check whether the attributes in the model changed according to expectation and whether the model "made" the right treatment decisions. Furthermore, the model was run in a series of simulations with test scenarios in order to check whether the outcomes of the patient populations were as expected. For example, a scenario in which none of the treatments have any effect must give the same health outcomes as a scenario in which none of the patients is ever treated at all, increasing the efficacy of treatments should lead to better health outcomes and increasing cost-prices should lead to higher costs.

The external validity of the model refers to the similarities between outcomes observed in patient populations and the outcomes of the model in comparable circumstances. The external validity of the model was evaluated in terms of two clinical endpoints: conversion to POAG in an OHT population and progression to blindness in a POAG population.

A cohort of ocular hypertension patients was simulated in the model in order to compare the incidence of conversion in 5 years with that observed in a recent systematic review [6]. The baseline age and IOP of the simulated patients was drawn from distributions based on the Ocular Hypertension Treatment Study population [31]. The treatment strategies specified in the model were 1) no treatment unless conversion is observed; and 2) treatment with a target pressure at 80% of the initial IOP. The results produced by the model are presented in Table 3. The incidence of conversion in the simulated patients was comparable to a weighted average of what was found in literature, and well within the range of reported conversion incidences. The relative risk of treatment found with the model results was 0.56 (0.082/0.146), which is exactly similar to the outcome of the meta-analysis of the efficacy of pressure lowering treatment in ocular hypertension [6]. The results also show that leaving treatment decisions to the model leads to very plausible IOP values for treated patients.

Two observational studies reporting the cumulative risk of blindness in populations with open-angle glaucoma were imitated in order to compare the incidence of blindness after 10 to 15 years. In a retrospective study in 186 patients, Chen et al. report the incidence of blindness in the better eye of a population treated for open-angle glaucoma [32]. We mimicked this study by modeling an untreated POAG population with an average baseline IOP similar to the average follow-up IOP reported by Chen et al. The results are presented in Table 4. The incidence of blindness in the model was lower than that reported. A possible explanation for the difference is the fact that Chen et al. used a retrospective design and included patients based on the availability of visual field measurements. This may have resulted in some selection bias toward patients with faster progression. Alternatively, the patient population in the study may have been distributed toward a higher risk of progression, for example due to the genetic makeup of the hospital population. Nevertheless, the difference may also be the result of some of the assumptions made in the model, particularly with respect to the linearity of MD loss in time. This issue is addressed in the discussion.

The second study mimicked with the model was described by Wilson et al. and concerned an untreated population of glaucoma patients in the west Indies [33]. At baseline, patients were on average 42 years old, had a baseline Advanced Glaucoma Intervention Study (AGIS) score of 3.7 (which corresponds to an MD of approximately –4 dB) [34] and an IOP during follow-up of approximately 21 mmHg. After 10 years, 45 out of 287 eyes had progressed to end-stage visual field, which was AGIS score 18. In this case, blindness in the model was defined as an MD lower than –18 dB. The results of the model simulation are presented in Table 4. The incidence of blindness found with the model was comparable to the reported study results.

Finally, in order to test the feasibility of the model, we have applied it to an average POAG population and compared the outcomes of three different treatment strategies to a reference scenario in which patients are never seen nor treated by the ophthalmologist. The three treatment strategies differed in terms of the target pressure and the frequency of visual field tests. A summary of results is presented in Table 5. All three treatment strategies lead to better outcomes and lower costs than the referent strategy. A higher frequency of visual field measurements and a lower target pressure resulted in lower average IOP, higher incidence of surgery, better outcomes, and lower total costs. Indeed, the costs associated with treatment were higher (from €1118 without treatment to €7938 in strategy C), but the costs associated with low-vision were much lower (from €40,500 without treatment to €15,255 in strategy C), resulting in overall cost-savings.

Discussion

We have been able to build a model that simulates the disease progression of ocular hypertension and glaucoma patients and that mimics the treatment choices that are made in clinical prac-

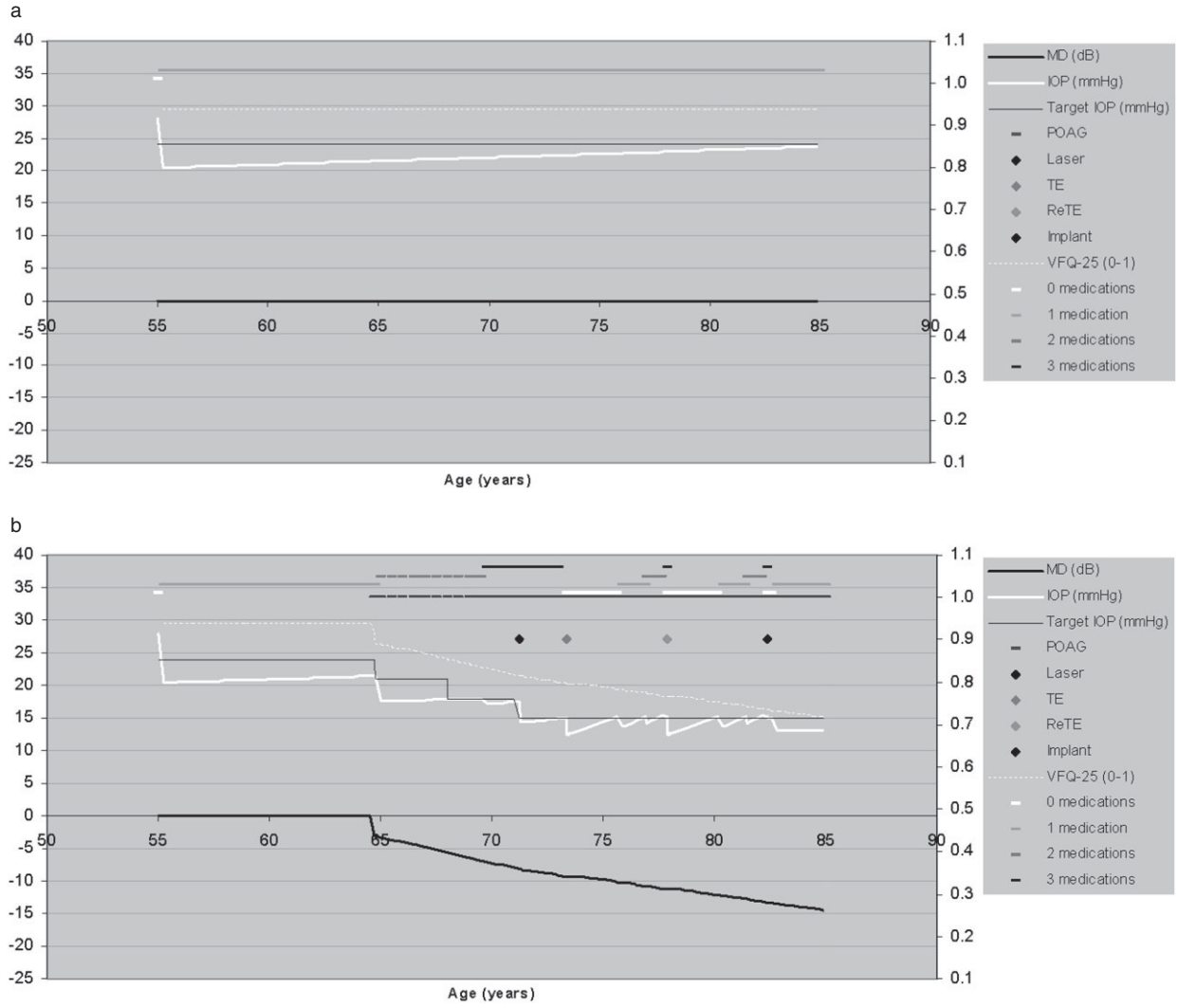

Figure 2 Examples of two simulated OHT patients. The patient in the top graph (a) does not develop POAG and receives one medication lifelong. The patient in the bottom graph (b) develops POAG at age 64.5, receives multiple medications and surgery, and progresses to an MD of −14 dB. MD, mean deviation (dB); POAG, primary open-angle glaucoma; IOP, intraocular pressure (mmHg); TE, trabeculectomy; ReTE, second trabeculectomy; VFQ-25, Visual Functioning Questionnaire score. In the graphs the topmost lines indicate the number of medications and presence of POAG, and the diamonds indicate the occurrence of an intervention. These series are not linked to either of the y-axes. IOP and MD are quantified on the left y-axis, VFQ-25 on the right y-axis.

tice. The DES model structure has enabled us to discern relevant characteristics of individual patients and of treatment strategies, which would have been impossible (or at the least impractical) within a decision tree or Markov structure. Still, a model remains a simplified version of reality and also in this model several relevant assumptions were made. First, we have simulated the disease progression in the better eye of the patient, assuming that the other eye is only slightly worse. In fact this comes down to

Table 3 Comparison of outcomes of the model simulating an ocular hypertension patient population and outcomes of a review of clinical studies

	Model		Review studies [15]	
	Control	Treatment	Control	Treatment
Age	55.2 ± 9.8			
Baseline IOP (mmHg)	25.9 ± 2.4			
IOP during follow-up (mmHg)	25.7 ± 2.8	18.6 ± 2.3	23–26	19–22
Conversion in 5 years (95% CI)	14.6% (13.3%; 15.9%)	8.2% (7.2%; 9.2%)	13.0%*	7.0%*
			9%–37%†	4%–25%†

*Incidence calculated as the total number of converting patients relative to the total number of included patients summed over all studies included in the meta-analysis.
†Lowest and highest incidences reported in the studies included in the meta-analysis.
CI, confidence interval; IOP, intraocular pressure.

Table 4 Outcomes reported by Chen [32] and Wilson et al. [33] and outcomes of the model simulating similar primary open-angle glaucoma populations

	Chen 2003 [32]	Model
Age	61 ± 13	61 ± 13
IOP during follow-up	17 ± 3	17 ± 3
MD at baseline in better eye	−3.4 dB	−3.4 dB
Bilateral blindness after 15 years	6.4% (95% CI: 2.9%; 9.9%)	2.2% (95% CI: 1.3%; 3.1%)
	Wilson et al. 2002 [33]	Model
Age	42	42
IOP during follow-up	21 ± 4.3	21 ± 4.3
MD at baseline in better eye	−4 dB	−4 dB
Blindness after 10 years	15.7% (95% CI: 10.0%; 21.4%)	16.5% (95% CI: 14.2%; 18.8%)

CI, confidence interval; dB, decibel; IOP, intraocular pressure; MD, mean deviation.

modeling both eyes and assuming that they progress equally. In reality glaucoma may progress asymmetrically. For example, Heeg et al. found that half of their cohort of glaucoma patients had unilateral glaucoma [35]. The disease severity in the better eye has the highest impact on quality-of-life, but the disease progression in the worse eye may have the highest impact on treatment decisions, also those concerning the better eye [28,36]. It is possible to model both eyes separately in the DES structure, but we have chosen not to. It would have added considerably to the complexity of the model (e.g., in terms attributes and relationships), whereas it was unclear whether it would improve the suitability of the model outcomes to inform guideline decision-making. The impact of the assumption that both eyes are symmetrically affected needs to be tested with univariate sensitivity analyses in presentations of the model results. The results of the current model in terms of the incremental cost-effectiveness of a certain treatment strategy can be regarded as valid for an OHT or POAG population with a symmetrically developing disease. Second, we have assumed that the natural progression of glaucoma can be described with a linear function of MD in time. An evaluation of the validity of this assumption is hampered by the fact that there are no records of long-term MD progression in untreated POAG patients, but the assumption is not contradicted by current evidence. The explicitness of the DES model structure allows for a univariate (structural) sensitivity analysis of this assumption, and the impact of a different disease progression pattern on the model outcomes can be evaluated quite readily. We have not included sensitivity analyses in this article because the conclusions from such analyses are only valid for the particular population and strategies that were analyzed, and no general conclusions regarding the model itself can be drawn from them. We have performed cost-effectiveness analyses of three treatment strategies with the model as a way of demonstrating how changes in the treatment strategy setting affect the model outcomes. A full cost-effectiveness analysis to inform guideline decisions, including full sensitivity and probabilistic analyses, is outside the scope of this article and is the subject of future research. Nevertheless, our preliminary results in Table 5 show that treatment of POAG is expected to lead to a gain of 1.2 QALYs with a cost-reduction of €25,000 per patient compared to withholding treatment. Recently, Rein et al. have reported an incremental cost-effectiveness ratio of $20,000/QALY for POAG treatment compared to no treatment [37]. The fact that incremental costs rather than cost-savings were found in this study is most likely due to the fact that almost no low-vision associated costs (i.e., home care, aids and services) were included in the calculations.

Despite the apparent advantages DES has within modeling complex treatment strategies, several disadvantages of the technique have previously been described [4]. These pertain mainly to the added simulation time, building time, data collection, and the degree of experience needed by the modeler. The increased simulation time is the result of the need to simulate individual patients rather than cohorts, and is inherent to microsimulation. This can become particularly problematic in probabilistic analyses, and even more so in expected value of perfect parameter information analyses, which require the execution of large numbers of first-order simulations. Our model needed approximately 30 minutes to run a first order analysis of 3000 patients. Nevertheless, more efficient programming with, e.g., specialized software or pure programming language can sometimes reduce computation times dramatically. Building the model and collecting data to inform the model may seem more strenuous than with simpler model structures, but it can be argued that the combination of building the model and collecting the data require equal efforts in Markov and DES models. Markov models often require (behind the scene) data processing to adjust the literature data to the specific health states, transition probabilities, and cycle length of the model; whereas in DES models the literature data can often be inserted in the model

Table 5 Model results (mean ± SD) comparing three treatment strategies to "no treatment" in an average primary open-angle glaucoma population

	No treatment	A. Target 24, 21, 18 mmHg. VF every 5 years	B. Target 24, 21, 18 mmHg. VF every year	C. Target 21, 18, 15 mmHg. VF every year
Life-years in the model	15.2 ± 8.0			
IOP during follow-up (mmHg)	29.3 ± 3.0	19.1 ± 2.1	18.5 ± 2.0	17.2 ± 2.1
Incidence of LT/TE/reTE/Implant (%)	0/0/0/0	20/11/1/1	25/17/3/2	45/33/7/4
Lowest MD (dB)	−24.5 ± 10.3	−14.1 ± 7.0	−13.4 ± 6.6	−12.0 ± 5.6
Incidence of blindness (%)	52.2	8.9	5.3	1.1
VFQ adjusted life-years (discounted)	8.5 ± 4.0	10.1 ± 4.8	10.2 ± 4.8	10.4 ± 4.9
QALY's (discounted)	9.1 ± 4.2	10.1 ± 4.8	10.2 ± 4.9	10.3 ± 4.9
Total costs (discounted)	€ 41,618 ± € 31,007	€ 25,648 ± € 24,366	€ 25,465 ± € 24,097	€ 23,466 ± € 22,742

IOP, intraocular pressure; LT, laser trabeculoplasty; MD, mean deviation; QALY, quality-adjusted life-year; reTE, second trabeculectomy; TE, trabeculectomy; VF, visual field measurement; VFQ, visual functioning questionnaire.

directly. Any extrapolation of the data occurs explicitly in the defined relationships that are part of the model. Therefore, DES models generally take more time to build but hardly any time to adjust. Even structural alterations can be made in an instant. Finally, the lack of experience with DES among health economists is only a disadvantage if it would prevent the application of the method where it would be appropriate. The transparent dissemination of discrete event models in the scientific literature could positively contribute to the experience with this methodology. Achieving insight in the model's structure and trust in its outcomes may require some extra effort due to the high level of flexibility, and therefore, variability in DES model structures. Decision trees and Markov models can be visualized with schematic drawings that are similar across all applications, i.e., the branching tree structures and the bubble diagrams, respectively, but such a standard format to communicate model structure is not (yet) available for DES models. This article aimed to transparently report on the construction and validation of a DES model for the complex strategies involved in glaucoma treatment. In order to do so, we have justified the choice for a DES model structure, explained how current knowledge regarding disease progression in glaucoma was synthesized within the structure of a DES model, and presented the results of the model validation. The resulting model was flexible and had good face validity. Also the internal and external consistencies were satisfying. We hope to have demonstrated the added value of DES in modeling complex treatment strategies, and to have made a contribution to the discussion on how to transparently report about model structure, assumptions, parameter estimates, and validation steps.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. This appendix contains graphical presentations of several aspects of the model design, and presents the sources and methods of the derivations of the most important structural relationships, and the sources, best estimates and distributions of the main parameter estimates in the base-case model.

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