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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

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| 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." |