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A Comparison Of Clinical Trial And Model-Based Cost Estimates In Glaucoma – The Case Of Repeat Laser Trabeculoplasty In Ontario

Omar Akhtar
The University of Western Ontario

Supervisor
Dr. William Hodge
The University of Western Ontario

Graduate Program in Epidemiology and Biostatistics
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

A COMPARISON OF CLINICAL TRIAL AND MODEL-BASED COST ESTIMATES IN GLAUCOMA – THE CASE OF REPEAT LASER TRABECULOPLASTY IN ONTARIO

(Monograph)

by

Ahmad Omar Akhtar

Graduate Program in Epidemiology & Biostatistics

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THE UNIVERSITY OF WESTERN ONTARIO
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ABSTRACT

Background and objective: For cost-effectiveness analyses (CEA) of glaucoma interventions to be of use they require valid and accurate cost and effectiveness data. Costs remain understudied relative to effectiveness. The impact of cost estimation methods on resultant estimates is unknown in glaucoma. Direct measurement of costs is labour-intensive and expensive. Decision-analytic modelling of costs using literature sources, expert opinion, institutional experience and assumptions provides a quicker, less laborious alternative to empirical costing. A lack of long-term effectiveness data in chronic diseases like glaucoma means that modelling is widespread and inevitable, both for CEAs and budget impact projections. The same problem precludes validation of models and there are concerns about their validity and possible arbitrariness given the discretionary nature of their construction. In this thesis we investigate whether costs from a decision-analytic model of repeat laser trabeculoplasty among glaucoma patients provide a valid alternative to direct measurement of costs alongside an effectiveness trial. Secondary aims were to compare the Ministry and societal perspective and to identify main cost drivers for repeat laser trabeculoplasty.

Methods: Trial-based costing was conducted as part of an effectiveness trial comparing argon- and selective-laser trabeculoplasty (ALT and SLT) after previous SLT among glaucoma patients at an ophthalmologic clinic in Ontario. For model-based costing a decision tree was formulated and populated with parameter estimates based on previous literature supplemented with assumptions. Mean trial and model cost were compared for ALT and SLT.

Results: Model and trial cost estimates differed minimally for the Ministry perspective (4% and 8% for SLT and ALT respectively) – this in spite of large differences in modelled and observed parameter values. Labour accounted for almost 90% of total cost. Model and trial costs were also similar for the societal perspective (differences of 8% and 1% for ALT and SLT), although there was more sensitivity to assumptions about patient time loss. Indirect and patient costs were at least as large as direct medical costs. Our results indicate that modelled costs are an acceptable substitute for directly measured costs for some clinical scenarios – glaucoma interventions in Ontario possibly being such a case.

KEYWORDS

Costs, cost analysis, economic evaluation, microcosting, trabeculoplasty, glaucoma, ophthalmology, cost-effectiveness analysis, perspective, indirect costs, decision models, clinical trials.

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While curiosity (ideally) provides sufficient incentive for scientific work, one has to get out of bed in the morning. I doubt I'd bother if I didn't have my family (Mum, Dad, Aemal) to look forward to and to fall back on – it's to them that I dedicate this humble technical offering. Aemal in particular was the one who, entirely accidentally, alerted me to this line of endeavour. It's a tribute to his perspicacity that this stab in the dark became a bona fide vocation.

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LIST OF ABBREVIATIONS AND SYMBOLS

ALT: Argon Laser Trabeculoplasty

CEA: Cost-effectiveness analysis (and cost-utility analysis)

DRG: Diagnosis-related group

HMMS: Healthcare Materials Management Services (at St. Joseph's Healthcare)

IOP: Intraocular Pressure

OAG: Open-Angle Glaucoma

ODB: Ontario Drug Benefit

OHIP: Ontario Health Insurance Plan

PGAs: Prostaglandin analogues

RCT: Randomized Controlled Trial

SJHC: St. Joseph's Health Care, London, ON

SLT: Selective Laser Trabeculoplasty

Chapter 1 - Introduction

The research presented in this thesis examines whether the choice of method used to estimate costs for cost-effectiveness analyses make a difference in glaucoma. Specifically, I assess whether cost estimates from decision-analytic modelling exercises serve as valid proxies for more labour-intensive empirical cost measurement in the case of repeat laser therapy among glaucoma patients. This introduction aims to provide context to subsequent chapters, addressing the basics of glaucoma and costing in economic evaluations.

Glaucoma is a chronic, blinding disease and the leading cause of irreversible blindness globally. Along with macular degeneration and diabetic retinopathy, it is the most important ocular public health problem in Canada and exerts an economic burden of close to 500 million dollars annually (Hodge et al. 2004). The number of glaucoma patients is set to increase in the coming decades due to the aging of the population, with commensurate increase in human suffering and demand on healthcare systems that are already under strain (van Gestel et al. 2010).

In glaucoma, ophthalmology and healthcare more generally, cost-effectiveness has become a prominent consideration in the adoption of health interventions. Healthcare is expensive, representing a large and increasing share of private and public expenditure in Canada and globally – a trend that shows no signs of abating (CIHI 2013). Issues of sustainability and cost containment have come to the fore and clinical effectiveness alone is no longer sufficient to recommend the adoption of an intervention – it must also represent value for money (Health Council of Canada 2009). As noted by Donaldson (2011), "every clinical decision is a purchasing decision", a sentiment that points to an approach quite different from the largely *ad hoc* development of healthcare previously (Crane et al. 2013). Economic evaluations, in particular cost-effectiveness analyses and cost-utility analyses (both subsumed under the former term, henceforth CEAs), provide a framework wherein clinical and cost data are jointly examined and questions of value for money may be answered.

Economic evaluation is "the comparative analysis of alternative courses of action in terms of both their costs and consequences" (Drummond et al. 2005). An economic

evaluation most often compares interventions X and Y, where Y produces better clinical effect (whether decreases in morbidity or mortality) but at higher cost. The final measure of interest is the *incremental cost-effectiveness ratio* or ICER, calculated as the difference in effectiveness divided by the difference in cost. This represents the cost per additional unit of health effect. With this information, and in conjunction with local context and decision rules, decision-makers may use the ICER to determine whether or not a given technology represents good value for money. CEAs are now required in a number of countries (including Canada) for manufacturers who wish their products to be listed on local formularies. At their best, CEAs provide valuable information for decision makers acting to optimize a constrained set of resources within a healthcare system – the unwillingness of American decision-makers to consider cost-effectiveness has been considered by some analysts to be partially responsible for the dire state of US healthcare spending (Neumann 2004). Unsurprisingly, to be useful to decision makers, CEAs require both cost and effectiveness data. Poor data threatens the validity of CEAs and may render analyses irrelevant at best and misleading at worst. While effectiveness data has been well studied, the soundness of current costing methods in ophthalmology has not been rigorously assessed.

Cost data has been understudied relative to effectiveness data (Lipscomb et al. 2009). The prominent study of effectiveness is unsurprising – without demonstration of safety and effectiveness, costing is a moot point. Clinical epidemiology and evidence-based medicine have placed the study of effectiveness on firm footing with such tools as the hierarchy of evidence – physicians have some gauge of whether or not estimates of the effectiveness of a given drug or technology are trustworthy (Guyatt et al. 2008). The practice of costing, on the other hand, leaves much to be desired. Costs by their very nature present difficulties not present with effectiveness measures. They are sensitive to a host of contextual factors, including characteristics of the parent health system, local patterns of healthcare delivery, absolute and relative local prices and the vagaries of cost accounting systems (Koopmanschap et al. 2001). Different payers have different perspectives on which costs are relevant, thus value judgements are necessarily involved (Philips et al. 2006). The cost of the same hospital procedure may differ by an order of magnitude within a given country. Such variations in effectiveness are unthinkable under

almost all circumstances (Adam 2006). In addition to the difficulties inherent in cost data, there is often little concrete explicit in guidelines for pharmacoeconomic evaluation, including scant guidance on which methods to use for cost estimation and the degree to which different methods produce different estimates as well as their implications for the results of CEAs and budget impact projections.

There is variability and lack of concrete guidance in the costing sections of pharmacoeconomic guidelines (Jacobs et al. 2005). There is commensurately poor quality of costing in applied studies (Graves et al. 2002). Poor costing limits the validity and uptake of CEAs, their use at a level commensurate with their promise, their usefulness as scientific information and may lead to inappropriate adoption and reimbursement decisions for technologies (Adam et al. 2003, Fukuda and Imanaka 2009). In conditions such as glaucoma, where there is chronicity and potential downstream effects in terms of increased blindness, falls and depression, inappropriate adoption decisions could prove to be very costly (Schmier et al. 2007). Among the unresolved issues in assessing costs is whether choice of method to estimate costs makes an appreciable difference in cost estimates. It is this issue we wish to address.

Bottom-up microcosting is considered the gold standard in costing (Gold et al. 1996). As with gold standards in effectiveness research, it is also an involved, laborious and often difficult process for which investigators wish to find simpler methods and shortcuts that are still valid (Dakin et al. 2011, Seidl et al. 2012)**.** In bottom-up microcosting, the range of resources consumed in providing an intervention is identified (e.g. drugs, labour, equipment and others), the quantities used are measured and valued in monetary terms for each individual patient. Capturing resource use for individual patients is labour-intensive, especially where the infrastructure is lacking – indeed, Mogyorosy and Smith (2004) note that "there is a trade-off between cost information accuracy and the cost of attaining cost information", it may simply be prohibitively labour intensive and costly to capture costs in such detail. The major tension in costing methods is between accuracy and feasibility. Two approaches exist to try to mitigate the difficulties of capturing individual level patient data. Firstly, the use of charges, prices and expenditures in place of actual costs – that is, the use of data designed for reimbursement or accountancy purposes as opposed

to capturing resource use. This is the contrast between microcosting and gross costing approaches and there is some evidence that the results of CEAs are sensitive to the choice of method in this respect (Clement et al. 2009).

A second method of mitigating the difficulties associated with empirical microcosting is the use of decision-analytic models. In decision-analytic modelling a conceptual framework representing the underlying condition, its epidemiology and the impact of the relevant healthcare interventions on outcomes and resource use is structured in a mathematical framework such as a decision tree or Markov model (Drummond et al. 2005). Development and population of such models may be a matter of hours or days as opposed to the months or years needed to capture bottom-up microcosts alongside a trial. Modelling in chronic diseases such as glaucoma necessarily makes use of expert opinion, institutional experience and assumptions in addition to values from extant literature, costs in particular are often treated in a 'grab and go' fashion (Lipscomb et al. 2009). For didactic purposes we may crudely dichotomize between rapid, easy, model-based approaches that do not require intensive data and make liberal use of assumptions, and the accurate but difficult empirical bottom-up microcosting. It is this distinction which we investigate in this thesis, henceforth we refer to these manners of costing as model-based and trial-based (or empirical) costing.

Models, at their vaunted best, are the preferred method of conducting CEAs due to their high generalizability and ability to synthesize across the evidence landscape (Sculpher et al. 2006). However there is often little room for validation of models – indeed, if data was available to validate the model against then models may not have been necessary initially. The discretionary nature of populating such models has led to charges of arbitrariness (McCabe and Dixon 2000, Sheldon 1996) and the often heterogeneous pastiche of sources means that the modelled population may not be reflective of the costs accruing to the decision-maker's population of interest – we may be modelling a chimera cohort. Modelled costs are used not only for CEAs but for budget impact analyses and projections of absolute costs, such as estimating cost savings associated with alternative courses of glaucoma treatment (Cantor et al. 2008) or thrombolysis in stroke (Mar et al. 2008). In addition to the ease of model-based costing, modelling is an unavoidable fact of

life in glaucoma for several reasons, foremost being the chronicity of the disease (and commensurate lack of long-term effectiveness data for most interventions), and the sheer number of possible treatment comparisons that preclude clinical trials for all but a minute number of treatments. As such, it behooves us to examine whether model-based costs are truly reflective of costs ascertained by more intensive empirical methods. Effectiveness trials present a perfect opportunity for validation of model-based costs as they allow for detailed data-collection while being more reflective of normal practice than efficacy trials, thus not warping cost profiles too egregiously.

Glaucoma suffers from having uncertainty in its treatment algorithm. The three main classes of treatment are medications, laser surgery and incisional surgery – all three work equally well and there is no evidence pointing to an unambiguous, preferred positioning of treatments so as to maximize patient benefit or value for money (Boland et al. 2013). The existence of alternate treatment modalities such as stents, non-incisional surgery and incipient neuroprotective treatments expands the putative therapeutic landscape. Furthermore, the course of the disease is lifelong and progressive, given the lack of cure. This combination of chronicity and multiple therapeutic options leads to a combinatorial explosion of possible treatment options to assess – considering possible combinations of medication types, doses and schedules alone resulted in at least 56,000 possible options (Realini and Fechtner 2002). Incorrect adoption decisions may result in the incurring of downstream costs and negative health consequences, hence the US Preventive Task Force's exhortation to comparative effectiveness research and economic evaluations on glaucoma treatment (Boland et al. 2013).

The sheer number of possible comparisons of glaucoma treatments precludes performing a clinical trial on each comparison. Furthermore, the short horizon of most trials squares poorly with the chronicity of glaucoma. As such, modelling is inevitable, and the lack of long-term effectiveness means that 'grab and go' type models will be used. Indeed, models are used to inform policy before clinical trials are finished (Freedberg et al. 1996). It behooves us to investigate whether the costs of such models are representative of the costs incurred in actual practice, such as with an effectiveness trial. If so, we may confident that for a certain class of clinical scenarios, the costs from literature-based

models concur with cost estimates from actual, empirical practice. In this thesis, we take a representative problem at one unresolved node of the glaucoma treatment algorithm – repeat laser trabeculoplasty. Repeat laser trabeculoplasty represents a clinical scenario in glaucoma whose answer has important implications for glaucoma treatment and technology adoption, and for which little data exists, necessitating modelling. An ongoing clinical trial comparing two modalities of laser trabeculoplasty after previous laser treatment provides an opportunity to examine model vs. trial-based costing in glaucoma.

Laser treatment is an attractive therapeutic option in glaucoma as it manages to avoid compliance and side effect issues of medication and the complications of incisional surgery. One modality in particular, selective laser trabeculoplasty (SLT) offers the theoretical advantage of repeatability – if confirmed, this would have large implications for the treatment of glaucoma given that it would relegate medication and surgery (currently both mainstays) to adjunct, supportive roles. The question of SLT's repeatability has existed since SLT's conception (Latina et al. 1998) but has never been assessed save for small observational studies (Hong et al. 2009, Riansuwan et al. 2007). The Repeat Laser Study is an ongoing clinical trial and compares SLT and another laser modality, Argon Laser Trabeculoplasty (ALT) among glaucoma patients who have previously had SLT. This is the first clinical trial to do so and will form the trial-costing component of this research. As we will see in chapter 2, extant CEAs of laser trabeculoplasty make use of model-based costing. The results of such economic evaluations are used as a point of persuasion directed at practitioners to adopt SLT (Taylor 2008, Craven 2014). As such, it is worth examining whether or not costs from such models concur with actual costs as ascertained by empirical methods in normal practice.

Our aim is to examine whether model-based cost estimates of repeat laser trabeculoplasty present a credible proxy for trial-based microcosting. If so, similar clinical scenarios may be approximated by the sort of models extant in glaucoma CEAs and we may forego intensive microcosting exercises – if not, the use of such models may be poorly representative of actual resource use. The use of detailed microcosting will provide the first comprehensive assessment of the cost profile of laser surgery in Ontario, providing

information to future analysts. A secondary aim is assessment of the extent to which patient-incurred costs (viz. travel and lost earnings) contribute to total costs.

1.1 – Outline of thesis

Chapter 2 comprises the clinical and economic background to the thesis. After a discussion of glaucoma and an examination of the clinical and cost-effectiveness literature on laser trabeculoplasty, a discussion of modelling and trial-based costing methods is presented. A more general examination of issues in costing acts to extend and supplement the discussion of costs in glaucoma. We also introduce our secondary aim of comparing the Ministry and societal perspective in repeat laser trabeculoplasty.

Chapter 3 presents the methods used. A detailed discussion of the clinical trial serving as a vehicle for trial-based costing is presented, as are the means by which unit costs and quantity use data were determined. A decision-analytic model, derived from a mixture of literature sources, assumptions and institutional experience is presented. We examine its structure, assumptions and planned sensitivity analyses. We then list our primary and secondary analyses. In chapter 4 results are presented as is a discussion of results, limitations and future directions in chapter 5.

Chapter 2 – Background and Literature Review

2.1 – Glaucoma – repeat laser trabeculoplasty and economic considerations

2.1.1 – Pathophysiology, epidemiology and economic burden

Glaucoma refers to a family of blinding diseases in which damage to the optic nerve results in progressive, irreversible loss of vision. Primary open-angle glaucoma (OAG) is the most common subtype of glaucoma, accounting for over 90% of glaucoma cases in Canada (LeBlanc 2007) and is the leading cause of irreversible blindness globally (Quigley and Broman, 2006). Along with age-related macular degeneration and diabetic retinopathy, OAG is the most important ocular public health problem in Canada, exerting an annual economic burden of nearly half a billion dollars (Hodge et al. 2004). OAG affects 1-2% of individuals over age 50, with an estimated 400,000 Canadians affected and over 10,000 blind. Aside from visual impairment, there is increased risk of falls, depression and an overall decrease in quality of life (Schmier et al. 2007). Blindness due to OAG is expected to increase globally in the coming decades due to an aging population, promising greater strain on health systems (Rouland et al. 2005). At present, there is no cure and the disease is lifelong.

The most important risk factor for development and progression of OAG is elevated intraocular pressure (IOP) due to excessive production of aqueous humour or insufficient filtration (Friedman et al. 2004, Le et al. 2003). Excess aqueous humour subsequently induces mechanical damage in the retinal ganglion cells (RGCs) of the optic nerve and leads to an array of structural, biochemical and apoptotic changes in RGCs, leading to neuronal death and subsequent visual field loss (Boland et al. 2013, Vass et al. 2007). If untreated, it progresses inexorably to total blindness.

Barring some attempts at developing neuroprotective interventions (Tsai 2013, Sena and Lindley 2013), the overwhelming majority of glaucoma treatments in use focus on reduction of IOP which acts to prevent development and progression of OAG related optic nerve damage. This may be accomplished by increasing outflow of aqueous through the trabecular meshwork or by decreasing production of aqueous. In this way, visual impairment and blindness may be delayed or prevented. IOP is currently the most important modifiable risk factor for glaucoma (Friedman et al. 2004, Le et al. 2003) and

numerous high-quality RCTs have demonstrated its association with patient-important final outcomes such as visual impairment and blindness (Boland et al. 2013).

2.1.2 – Types of treatment, an uncertain treatment algorithm

Current therapies fall into three categories; medication, laser therapy and surgery. In the most common treatment algorithm, pressure lowering is initially accomplished using medical or laser therapy, and if these fail to control IOP, surgery is indicated (Schwartz and Budenz 2004). However, there is considerable variation in practice with initial use of surgery or laser being demonstrated to be at least as effective as initial medication and potentially more beneficial, including having a more attractive economic profile (Burr et al. 2012, Katz et al. 2012)

A recent report by the US Preventive Services Task Force noted that there is no standardized, optimal, evidence-based treatment algorithm for glaucoma and that determining the best sequence of treatments in terms of clinical effectiveness and optimal resource use remains an active area of investigation (Boland et al. 2013). All available treatment options (i.e. medication, laser trabeculoplasty and surgery) for glaucoma seem to be equally effective and there is insufficient evidence to point to a preferred sequence of treatment components, or how to combine treatments to provide optimal patient outcomes and satisfaction in a way that represents the best use of resources. This being said most practitioners use incisional surgery last in the three part algorithm. Aside from the ambiguity about positioning the components of glaucoma care, the advent of novel therapeutic modalities such as stents (Minckler et al. 2006), non-incisional surgery (Rulli et al. 2013) and neuroprotective techniques (Tsai 2013) expand the landscape of possible therapeutic options and combinations. Given that healthcare often proceeds in an ad-hoc manner (Crane et al. 2013), it's likely that the current "drugs first" algorithm is based on historical inertia, reluctance to begin with initial surgery and individual physician preference more than any evidence indicating its superiority. As noted by Rouland et al. (2005), experts disagree on optimal glaucoma treatment practices and actual practice varies from recommended practice, especially regarding the initial use of medication vs. laser or preferred medication regimen.

In addition to issues of ordering the elements of the treatment algorithms, there are considerations of the optimal parameters of each treatment component. Even considering pharmacotherapy alone, the optimal combination of drugs has yet to be established (Tabet et al. 2008). Varying dosages and combinations of drugs alone leads to at least 56,000 possible combinations (Realini and Fechtner 2002) and there is the further issue of whether drug preservatives are beneficial or cause ocular surface problems (Anwar et al. 2013).

The use of laser also presents a host of minor parameter issues, such as optimal amount of the eye angle to treat (McAlinden 2014) and whether or not different degrees of eye pigmentation represent differential susceptibility to complications (Harasymowycz et al. 2004). Given the chronicity of glaucoma, poor decisions early on may lead to problematic downstream effects – this same chronicity means that there is also a lack of long-term effectiveness data, especially on newer therapeutic modalities. Boland et al. (2013) note that much comparative-effectiveness and cost-effectiveness research is needed to provide optimal quality of care which represents the best use of resources.

2.1.3 – Medication, filtration surgery and their associated problems

Medications are the most common first-line treatment in OAG (Vass et al. 2007). Several classes of medications are used, most commonly prostaglandin analogues and beta-blockers. Additional options are carbonic anhydrase inhibitors, adrenergic agonists and cholinergic miotics. In general these medications are used topically as eye drops. Patients initially use a single drug to control IOP with prostaglandin analogues generally being the first choice. Latanoprost is the most commonly prescribed of the prostaglandins given its favourable side-effect profile, demonstrated effectiveness, ease of use and commensurately higher adherence (McKee et al. 2005, Denis et al. 2010). With disease progression there is increasing use of combination pharmacotherapy to control IOP (Schwartz and Budenz 2004).

While pharmacotherapy is effective at controlling IOP and thus preventing progression of visual impairment there are several problems associated with their use. Most notably, there are issues of compliance and side effects. Compliance is poor even with monotherapy regimens (Rotchford and Murphy 1998) and there is a voluminous literature

on how to improve adherence to medication (Robin and Grover 2011, Tsai 2006, Sleath et al. 2011, Schwartz and Quigley 2008). The situation is compounded in combination therapy regimens, where different drugs may need to be taken at different points through the day (e.g. a Brimonidine and Latanoprost combination requires the former to be taken thrice daily and the latter once at night). Lack of compliance is associated with worse outcomes, including an increased risk of progression to surgery and blindness (Sleath et al. 2011). The situation is pervasive enough that in commenting on the results of a cost-effectiveness analysis comparing laser therapy and medication, Craven (2014) felt that the assumption of 75% medication adherence was optimistic.

Furthermore, there are potentially serious side effects of drugs. When beta-blockers such as Timolol are administered as eye drops, the drug enters the systemic circulation through Schlemm's canal and may induce cardiovascular and respiratory sequelae. Carbonic anhydrase inhibitors are poorly tolerated in elderly populations and may cause psychiatric side effects (Burr et al. 2012). Latanoprost may induce changes in iris and eyelash colour. Side effects, in addition to complexity of administration, contribute to poor compliance. Furthermore, there are diminishing returns with the addition of further drugs, with the addition of a third or fourth medication unlikely to bring about meaningful reductions in IOP (Neelakantan et al. 2004). Finally, given the lifelong course of glaucoma, regular use of medications can become very costly over time (Stein et al. 2012). As such, the fewer medications that patients are obliged to take, the better.

Trabeculectomy is an incisional procedure in which a section of the trabecular meshwork is removed, providing an uninterrupted conduit for aqueous humour to flow out of the eye. It remains the most common glaucoma surgery. It is most commonly indicated in cases where IOP is medically uncontrolled, although it may be used as first-line treatment (Burr et al. 2012).

As with any surgery, trabeculectomy carries a risk of serious side effects including hemorrhage, infection and hypotony. All of these complications may cause severe visual impairment or blindness (Liebmann and Ritch 1996). Troublingly, the long-term effectiveness of trabeculectomy does not match its high rate of initial success, and some patients require further therapy or further surgeries which carry a higher failure rate (as in

the Advanced Glaucoma Intervention Study (Ederer et al. 2004) where the 10-year treatment failure rate was 20-30%). As with medication, trabeculectomy presents an effective intervention but one whose use we may wisely wish to defer if possible.

2.1.4 – Laser trabeculoplasty

The use of lasers is most often situated between medication and surgery in the treatment of glaucoma. They are an attractive option as they manage to avoid issues of compliance, side effects and surgical complications. The general principle underlying laser trabeculoplasty is to focus a laser beam on the trabecular meshwork and thereby induce structural or functional changes which permit increased outflow of aqueous humour.

Lasers have consistently been shown to be as effective as medication and incisional surgery in controlling IOP (Boland et al. 2013, Rolim de Moura et al. 2007, Shi and Jia 2012). There is evidence that eyes treated with lasers have a lower rate of progression to blindness and surgery than those treated only with medication (Rolim de Moura et al. 2007, Katz et al. 2012). Furthermore, lasers act as powerful adjuncts to medication and incisional surgery, lowering IOP in cases of the failure of medication (Damji et al. 1999, 2006) and failed surgery (Francis et al. 2011). Lasers are increasingly being used as a first-line treatment. Insofar as they act to increase the outflow of aqueous humour (much like several extant classes of medication), practitioners are exhorted to consider using lasers in place of medications as a ‘first eye drop’ (Taylor 2009).

While lasers present theoretical benefits and have proven effectiveness, there are several open questions around their use. Most notably, it is not known whether one promising modality (selective laser trabeculoplasty) can be used repeatedly, as glaucoma’s lifetime course requires. At present, lasers do not constitute the vaunted silver bullet that the glaucoma community would have hoped for. We will explore these questions further below and their implications for the treatment algorithm.

There are two types of laser trabeculoplasty – argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT). The two lasers have been shown to be equivalent in their effectiveness (Samples et al. 2011, Pignatto et al. 2009), but they differ in the type of laser used and the mechanism by which they exert their effects.

In ALT, high energy laser pulses are focused on the trabecular meshwork for multiple applications of 0.1 seconds each (Pignatto et al. 2009). The high energy and long duration of the pulses produces histological damage of the trabecular meshwork (Noecker et al. 1998). It is thought that damaged tissue contracts and provides increased space for aqueous outflow. This histological damage has ramifications for repeatability of ALT. Treatment effectiveness generally decreases over time and repeat ALT is not possible due to damage of the targeted tissues (Feldman et al. 1991, Richter et al. 1987, Starita et al. 1984, Weber et al. 1989). The finite repeatability of ALT is not commensurate with the progressive, lifetime course of glaucoma. ALT was thus demonstrated to be less of a non-medicinal/non-surgical panacea than a technique for buying time.

The problems with ALT led to the search for a laser modality that would be equally effective but using shorter pulses with lower energy. Latina and his collaborators developed an Nd:YAG laser that showed promise in *in vitro* preparations of trabecular cells (Latina and Park 1995). SLT acts as a 'cold laser' due to its use of lower energy pulses and shorter bursts. This was found to produce equally effective IOP reduction, but without the major histological damage of ALT. The precise mechanisms by which SLT reduces IOP are not fully understood, but it is thought to induce a suite of biological mechanisms that act to augment trabecular outflow, as opposed to the putatively mechanical effects of ALT (Kagan et al. 2013).

A consequence of SLT's non-destructive mechanism of action is that it is, in theory, repeatable. If so, its utility is considerable. Compliance is, definitionally, 100%. Controlling IOP with SLT means the use of medication and trabeculectomy would potentially be minimized, as would their associated problems. Determining the repeatability of SLT and its interaction with other treatment elements is of paramount importance for determining the optimal treatment of glaucoma. If SLT is indefinitely repeatable, current practices would become questionable and drugs and incisional surgery would be relegated to a supportive role instead of being mainstays. Economic evaluations that are used to promote the adoption of SLT are sometimes predicated on the assumption of its repeatability. ALT's gradual widespread replacement with SLT is likely predicated on the same point.

SLT's theoretical repeatability has been known since its introduction, and yet it has not been verified – this is to say nothing of the long-term effectiveness data that would be needed to determine the true extent of SLT's repeatability over a more meaningful timespan nor of its downstream interactions with other treatment modalities. A review by Samples et al. (2011) found over 100 studies assessing the effectiveness of first-application laser trabeculoplasty. The only studies assessing the repeatability of SLT are three small studies by Hong et al. (2009), Riansuwan et al. (2007) and Khouri et al. (2014). Notably, there are no bona fide, prospective, sufficiently powered RCTs assessing whether SLT produces meaningful IOP reductions on second application. The importance of this question, the amount of time in which an answer could have been provided and the puzzling lack of empirical attention has led at least one commentator to consider SLT's repeatability to be more industry dogma than clinical verity (Girkin 2007).

The need for a definitive answer is a constant refrain in systematic reviews of laser trabeculoplasty (Wang et al. 2013, Shi and Jia 2012, Samples et al. 2011). Definitively assessing SLT's repeatability is of paramount importance, is one of the parameters needed for a good treatment algorithm, and is one of reasons the clinical trial informing this thesis is being undertaken.

2.1.5 – Laser trabeculoplasty effectiveness findings

Laser trabeculoplasty has consistently been shown to be equally effective to medication in reduction of IOP, irrespective of type of laser (Samples et al. 2011, Rolim de Moura et al. 2007, Shi and Jia 2012, Damji et al. 1999 and 2006, Juzych et al. 2004). In addition to their benefits in terms of avoiding issues of compliance and side effects, lasers have been shown to reduce number of medications required as adjunctive therapy and there is evidence of lower progression to blindness or surgery among patients who undergo laser therapy as opposed to those who solely undergo pharmacotherapy (Katz et al. 2012). When used as initial therapy, SLT in particular offers the benefit of requiring less treatment steps to maintain optimal IOP than eyes treated only with medication (Katz et al. 2012). Comparisons of ALT and SLT whether as initial therapy or subsequent to failure of medication have invariably produced equivalent results in lowering IOP (Damji

et al. 1999 and 2006, Samples et al. 2011). The general tenor of the literature is that ALT and SLT are equivalent, and both are equivalent to medication.

Long-term effectiveness-data on ALT indicates that it is not a repeatable procedure, failing to meaningfully reduce IOP on repeated applications – there is little evidence on SLT's repeatability. ALT's finite repeatability is presumably due to the damage it inflicts on the trabecular meshwork. SLT is effective in lowering IOP in previously failed ALT (Latina et al. 1998, Birt 2007) – the converse has not been demonstrated. As described above, the repeatability of SLT is a question of interest that has never been assessed by a sufficiently powered, prospective clinical trial. Two small retrospective studies have produced preliminary evidence for its possible repeatability (Riansuwan et al. 2007, Hong et al. 2009). Riansuwan et al. (2007) conducted a chart review of patients who had undergone up to four rounds of SLT and found that decreases still occurred, although of diminishing magnitude. In Hong et al.'s 2009 study SLT was performed in 44 eyes that had previously undergone SLT. There was IOP reduction, although to a lesser magnitude than seen during the first SLT treatment. A third study by Khouri et al. (2014) conducted a retrospective chart review on 51 eyes and demonstrated that a second application of SLT may successfully reduce IOP in patients for whom initial SLT failed to provoke a satisfactory reduction – this raises the possibility that SLT is both repeatable and a viable option for initial non-responders. These studies are preliminary evidence that SLT is repeatable, albeit finitely so and with diminishing usefulness with repeated applications, which also calls its utility into question. As noted by Rolim de Moura (2007) – there is no indication that SLT is actually a superior laser modality – it's merely that ALT's non-repeatability has been demonstrated while nothing is known of SLT's repeatability or non-repeatability.

Trabeculoplasty results compared to medication

There is an extensive literature on the effectiveness of medications, whether comparing monotherapies or combination therapies. The findings of such studies are beyond the scope of this review – the interested reader may consult Vass et al.'s review for the Cochrane Collaboration (2007).

A Cochrane review of laser therapy versus medication in OAG (Rolim de Moura et al. 2007) notes that laser trabeculoplasty (irrespective of laser type) results in IOP lowering equivalent to medication (whether prostaglandin analogues, beta-blockers or combination therapies). Furthermore, the 5-year risk of glaucoma progression is higher in eyes treated with prostaglandin analogues than with lasers, as is uncontrolled IOP at 2 years.

Early work assessing the effectiveness of ALT was undertaken in the Glaucoma Laser Trial and the GLT Follow-Up Study (Glaucoma Laser Trial 1995). Equivalent reductions in IOP were found between eyes treated with ALT and eyes treated solely with medication. Furthermore, eyes treated with ALT had better visual field and optic disc status (Glaucoma Laser Trial 1995). However, long-term effectiveness data indicated that retreatment was not possible with ALT, which limits its usefulness.

The literature on SLT versus medication demonstrates comparable results, with SLT producing equivalent reductions in IOP to medication. To take two highly cited examples – Melamed et al. (2003) found equivalent reductions at 18 months in the SLT group as compared to the Latanoprost group. McIlraith et al. (2006) found an equivalent reduction to Latanoprost with no difference in success rates at 1 year (defined as 20% reduction in IOP from baseline) – this was true whether SLT was used first, meds alone first or meds with adjunctive SLT. Katz et al. (2012) compared SLT to prostaglandins as first-line treatment and found similar IOP reductions after 12 months of follow-up and less treatment steps needed to maintain target IOP in the SLT group. These studies not only demonstrate SLT's equivalence to medications, but its plausible use as first-line treatment with the attendant theoretical benefits, calling into question the widespread 'meds first' practice.

ALT vs. SLT

Damji et al. (1999, 2006) conducted the first trials comparing ALT and SLT. Equivalent reduction in IOP at 1-year was demonstrated and resulted in FDA approval for the use of SLT in practice. Samples et al. (2011) concluded that there is no evidence for superiority of any particular form of laser trabeculoplasty after reviewing 145 studies. The equivalent effectiveness of ALT and SLT is consistent and uncontroversial.

SLT has been shown to reduce IOP in patients with previously failed ALT (Birt 2007). The viability of ALT after previous SLT has not been investigated. This is a question of clinical import, for reasons worth expanding upon.

While ALT has increasingly been replaced by SLT, it's not a foregone conclusion that SLT is repeatable, or superior (Rolim de Moura et al. 2007). It has not been demonstrated that SLT is repeatable, it has merely been demonstrated that ALT is not. The fact that SLT can be repeated after ALT means that ALT can be used as first laser treatment. If ALT is not usable after SLT, ALT is necessarily relegated to the beginning of treatment, essentially to buy time. This is a useful piece of disambiguation of ALT and SLT's placement in the treatment sequence.

Furthermore, if the two are absolutely equivalent, then costs become a salient concern. Considering that the two laser modalities use two different lasers (both of which are expensive), each of which requires a room, an examination chair and maintenance, disinvestment is a possibility if one modality is demonstrated to offer no clinical benefits and to cost more (Haines et al. 2014).

2.1.6 – SLT repeatability and the current clinical trial

The current thesis research comprises a costing study undertaken as an independent sub-study alongside an ongoing clinical trial investigating repeat laser trabeculoplasty (ALT or SLT) after previous SLT in glaucoma patients. The Repeat Laser Study is a multi-centre effectiveness, non-inferiority trial. This trial is the first sufficiently powered, bona fide prospective RCT to test SLT's repeatability. Aside from providing an answer to the question of whether or not SLT is repeatable, it also answers the above outlined question of whether or not ALT is usable after SLT with all of its ramifications. The ultimate aim of this thesis is to assess whether the cost estimates from the clinical trial for each laser modality match cost estimates for a decision-analytic model of the same situation. The reasons for our interest in this question will be expanded upon through the rest of chapter two.

2.1.7 – Economics of laser trabeculoplasty

A brief overview of economic evaluation

The current fiscal climate demands accountability for healthcare dollars spent (Neumann 2009). Rising healthcare costs mean that decision-makers want to provide the same quality of care or better while minimizing costs – thus judgements of economic efficiency and value for money are necessary (Health Council of Canada 2009). Economic evaluation provides a framework where clinical and cost data are jointly examined to assess value for money. Drummond et al. (2005) define economic evaluations as examination of alternative courses of action in terms of their costs and consequences. Such analyses are required in Canada (CADTH 2006) and in several other countries for manufacturers wishing to have their products placed on formularies. They are also used by decision-makers to optimize the health benefits obtained from a limited budget.

Cost-effectiveness analyses and cost-utility analyses (both subsumed under the former term, henceforth CEAs) are the most common forms of economic evaluation. A CEA most often compares interventions X and Y, where Y produces better clinical effect (whether decreases in morbidity or mortality) but at higher cost. The final measure of interest is the *incremental cost-effectiveness ratio* or ICER, calculated as the difference in effectiveness divided by the difference in cost. This represents the cost per additional unit of health effect. Based on budgetary constraints and local rules on what an appropriate price is for a unit of effectiveness, decision-makers may decide whether or not a given intervention represents good value for money and should be purchased. CEAs may also be used to set the price of services, to make decisions for disinvestment (Haines et al. 2014), and to organize a constrained budget among treatment alternatives to produce maximum health output.

At their best, CEAs provide valuable information for decision makers acting to optimize a constrained set of resources within a healthcare system – the relative refusal of most American healthcare policy makers to consider cost-effectiveness has been considered by some analysts to be at least partially responsible for the dire state of US healthcare spending (Neumann 2004). Unsurprisingly, to be useful to decision makers, CEAs require relevant, transparent and accurate cost and effectiveness data. Effectiveness data

is at least as important, but we will be focusing on costs in this thesis. **Costs remain understudied relative to effectiveness** (Lipscomb et al. 2009) and the lack of transparent, accurate cost data impacts the validity of CEAs and may lead to inappropriate reimbursement decisions, as well as preventing their use at a level commensurate with their promise (Tan et al. 2009, Adam et al. 2003). The goal of CEAs in glaucoma research is maintain quality of life and improve visual function at sustainable cost (European Glaucoma Society 2008) – this mirrors the call of Boland et al. (2013) for comparative effectiveness research to maximize patient outcomes at best value for money. This is especially true given the heavy and modifiable economic burden of visual problems (Rein 2013) and the lack of attention that has been paid to glaucoma by health economists (Kobelt 2002).

The cost and effectiveness data for CEAs may be obtained alongside a clinical trial (or population-based study) – alternatively, a synthesis of literature-based sources (and institutional experience, expert opinion and assumptions where these are unavailable) may provide relevant figures to populate a decision-analytic model such as a decision tree or Markov model. There are several potential problems associated with the use of clinical trials for cost-effectiveness research, including their frequent failure to reflect normal clinical practice, their selective case mix, short duration of follow-up, failure to consider the evidence landscape in its entirety and poor generalizability (Drummond et al. 2005). While trials are the gold standard in effectiveness research because of their high internal validity and facilitation of inference, models are considered more useful for CEA because of their high generalizability and facilitation of decision-making (Sculpher et al. 2006).

Previous economic work on laser trabeculoplasty

The existing literature on the cost-effectiveness of any laser trabeculoplasty modality is scant (Cantor et al. 2008) – indeed, glaucoma in general has been understudied by health economists and there is a noted paucity of data on economic aspects of glaucoma (Kobelt 2002, NICE 2009). Extant studies on trabeculoplasty compare laser treatment to medication or, less frequently, to trabeculectomy – at the time of writing, there are no economic evaluations comparing SLT and ALT, which remains a question of interest (cf. section 2.1.5 above, subsection ALT vs. SLT). At the time of writing, there is one full

cost-effectiveness analysis of laser trabeculoplasty (Stein et al. 2012). The other studies listed below assess the absolute magnitude of costs as to project the budget impact of different treatment strategies. Given the lack of solid empirical evidence on SLT's repeatability, current studies which assume repeatability should be taken as a cautious assessment of one among many possible states of affairs, thus far unsubstantiated. In general, laser trabeculoplasty compares favourably to drugs in terms of economic profile.

With regards to costs in glaucoma in general, Rouland et al. (2005) list the following findings; costs are correlated with disease severity, negatively correlated with degree of IOP control, and are strongly correlated with number of post-diagnosis treatments. Thus preventing disease progression and minimizing number of treatments needed is desirable not only for clinical reasons but from an economic standpoint.

One of the first attempts to assess the economic impact of laser trabeculoplasty was Lee and Hutnik's 2006 study where they projected and compared the costs of SLT vs. medication (including mono-, bi- or tri-drug regimens) over the course of 6 years in Ontario. In the SLT group, it was assumed that treatment remained effective for 2 years or 3 years prior to retreatment with SLT. This is subject to dispute as Pan (2005) found that 32% of patients experience treatment failure within 1 year, a result broadly echoed by Weinand et al.'s study (2005) finding that 40% of patients failed within 1 year. It was assumed that the laser group would need no adjunctive medication, whereas SLT is most often used with adjunctive medication. Costs of complications were not considered. Given these assumptions, it is unclear whether there is in fact a patient group to whom these costs would apply – this to say nothing of the initial supposition of repeatability. Under these assumptions, SLT offered savings in absolute costs over pharmacotherapy at the end of 6 years.

Seider et al. (2012) undertook a somewhat similar study in the USA. This research was undertaken in the context of generic versions of widely-prescribed glaucoma drugs being available, especially the recently generic Latanoprost. In comparing SLT to medication, they aimed to find the point at which SLT became cheaper than drugs. SLT costs comprised costs of the procedure and prednisolone for complications, rates of which were obtained from a previous study. For drugs, it was assumed that 100% adherence held and

the price of generics was used. SLT became cheaper than branded Latanoprost at 12 months post-laser, generic Latanoprost at 13 months and generic Timolol at 40 months. The authors noted that they did not model several features of interest, including the costs of treating complications or the need for surgery. Furthermore, 100% adherence was assumed, whereas compliance is generally poor with glaucoma medications. While the stated study perspective was societal, only direct medical costs were considered which corresponds to a third-party payer perspective. Much like Lee and Hutnik's study, the restrictive assumptions around SLT and failure to consider different downstream sequelae restrict the range of patients to whom these results apply.

Cantor et al. began their 2008 report by noting the paucity of economic evaluations despite the significant burden exerted by glaucoma. A Markov model was used to compute cumulative costs over the course of 5 years for laser trabeculoplasty (regardless of modality given their equivalency, including equivalent charges), trabeculectomy and medication. The transition probabilities were derived from a wide range of studies and supplemented with institutional experience and assumptions where unavailable. There was no formal evidence synthesis, nor any indications that the results from different studies were applicable to the same cohort as the one being modelled – this is not uncommon in cost modelling exercises. Trabeculoplasty compares favourably to medication alone or surgery, even taking adjunctive medication into account. Cantor et al. (2008) note that their model provides a conceptual framework to think about the structure of the clinical scenario, presumably such that it can be modified and fitted with cost data specific to the decision-maker's context.

Stein et al. (2012) conducted a cost-utility analysis over a 25 year horizon among patients who newly present with mild open-angle glaucoma. A Markov model was used to compare laser trabeculoplasty (without regard to modality), prostaglandin analogues and no treatment. All patients started with mild glaucoma and could transition sequentially to moderate, severe, unilateral blindness and finally bilateral blindness. Cycle length was 1 year. As with Cantor et al.'s study above, a pastiche of sources was used to populate the Markov model. Rates of progression for untreated patients were from the Early Manifest Glaucoma trial. The Glaucoma Laser Trial was used to model progression among those in

the laser or prostaglandin group. They used trial findings that prostaglandins are 30% more effective than the medication used in the GLT, so the rate of disease progression was decreased by 30% from GLT results. Long-term progression to blindness was estimated using a study undertaken in St. Lucia. The authors considered a more comprehensive set of costs than those of the above studies, including adjunctive medications, examinations associated with complications and progression to surgery. Laser repeatability was not assumed – merely that laser costs were incurred in year 1 and adjunctive medication was used as needed thereafter. Economic favourability was strongly dependent on adherence to medication – if there was 100% adherence, PGAs were more cost-effective than laser. If more realistic adherence was assumed, laser became more cost-effective.

The studies listed above either used decision-analytic models or sets of assumptions with costs affixed as opposed to direct, empirical measurement of costs. The models used a pastiche of sources to estimate model parameters without formal evidence synthesis, likely due to lack of extant data. These sources were supplemented with expert opinion and institutional experience where no studies were available. Given the 'grab and go' nature of much modelling in chronic disease (Hoerger 2009, Lipscomb et al. 2009), it is unclear whether or not the chosen sources correspond to the target cohort to be modelled, nor whether the results are applicable to any actual group of patients. The results of these studies are also used to bolster SLT's claims of economic supremacy (Thompson 2009, Craven 2014). At the time of writing, there have been no attempts to ascertain whether costs from such modelling exercises match costs ascertained by direct measurement, and thus, whether they provide useful information for decision-makers. We address this question in this thesis.

2.1.8 – Modelled vs. directly measured costs, aims of the thesis

Modelling is all of the following – an unavoidable fact of life (Buxton et al. 1997), the preferred method of conducting CEAs (Sculpher et al. 2006), a tool for assessing the epidemiologic and economic impact of diseases and interventions (Goldhaber-Fiebert 2010), a way of developing policy and informing current decisions where trials are incomplete or infeasible (Freedberg et al. 1996) and a less labour intensive method of

assessing costs. While modelling offers benefits over clinical trials in terms of generalizability and usefulness for decision-making, there are problems associated with their use. Notably, validation of models is difficult (especially in chronic disease, due to lack of long-term data to compare model predictions to). Furthermore, the discretionary nature of populating models leads to the possibility of arbitrariness (McCabe and Dixon 2000, Sheldon 1996) – a situation compounded by the possibility of modelling the same clinical situation with multiple models (for example, Simonella and Canfell's 2014 examination of different models of HPV vaccination). Finally, while the use of disparate sources increases generalizability and use of the whole evidence landscape, there is often no assessment of whether the sources selected all represent the target population of interest – the model may assess the costs associated with a chimera cohort.

Glaucoma presents two problems common to chronic diseases that present troubles for the use of clinical trials and which necessitate modelling. The sheer number of potential treatment comparisons is too large to investigate each of them by clinical trial. Furthermore, the chronicity of the disease precludes the use of clinical trials, most of which have 1-5 years of follow-up. This mismatch of clinical trials with the combinatorial nature of possible treatment sequences and chronicity of glaucoma means that decisions will have to be made in the absence of clinical trials. As a result, the use of modelling is inevitable in attempting to place treatment decisions on semi-rigorous, evidence-based footing. Furthermore, such models are frequently put to uses other than assessing cost-effectiveness – model based cost data in particular is used for projecting budget impact for glaucoma (Lee and Hutnik 2006, Cantor et al. 2008, Dirani et al. 2011) and other diseases, such as burden of stroke (Mar et al. 2008). There has been little work in glaucoma assessing the concurrence of the costs from such models with empirical costs, although modelled costs are quoted in the literature and are, ideally, meant to inform decision-making rather than being merely academic exercises.

Models, in theory, offer several benefits denied to efficacy RCTs for the conduct of CEAs, although RCTs were at one point seen as an obvious vehicle to conduct CEAs. This is partially because it is possible to collect detailed, high quality, prospective data on resource use and costs alongside effectiveness data (Petrou and Gray 2011) – the

usefulness of RCTs in inferring effectiveness was also likely thought to transfer to assessing cost-effectiveness. There are, however, several problems with the use of trials for assessing cost effectiveness. Single efficacy trials, are poor vehicles for CEAs for the following reasons:

- Trials often do not reflect actual clinical practice, given the presence of highly motivated clinicians, selective patient samples, above average adherence to medication, increased vigilance and the use of invasive gold standard methods of assessing efficacy. This is particularly true of efficacy trials, whereas effectiveness trials fare better (Buxton et al. 1997). As noted by Goldhaber-Fiebert (2010), it may even be preferable to use the results of observational studies in models, whereas this would be unacceptable for assessing efficacy. Generalizability is important in cost-effectiveness research as results have to be adapted to the decision maker's context and reflective of everyday practice – efficacy trials lack ecological validity in this respect (Sculpher et al. 2006). As noted by Caro et al. (2010), the cost data from clinical trials is suspect because the study environment so modifies normal practice that any estimates of resource use are likely poor reflections of reality. It is likely that the use of effectiveness trials bypasses most of these difficulties as they are meant to assess performance in routine clinical practice and are less prone than efficacy trials to warp measures of typical resource use (Buxton et al. 1997).
- While effectiveness research alone is comfortably couched in an inferential framework, costs and cost-effectiveness are more usefully conceptualized in a decision-making framework (Claxton 1996). Given the intrinsically context-dependent nature of cost data – depending, as it does, on local patterns of healthcare delivery, patient case mix, absolute and relative prices of resources, and the vicissitudes of local cost accounting (Koopmanschap et al. 2001) – inferences about differences in cost between two treatments fail to hold at a level higher than the institution at which the trial was performed. Even unit costs for the same inpatient procedure can differ by an order of magnitude within a country (Adam 2006). Even if we were interested in inferring differences in cost, cost data presents statistical difficulties not seen with effectiveness data, being heavily

right-skewed and heavy-tailed (Drummond et al. 2005). As a result, larger sample sizes are needed than to assess costs than effectiveness, but RCTs are generally only powered to assess the latter. This is difficult enough, as evinced by the flourishing of multicentre and multinational RCTs because of the difficulty of amassing participants at a single site. Finally, the practice of statistical wizardry is no substitute for high-quality data collection (Graves et al. 2002).

- Most trials have short horizons, lasting several months or a few years at most. This is incommensurate with the course of chronic diseases and fails to capture relevant downstream costs. As such, even where trials are used for CEAs, there are attempts to extend the findings with modelling (Sadatsafavi et al. 2014, Samsa et al. 1999).
- A single trial is one feature in the evidence landscape. It is preferable to use all the available evidence about a given clinical problem (Goldhaber-Fiebert 2010, Drummond et al. 2005).

A final consideration is that modelling may be considerably easier than collecting resource use and cost data alongside a clinical trial. The process of developing a conceptual framework and populating it with values from extant literature, institutional experience, assumptions and expert opinions may take several hours or days. This is as opposed to the often painstaking, labour-intensive and expensive cost collection that occurs alongside a trial, which definitionally is not over until the trial is over – a period of several months to several years. As we will see below, the tension is costing methods is between accuracy and feasibility. For didactic purposes we may crudely dichotomize between less labour-intensive modelling methods and methods that require direct measurement of costs at the individual level, trial-based costing being typical of the latter. All of the studies listed above used such modelling methods. Our aim is to assess whether such models may be used in place of more laborious and detailed costing methods in determining costs in glaucoma.

Let us note overstate the case against trials. Effectiveness trials provide an excellent tool for validation and offer the opportunity for the collection of detailed patient-level cost data, effectively functioning as a ‘gold standard’ costing method to which we may

compare model estimates. As noted above, modelling is not without problems. Many models in chronic diseases and in glaucoma use what have been termed ‘grab and go’ techniques (Lipscomb et al. 2009, Hoerger 2009) where models are populated with whatever data sources are at hand and convenient – especially for cost data. Models are often populated with a pastiche of sources, most often single extant studies that treat of the model parameter of interest, and expert opinion or institutional experience where this is unavailable. There is often no formal attempt at evidence synthesis, likely because a lot of the data simply does not exist. Simplifying assumptions are made, often of a questionable nature as with SLT’s indefinite repeatability or a lack of complications. Thus there is concern about the arbitrariness of the values used to populate models (McCabe and Dixon 2000). Even where the conceptual framework or overall model structure seems sound, the discretionary nature of populating models is a cause for concern (Sheldon 1996). This is not aided by the possibility of representing the same clinical question by multiple models (Simonella and Canfel 2014). The use of disparate sources is to be commended, but heterogeneity may be a cause for concern. As in meta-analysis where excessive heterogeneity precludes synthesis, model population with disparate sources may mean that parameters relevant to several disparate populations are forced into a single cohort that is not representative of any individual decision-maker’s target population.

There are few opportunities for validation of models – if we had data against which to test our model predictions, we may not have been engaged in modelling initially (McCabe and Dixon 2000). Indeed models and trials are occasionally presented as parallel, equally valid modes for conducting CEAs, as in the ISPOR reporting guidelines (Husereau et al. 2013) where there are separate instructions for trial and model-based evaluations, or Siapka et al.’s 2014 review of costs in HIV programs where costs were divided into empirical and model-based costs. Whether or not the two concur has not been assessed in CEAs in glaucoma and thus it is unknown whether simpler modelling exercises may be used in place of trials. However, where validation is possible, it augments the credibility of the model and is to be recommended (Goldhaber-Fiebert et al. 2010). Effectiveness trials provide a setting wherein a model may be validated,

representing as they do an opportunity to collect prospective, high-quality cost data and being close enough to real practice that it provides a credible proxy.

It is worth noting that some authors decry the rudimentary state of modelling in health economics. Caro et al. (2010) make the case, with some exasperation, for using microsimulation and discrete-event simulation type models instead of the cohort-based Markov models and decision trees currently in use. Under the guise of transparency and intelligibility to physicians models are made so simple that they sacrifice accuracy – this is potentially disastrous where decisions are to be made. Recent work in chronic diseases such as glaucoma (van Gestel et al. 2010) and osteoporosis (Hiligsmann et al. 2009) demonstrate that microsimulation techniques are feasible and demonstrate advantages over cohort-based decision-analytic approaches in terms of result reliability and agreement with extant data. This is especially useful where the memorylessness property of Markov models fails to hold (e.g. risk of second fracture after initial fracture in osteoporosis, putatively decreasing effectiveness of SLT with previous SLT).

Goldhaber-Fiebert et al. (2010) note that improving the dissemination of models and analytic approaches is important for securing the use of model-based approaches by decision-makers. Cantor et al. (2008) explicitly refer to their model as a conceptual framework in which glaucoma treatment may be viewed. With better dissemination of models, a given hospital or government may decide to populate said model with locally relevant parameters and values. Another possibility is validating the results of a model with relevant empirical studies once available in an iterative process of model-building and updating (Freedberg et al. 1996). This models the efforts of the Cochrane Collaboration to keep their systematic reviews up to date. Ultimately, the goal is to aid decision-making. To do so, models are an integral part and it is worth ensuring that they are of use rather than exercises in symbol-pushing.

The aims of this thesis

The use of modelling is widespread in the assessment of technologies in glaucoma, whether for purposes of cost-effectiveness analysis or budget impact. However, much of this modelling is ‘grab and go’ in nature. As shown above, such approaches may be problematic. However, this has never been assessed. We aim to compare the costs

obtained from a decision-analytic model of repeat laser trabeculoplasty with those of an effectiveness trial. Effectiveness trials offer an opportunity to assess costs in a setting more closely reflective of normal clinical practice than efficacy trials (Buxton et al. 1997) and provide the chance to validate our literature-based model.

Repeat laser trabeculoplasty is, in some respects, typical of the problems we may encounter in assessing costs or cost-effectiveness in glaucoma. Whether for cost-effectiveness or budget planning purposes, and whether comparing either modality to medication, surgery, or to one another, there is little existing data on rates of success or failure upon laser repetition. We are obliged to model the costs based on extant data sources – as will be observed in the methods section, said sources are disparate in nature and there are few parameters that are estimated with bona fide evidence syntheses. In assessing the agreement or disagreement of costs from the model to those of the trial, we may begin to answer some questions of interest.

Firstly, we may answer the question of whether models of this sort correspond to the real-life clinical situations they purport to represent, and thus whether or not they are of value to decision-makers. Are there features of this clinical scenario that make it or more less amenable to this style of modelling? Given that we are ultimately interested in assessing multiple nodes of the whole disease glaucoma treatment algorithm, and given that we are unable to assess all such nodes by clinical trial, are there scenarios wherein we are confident enough in results of a model to bypass a trial or other direct measurement of costs?

In the next section, we treat costs in a slightly more general fashion, justifying our choice of costing methods and presenting some of our secondary analyses of interest.

2.2 – Further concepts and difficulties in costing – a supplementary discussion

2.2.1 – Overview

Accurate, transparent cost data is necessary for at least two reasons – ensuring the validity of economic evaluations and for budget planning purposes (Adam et al. 2003). As outlined in the previous discussion on economic evaluations, judgements of economic efficiency and value for money have become increasingly salient in discussions on

healthcare. Economic evaluations provide a method whereby value for money may be assessed. Unsurprisingly, good cost and effectiveness data is needed for credible, useful analyses – the old adage of "garbage in, garbage out" obtains in cost-effectiveness research. Furthermore, insofar as these results are meant to inform policy, poor cost data and inefficient reimbursement decisions may have consequences for healthcare budgets and population health. For these reasons, we would hope, that knowing how to cost an intervention was straightforward.

Costing is, conceptually, a simple tripartite process– *identification* of the range of relevant resources used, *measurement* of the amounts used in natural units (e.g. hours of physician time, number of bandages) and *valuation* of resources in monetary terms (Drummond 2005). In practice, there are considerable difficulties in estimating costs as reflected by the disparities in pharmacoeconomic guidelines regarding costing and the commensurate variation in the methods and quality of applied studies (Adam et al. 2003, Graves et al. 2002). Costing has been understudied relative to effectiveness (Lipscomb et al. 2009) – differences in the treatment of cost means that CEAs have not had a policy impact commensurate with their promise (Tan et al. 2009). Poor costing methods threatens the validity of CEAs, may lead to poor reimbursement decisions and may be one reason that CEAs ultimately lose their credibility as scientific information (Fukuda and Imanaka 2009).

This section treats some general issues of cost, as an addendum to and expansion of the above section on glaucoma and model-based costing. This section is structured as follows – I begin with elementary concepts that all attempts at costing must reckon with – opportunity costs and perspective. In discussing perspective I introduce one of the secondary aims of this thesis – to assess the difference between the Ministry and societal perspective for repeat laser trabeculoplasty.

Secondly, we note some of the difficulties inherent to cost data. Most problematic is the highly context-dependent nature of cost data, the problems this presents for portability of results and the crucial role of transparency in costing. We end with a discussion of costing methodology, partially for the sake of completeness and partially to put our

microcosting methodology in context, as well as for future directions with the introduction of case-costing in Ontario.

2.2.2 – Opportunity costs and their relation to expenditures

The cost of an intervention or treatment is the value of the inputs and resources used in its production and delivery, measured in monetary terms – a procedure that requires more labour or material inputs costs more (and should have a higher price) than a less resource intensive one. In using resources for one purpose we are unable to use them for another. This is captured in the concept of the opportunity cost of a resource wherein cost is defined as the value of the benefits that were forgone because the resource was not available for its best alternative use (Drummond et al. 2005). Opportunity costs remain the preferred concept for costing interventions as their use is necessary for making judgements on economic efficiency, as economic evaluations purport to do (Gold et al. 1996).

The prices charged by providers for services often bear little relation to the opportunity costs of said services. Insofar as prices are often the most easily available data with an economic 'flavour' they are used in CEAs in place of the costs of interventions – this may introduce bias in the results of CEAs (Drummond et al. 2005). The prices of procedures are often informed by attempts to recover expenditures and cross-subsidize across departments and procedures within a hospital – prices are set by reimbursement demands rather than resource use per se (Finkler et al. 2007). Insofar as the charges set by providers arise from accounting considerations rather efficiency in resource use, their use is economics is less than optimal.

This was especially relevant in healthcare systems such as the US Veterans Health Administration in the late 1990s as it lacked itemized billing. Under these circumstances, capturing measures of resource use was especially daunting and the only real alternative was recourse to hospital expenditures (Barnett 1999). Hynes et al. (1999) noted that the use of prices in VA cost studies could produce considerable bias and recommended that the effort be taken to derive economically sound cost estimates – effort that was considerable at the time given their accounting infrastructure. The present-day situation in parts of Canada is more promising. Clement et al. (2009) note that proper microcosting

systems are in place in the Calgary Health Region that allow accurate capture of resource use.

The use of prices is acceptable to those who are planning budgets and more concerned with the absolute magnitudes of expenditures, although their deviation from true costs has implications for efficiency. Under conditions where prices and tariffs concur with costs, they may be used with little bias, although they may differ considerably in terms of absolute magnitude (Drummond et al. 2005). There are methods available to adjust charges and make them more indicative of economic cost (e.g. charge-to-cost ratios). Finally, the use of charges in economic evaluations presents very low-resolution data which is not easily transportable across jurisdictions, as they encompass the vicissitudes of their parent system and flatten several pieces of information (cost accounting system, case mix, absolute and relative prices of resources) into a single measure.

2.2.3 – Perspective in economic evaluations

Not all resource expenditures are relevant to all vantage points – as an example, the time patients spend recuperating after an operation is of concern to the patient (lost wages) and to society (viz. its aggregate productivity), but not to the hospital or a third-party payer, who are concerned solely with the costs of the procedure itself. This notion of relevant resource use is captured by the *perspective* of an economic evaluation which is the vantage point from which the analysis is conducted. The perspective determines the range of costs that will be included in the analysis. The main perspective of interest in Ontario is that of the provincial payer (e.g. the Ontario Ministry of Health and Long-Term Care). Other perspectives include the societal perspective (all costs, regardless of who incurs or pays them), the hospital and patient perspectives. An intervention that looks cost-effective from one vantage point may look like a waste of resources from another viewpoint, an oft-invoked example being Weisbrod et al.'s 1980 study comparing community and hospital-based programmes for mental illness. From the providing agency's point of view, the community program costs an extra $1,700 per annum. However, from the societal perspective there is a net saving of $400 per year on account of increased productivity of patients and decreased costs to the justice sector. Notably, it's not that either is the *correct* answer (although, advocates of a welfarist grounding of

CEA would disagree), but there is a legitimate difference in the decision-making context and goals of the analysis – thus, value judgements are intrinsically involved in costing exercises (Philips et al. 2006).

Costs are most often differentiated into direct medical costs, direct non-medical costs and indirect costs (Tan 2009). Perspectives differ in the range of costs that full under their respective purviews. Direct medical costs are associated with the intervention under study and are the costs associated with producing a health output – e.g. drugs and physician time. Direct non-medical costs refer to patient out-of-pocket expenses associated with the intervention – e.g. travel, house modifications and informal caregiving. Indirect costs are productivity losses due to mortality or morbidity, e.g. lost earnings and decreased capacity for leisure due to morbidity.

All perspectives account for direct medical costs – one would be hard pressed to justify a costing of an intervention that failed to account for the constituent medical services. Patient expenses and indirect costs are considered much less often (Neumann 2009). In Ontario, direct medical costs are to be considered and the primary perspective is that of the Ministry. Other perspectives and cost categories form secondary analyses and may be undertaken at the analyst's discretion.

The societal viewpoint is the most general perspective (all other perspectives are subsets of the societal perspective) – it is also the perspective most often recommended by guidelines (Currie et al. 1999). In practice, however, most analysts adopt the perspective of a public payer or healthcare provider – this in spite of large amounts of erroneous labelling of payer analyses as societal (Neumann 2009). There is, furthermore, contention about the relevance of the societal viewpoint (Currie et al. 1999) as well as the components that should be included under a societal viewpoint and how best to cost them (Neumann 2009).

Disagreements about the societal perspective vs. provider perspective reflect more fundamental disputes about the theoretical underpinnings of CEA. The insistence on the societal perspective reflects an attempt to ground health economics firmly in Paretian welfare economics (Drummond et al. 2005). On this view, the goal of healthcare interventions is to increase utility in the aggregate, requiring that all costs should be

considered regardless of who they accrue to. A high-fidelity, theoretically sound CEA would consider societal costs and preferences. In doing so the costs and benefits of healthcare programs become comparable to other healthcare programs and programs in other sectors (e.g. implementing a glaucoma screening program vs. allocating funds to education or the justice sector).

The use of the provider perspective is rooted in a more pragmatic approach to economic evaluation, often denoted the decision-making, extra-welfarist or constrained optimization approach (Drummond 2005, Sculpher et al. 2006). On this view, the goals of CEA are more modest and pragmatic. It is assumed that a given decision-maker seeks to maximize health subject to resource constraints – the goal of CEA is to aid the decision-maker make optimal choices within the purview of their program. In our case, given that the Ivey Eye Institute must treat glaucoma patients, how may it best bring about lowering of intraocular pressure (i.e. best effectiveness) within its budget? Instead of discussions about inter-sector utility comparisons, the decision problem is framed in terms of comparing technologies ALT and SLT in terms of mmHg intraocular pressure lowering and costs.

The issues of the 'correct' grounding of economic evaluations is, like all fruitful clashes of abstractions, unlikely to be resolved any time soon and guidelines differ in whether they indicate the societal perspective as the recommended perspective (Gold et al. 1996) or as an optional perspective that may be done if there's reason to suspect that indirect costs make a substantial difference (CADTH 2006). In practice, obtaining values for the societal perspective is difficult (Lensberg et al. 2013). Even with the theoretical soundness of the societal perspective, it is difficult to obtain values relevant to the societal perspective and comparison across sectors is challenging.

One of the secondary aims of this thesis is to assess the extent to which the societal perspective differs from the third-party payer perspective in the case of repeat laser trabeculoplasty. In doing so we may assess the contribution of patient costs to total costs and the types of costs that patients incur during glaucoma treatment. At present there are no studies assessing the magnitude of indirect costs for glaucoma treatment in Ontario. A previous study by Sharma et al. (2010) assessed patient-borne costs at tertiary glaucoma

clinics in the UK. Unfortunately, they failed to compare such costs to direct medical costs for the same patients, leaving us without a feeling for how large a component of total costs they accounted for. Rouland et al. (2005) note that patient borne costs comprised 55% of total glaucoma costs in France, whereas Kobelt-Nguyen et al. (1998) found that they were only 25% of total costs. The situation for Ontario has not been assessed.

2.2.4 – Context-dependence, guidelines and applied studies, transparency

Costs are highly sensitive to contextual factors. The unit cost of the same hospital procedure may differ by an order of magnitude within the same country (Adam 2006). Possible causes include differences in case mix, relative and absolute prices of resources, patterns of healthcare delivery (e.g. are the same types of personnel used, is it inpatient or outpatient) and cost accounting and estimation procedures (Koopmanschap et al. 2001). As such, recording the cost of an intervention in one setting encodes several characteristics of the parent healthcare setting in addition to the intervention. Thus transparency is necessary to ensure portability of results between settings. CEAs remain insurmountably local if there is no possibility of portability and this limits their broader usefulness – each new setting will have to undertake a de novo analysis. The portability of results becomes even more important when there is interest in cross-country comparison of procedure costs for benchmarking purposes or for comparison of the same procedure in multicentre or multinational trials (Wordsworth et al. 2005). There are difficulties in pooling cost data across the different sites of multicentre trials that are not present with effectiveness data (Goeree et al. 1999).

A deeper problem with costs has to do with the possibility of legitimately different answers and irreducible arbitrariness in their construction. The presence of different study perspectives and the resultant different answers is a simple demonstration of how the same procedure may have two different costs. As noted by Finkler et al. (2007), the apportioning of hospital overhead costs (overheads being shared resources that cannot easily be traced to a single department or procedure – e.g. building, electricity, laundry) is arbitrary and hospital expenditures are exact only at the whole-hospital level. As Barnett (2009) notes, microcosting methods are unable to directly assess overhead costs – a weighting method must be decided upon based on the needs on the analysis. Unlike

effectiveness measures there may not be a 'true' value to be inferred but appeals to transparency, accuracy and relevance of results (Finkler et al. 2007) – the goals of costing research as not to discover any truths about nature but to provide useful information to decision-makers. As such, there is an even stronger need for transparency and accuracy of results in costing exercises. To the extent that results are credible and portable between settings, analyses succeed.

Furthermore, there are variations in costing methods and data sources. As noted by Mogyorosy and Smith (2004), cost analyses may be retrospective or prospective, empirical or model-based. Frick (2009) lists ten possible sources of data to inform microcosting studies. Chumney (2004) notes that there are many methods possible to construct gross costing tariff charges. As a result, Tan et al. (2009) note that apparent differences in the costs of procedures may be due to methods of ascertaining cost rather than actual differences in resource use.

These difficulties with costing are reflected in guidelines and applied studies. There has been a search for standardization in pharmacoeconomic guidelines for as long as there have been guidelines (Mullins and Ogilvie 1998). Comparative analyses of guidelines notes that not only is there variation and lack of concrete guidance in costing guidelines – there are veritable gaps (Jacobs et al. 2005, Adam et al. 2003). Adam et al. (2003) assessed both guidelines and applied studies, seeking to categorize reasons for variability in applied studies. They identified four possible sources of variation; guidelines disagreeing in their recommendations, guidelines agreeing in principle but providing little detail on how to comply, guidelines failing to consider certain methodological issues, and simple failure of investigators to follow guidelines. This last point is confirmed by Graves et al. (2002) who found the quality of costing of 45 studies to be poor and found a propensity for researchers to be more concerned with statistical analyses than with collecting high-quality cost data. Clement et al. (2009) note, in the context of an applied study, the absence of concrete guidance for investigators undertaking costing research. Variability in methods used in applied studies raises questions about the validity of results, reduces the transferability and comparability of results between settings and ultimately reduces value to policy-makers.

At the very least, there should be transparency about methods, data sources and assumptions – the presentation of costs in disaggregated tables allows the different contextual factors affecting costs to be assessed by other users and the results to be adapted accordingly. The presence of analyst leeway and a lack of standardization in costing methods is not an excuse for opaqueness or a lack of rigour. The lack of concrete guidance may come down to the genuine need for analyst leeway – standardization may not be possible or even desirable (Whitehurst and Bryan 2013). Insofar as the ultimate goal is to inform and change policy, problems in costing should be commensurately interesting and genuinely challenging, not a case of mere sloppiness.

2.2.5 – Microcosting vs. gross costing methods

Given the difficulties associated with direct measurement of cost, analysts are interested in finding easier methods of cost estimation that are still valid (Dakin et al. 2011). One such method is the use of modelling in place of direct measurement – this is the distinction which this thesis investigates. A second distinction is between microcosting and gross costing methods (Clement 2009, Tan 2009). Microcosting approaches measure and cost out the individual components of resource use in providing a service (e.g. physician and nurse time, disposables and other relevant cost categories). Gross-costing approaches comprise a number of methods that charge at a more highly-aggregated level of service provision (e.g. charging per day of inpatient stay or episode of care based on diagnosis – as opposed to enumerating and costing the resources that are used in providing the episode). Gross costing methods are further divided into tariff-based methods and cruder budget apportionments. Tariff-based methods are based on diagnosis-related groups (DRGs) and cognate categorization systems where patients are classified into categories capturing cases of similar clinical, utilization and length of stay characteristics (Clement et al. 2009). Estimates based on apportioning bottom-line expenditures to individual services make use of different weighting systems for departments, procedures or even a general patient per diem (Tan 2009, Drummond et al. 2005).

The choice between microcosting and gross costing methods is often framed as a trade-off between accuracy and ease of data collection, with microcosting approaches offering

better accuracy but being more difficult to undertake (Drummond et al. 2005) – a similar trade-off exists in modelling vs. measuring of costs. Guidelines treat the issue of costing methods in a manner that allows a great deal of leeway. The general tenor is that microcosting is preferable, but the needs of the analyst and the feasibility of data collection determine the methods chosen. As noted by Mogyorosy and Smith (2004) – "there is a trade-off between cost information accuracy and the cost of attaining cost information". In practice, there is a veritable zoo of methods. Hybrid methods are often used, wherein the most costly or variable components are valued more precisely, while other components are treated in a looser fashion. Costs may be collected retrospectively, prospectively, empirically or structured in a model (Mogyorosy and Smith 2004), from administrative databases, insurance data, expert panel, surveys and interviews with patients and providers, patient chart review, and direct observation, among others (Frick 2009). Thus the validity of costing methods exists on a continuum rather than the discrete poles of microcosting and gross costing (Evans and Crawford 2000).

Bottom-up microcosting refers to the enumeration and costing of every input consumed in the treatment of each individual patient – clinical trials provide an obvious vehicle for undertaking such costing as it takes little effort to add a resource use form to existing data record forms. Bottom-up microcosting is considered to be the closest thing to a 'gold standard' in costing (Gold et al. 1996, Tan 2009) and is thought to represent the most accurate approach to costing. Microcosting overs the following advantages over gross costing methods:

- Given the use of individual level data, it's the only method that allows for inferential statistics and null-significance hypothesis tests of cost differences between treatments. However, as noted above, the usefulness of inference in health economics is not entirely clear (Claxton 1996).
- Cost differences between treatments may derive from differences in the unit costs of resources or intensity of resource use – bottom-up microcosting provides sufficient granularity that this difference may be parsed out (Tan 2009). For this reason it is also recommended to be used in multicentre clinical trials, where differences between centres may be considerable and pooling costs across centres

is not possible (Wordsworth et al. 2005, Goeree et al. 1999). This is denied to DRG-type measures that may detect differences between disease groups but fail to account for variation within DRGs.

- Bottom-up microcosting allows for the discernment of the distributional form of costs and resource use.
- Since microcosting definitionally entails the tabulation and valuation of resource use, it comes closest to the ideal of capturing the opportunity costs of interventions. Gross costing measures are informed by reimbursement concerns rather than resource use and their use in efficiency judgements may be unsound.
- Bottom-up microcosting allows the analyst to conduct subgroup analyses and identify demographic characteristics associated with levels of resource use.
- Finally, the transparency of well-executed microcosting is such that it is the most likely costing method to allow generalizability of results. In theory, it is not dependent on the vicissitudes of accounting systems as top-down methods (Wordsworth et al. 2005). Since components of resource use and unit costs are assessed separately, decision-makers can adapt the results to their own settings, substituting appropriate values.

The onerousness of collecting microcosting data might be overstated when it comes to Ontario. Microcosting data was certainly difficult to collect in the VA hospital system or other systems where patient-specific resource use and encounters were not recorded in detail (Hynes et al. 1999). For this thesis, we use microcosting for both trial and model-based costing. All the studies on the costs of trabeculoplasty listed above use some variant of microcosting insofar as they attempted to value individual components of resource use rather than tariffs or charges. While Ontario is moving to case-costing (a tariff-based method that uses the case-mix grouper, or CMG, instead of the American DRGs), there is no data available for St. Joseph's Hospital at the time of writing this thesis. It is expected that the easy availability of a summary measure for the cost of a procedure will find its way into economic evaluations – comparing the new case-costing methods to microcosting and assessing their impact on the outcomes of CEAs will be an active area of research.

Comparative costing

The impact of costing methods on the results of economic evaluations is acknowledged to be understudied (Clement et al. 2009, Tan et al. 2009). There is more literature comparing tariffs to microcosts in terms of absolute cost magnitudes. This focus is unsurprising considering that DRG-type measures were developed to place hospital reimbursement on less arbitrary footing and to bring it in line with resource use while being easier than undertaking full microcosting. Such studies are undertaken as hospitals wish to ensure that they are being adequately compensated for procedures, while other parties are presumably interested in making sure that hospitals are not being overcompensated. Furthermore, extant studies tend to focus on inpatient procedures and intensive care. This is also unsurprising – both are expensive. Intensive care accounts for less than 10% of beds but over 20% of expenditure (Edbrooke et al. 1999) – disparities in reimbursement could be costly for hospitals. However, increases in chronic disease and the aging of the population means that healthcare is steadily moving towards ambulatory procedures and outpatient care which may prevent a different set of difficulties in costing (Donaldson 2011). Indeed, Chapko et al. (2009) found poorer agreement between micro and gross costing for outpatient visits than inpatient procedures.

There are two findings from comparative costing: firstly microcosting and gross costing estimates differ in absolute magnitudes of cost but preserve the relationships between the costs of different procedures (e.g. if the microcost of x is greater than the microcost of y, the same relation generally holds for gross costs, Drummond et al. 2005). This finding is supported by hospital studies comparing charges and costs, most often in the context of cardiology (Cohen et al. 1993, Taira et al. 2003, Clement et al. 2009). Given the extent to which costs and charges differ (e.g. Cohen's finding that the hospital charge for percutaneous transluminal coronary angioplasty is 60% higher than true costs, about $3,300 in monetary terms) their use in settings where absolute cost magnitudes are important is to be advised against (Taira et al. 2003). Drummond et al. (2005) posit that the use of charges in economic evaluations may be acceptable, as the order-preserving nature of charges means that ICERs will differ quantitatively but not in terms of the recommendation they make. However, there is evidence to the contrary. Clement et al.

(2009) assessed the use of microcosting and two tariff-type methods (refined DRG grouper and CMG) for assessing the cost-utility of a drug-eluting stent vs. a bare metal stent in patients with coronary artery disease. They found that the choice of method could impact on the magnitude of ICERs to the extent that it may affect reimbursement decisions. They note that tariff-type methods may not reflect true costs to healthcare systems and that they may impact on the results of CEAs to the extent that policy is affected.

Secondly, there is heterogeneity in DRG-type systems and resulting estimates across disease groups and countries – the result is that the degree and direction of deviation from microcosts differs by geographical and disease areas. Insofar as the degree and direction of bias is hard to gauge a priori, transportation of results across jurisdictions becomes even more problematic than it is initially. DRGs are explicitly meant to inform local reimbursement. As such, they rely on local patterns of health practice and the different cost accounting systems in place – Tan et al. (2014) note variations in cost accounting systems among 12 European countries and Chumney (2004) notes the possibility of constructing DRG-type measures based on different nosological classification systems. Furthermore, the quality and reliability of DRGs differ between countries. DRGs were introduced rapidly in Italy, there is no transparent algorithm to their construction and they are occasionally used more as tools to incentivize for or against the use of certain procedures than as proxies for true cost (Fattore and Torbica 2006) – this is in contrast to the more recent CMG system in Canada that shows high agreement with costs in cardiology (Clement et al. 2009).

The unit costs of the same inpatient procedure can differ by an order of magnitude within the same country (Adam 2006) – as such, merely converting to one's local currency is insufficient. DRG-measure compress several relevant pieces of information into a single measure and it is difficult to tease them apart without additional knowledge. A further difficulty is that tariffs are used in systems with prospective payment models of hospital funding; some authors, however, have attempted to import such tariffs to their own health systems (that use alternative models of funding such as global funding) and use them for budget impact analysis or economic evaluation. Aside from the initial difficulties of

transporting DRGs across borders, in systems with global budgets DRG-type measures fail to make sense and do not correspond to the costs borne from any definable perspective (Le Pen and Berdeaux 2000). This points to the broader need for understanding the difference between costs and charges in economic evaluations as well as some familiarity with the healthcare system of interest.

Finally, tariffs differ in magnitude and direction in different diseases. For percutaneous interventions in cardiology, Cohen et al. (1993) found that charges were higher than costs in the USA, whereas Clement et al. (2009) found that costs were higher than charges in Canada. Heerey et al. (2002) found that even for different codes for acute myocardial infarction in Ireland, DRGs differed from costs from -9% to +66%. Mercier and Naro (2014) assessed agreement between DRG and microcosts for all inpatient surgical procedures in a French hospital and found poor agreement. The situation may be worse when attempting to assess costs of whole programs, such as HIV screening in nonclinical settings (Shrestha et al. 2014). The cost per case detected differed by an order of magnitude depending on the costing method chosen.

There is a grand total of one study assessing the impact of microcosting vs. gross costing on estimates in glaucoma. Kang and Lee (2009) assessed the costs and charges associated with the treatment of all outpatient glaucoma patients over the course of 1 year at a South Korean hospital for a budget impact analysis. The average annual cost per patient was twice as high using microcosting as gross costing – the total budget impact projection was close to $6,000,000 higher in the microcosting case ($11,300,000 vs. $5,400,000). This indicates that it may be worth assessing the impact of costing methodology in glaucoma.

In conclusion, the state of costing leaves a lot to be desired. Costing in glaucoma has received scant attention and there is little indication of whether choice of method impacts cost estimates. We investigate one aspect of costs, namely empirical vs. model-based costs, in repeat laser trabeculoplasty. With the advent of case-costing in Ontario, assessing the agreement between microcosting and gross costing and the effects of their use on CEAs will be an active area of research.

Chapter 3 - Methods

This study aims to compute and compare clinical trial and model-based cost estimates for repeat laser trabeculoplasty (ALT or SLT) and one year of follow-up among Ontario open-angle glaucoma patients at a tertiary general ophthalmology clinic. In section 3.1 I provide an overview of the intervention, population, costing methods, data sources, primary and secondary objectives, and final measures. Section 3.2 is an examination of the clinical trial which provides the vehicle for the empirical costing study. Section 3.3 introduces a decision tree model used to estimate costs for the same clinical scenario. The structure, assumptions and sources of model parameters are discussed. The treatment of the intervention in sections 3.1-3.3 lead naturally to a list of cost components to be considered and in section 3.4 we will describe the sources of quantity use and unit costs for all cost components, for both the trial and model. Section 3.5 will deal specifically with issues of indirect and patient-borne costs which are relevant for an analysis from the societal perspective. Finally, section 3.6 will present the final measures of interest and analyses to be undertaken.

3.1 - Overview

Intervention to be costed:

The application of laser trabeculoplasty (ALT or SLT) after previous 360 degrees of SLT plus a schedule of 6 follow-up visits as per normal clinical practice over the course of a year. Unscheduled follow-up visits, adjunct medications and progression to incisional surgery represent deviations from normal care and will count as additional costs.

Target population and sample population:

The target population of interest comprises Ontario open-angle glaucoma patients eligible for repeat laser trabeculoplasty as would be seen in a tertiary ophthalmology practice. This population is approximated by a sample from the RCT at the Ivey Eye Institute of

St. Joseph's Health Care (a tertiary ophthalmologic clinic in Southwestern Ontario) for trial-based costing and is modelled directly in the model-based costing.

Trial vs. model-based costing methods:

In trial-based costing we arrive at a total cost estimate for each patient in the clinical trial. This is done through obtaining values from data record forms, patient charts, administrative data, interviews with personnel and a patient questionnaire. These patient specific cost estimates are used to calculate a trial-based mean cost per patient for each laser modality. In model-based costing a decision tree based on a mixture of literature, institutional experience and expert opinion estimates is used to derive expected cost per patient. The limited amount of data available on repeat laser trabeculoplasty precluded the use of meta-analysis or systematic review and requires a pastiche of sources to be structured – in this respect, the costing is typical of 'grab and go' scenarios in chronic diseases generally (Lipscomb et al. 2009, Hoerger 2009) and glaucoma specifically.

Final outcome measures:

Each method produces a mean dollar value per patient, valued in 2014 Canadian dollars. The metric of interest is the disparity between bottom-up and top-down cost estimates *within* a technology (e.g. SLT bottom-up vs. SLT top-down). The RCT was designed specifically as a non-inferiority trial, there are no differences in the clinical pathway between ALT and SLT and cost differences are expected to be minimal. Thus we eschew an incremental analysis and analyze within technology.

The perspective for the reference case is that of the Ontario Ministry of Health and Long-Term Care (henceforth the Ministry) as per CADTH guidelines (2006). The societal perspective will be presented as a secondary perspective of interest.

Primary objective:

To assess the extent to which clinical trial and model-based costs agree for repeat laser trabeculoplasty, and thus whether modelling costs provide an acceptable substitute to the more laborious and expensive direct measurement of cost.

Secondary objectives:

To use a microcosting methodology to present a comprehensive profile of the costs involved in repeat laser trabeculoplasty.

To assess the impact of indirect and travel costs to overall cost estimates and thus the difference between total costs from the Ministry and societal perspectives.

To assess the sensitivity of the decision-analytic model to a variety of assumptions and potential scenarios, thus identifying main drivers of cost and overall robustness of the model.

3.2 - Trial section

3.2.1 - *Ethics statement*

The RCT received approval from The University of Western Ontario Health Science Research Ethics Board (REB# - 103028). The addition of a patient cost questionnaire for this economic sub-study received REB approval as an amendment.

3.2.2 - Trial description

The Repeat SLT study is a multi-centre effectiveness trial assessing the effects of repeat laser trabeculoplasty (SLT or ALT) after previous SLT. There are sites in London, Toronto, Edmonton, Calgary and Halifax –the present study only considers data from the London site (the Ivey Eye Institute at St. Joseph's Health Care). It is an effectiveness trial insofar as the inclusion criteria are meant to admit a range of glaucoma patients as would be seen in the clinic – the results are explicitly meant to be generalizable to the broader glaucoma population eligible for repeat laser trabeculoplasty in western countries.

3.2.3 - Treatment and follow-up schedule:

Baseline data (demographic variables and baseline IOP) is collected after patients are screened for eligibility and given informed consent. Patients are randomized to receive either ALT or SLT over 180 degrees of the angle based on a centralized web-based randomization and allocation schedule.

After receiving laser treatment (and a drop of Brimonidine to prevent post-laser spikes in IOP) there is a follow-up visit at 1 hour and patients are prescribed topical steroid (4 drops 4x/day). There are subsequently follow-up visits at 1 week and 1, 3, 6 and 12 months post-laser. The primary effectiveness outcome measure is IOP lowering 1 year

from baseline – the trial was designed specifically as a non-inferiority trial as there was no indication that either laser modality would outperform the other (Samples et al. 2011, Rolim de Moura et al. 2007, Shi and Jia 2013). Furthermore, both laser procedures are counted under the same OHIP code and there is no variation in the structure of the post-laser clinical pathways between the two.

3.2.4 - Intervention structure and cost components:

The intervention may thus be conceptualized of as 1 laser surgical visit and 6 follow-up visits consisting of a partial assessment and IOP check. Because one such visit occurs at 1 hour post-laser, we may alternatively use the idea of 6 discrete visits, one of which is the laser and 1 hour follow-up. An ophthalmologist is present at all visits and an ophthalmic technician provides assistance and reads intraocular pressures from the tonometer. There are no disposables used except for a drop of Brimonidine post-laser. Unscheduled visits, adverse events or changes in medication are available from patient charts and administrative data – these represent additional costs incurred beyond the normal course of treatment. Patient travel time and lost productivity is captured via questionnaire. Table 1 displays the expected clinical pathway in tabular form and provides a list of resource categories to consider, as will be elaborated upon in section 3.4. In particular, this particular schedule of laser and prescribed follow-ups is assumed to be normal clinical care and will be the default pathway in the decision-analytic model, relative to which all deviations occur.

Table 1 – Structure of intervention, constituent visits and their required resources

Node in clinical pathway of repeat laser trabeculoplasty	**Resources consumed**
First visit – laser treatment and follow-up at 1 hour to check for adverse events	Personnel (physician and ophthalmic tech time – laser treatment), drops of Brimonidine, capital costs of laser, patient costs (travel costs and parking, informal caregiving, lost time), Maxidex (4 drops 4x/d), any other medications.

1-hour follow-up	Personnel (partial assessment and tonometry, tech time), patient costs, changes in medication.
1 week follow-up	"
1 month follow-up	"
3 month follow-up	"
6 month follow-up	"
1 year follow-up	"
Unscheduled follow-ups and complications	Additional personnel costs, patient costs, medication.
Only for model, unlikely to be observed during trial – incisional surgery (trabeculectomy).	Personnel costs (physician, nurses, anaesthetist), medications (Ocuflox antibiotic, prednisolone)

Trial based costs

One criticism of trial-based economic evaluations is that there are often personnel and procedures encountered that are specific to the conduct of the trial and not indicative of actual clinical practice, rendering cost estimates biased relative to actual practice (Drummond et al. 2005, Sculpher et al. 2006). This trial is explicitly designed to mimic normal clinical practice at Ontario tertiary ophthalmologic clinics. There are no trial-based costs as such save for dilation and visual field examination by a technician at the 6 month follow-up visit – these costs will not enter the cost estimates. There are no extraordinary recruitment manoeuvres, increased vigilance or staff that would not be included in 'real world' practice – thus there is no need for cost adjustments of trial costs.

3.2.5 - Participants

The patients for this trial comprised those with primary open-angle glaucoma (OAG) who had previously undergone SLT and whose IOP was currently uncontrolled. The inclusion criteria admitted several different subtypes of open-angle glaucoma for whom laser trabeculoplasty is indicated – this is to increase the generalizability of the results, reflective of what is seen in ophthalmology practices. The target population to whom

these results are applicable are OAG patients in Ontario for whom repeat laser trabeculoplasty is indicated, save for complex cases or special populations (extensive ocular comorbidities, pediatric patients) as reflected in the exclusion criteria. The inclusion/exclusion criteria for this costing study are the same as those for the trial, with the added constraint that patients had to be registered at the London site. For collection of indirect costs, patients further had to have a visit in the time span between ethics approval (February 2014) and the end of data collection for this thesis (early August 2014) and to provide oral consent to participate.

Inclusion criteria for the trial

1. Registered at one of the centres of the trial.
2. More than or equal to 18 years of age
3. Diagnosis of OAG including OAG, ocular hypertension, pigmentary dispersion syndrome and pseudoexfoliation syndrome.
4. Previous 360 degree SLT (1*360 or 2*180).
5. IOP>16mmHg on at least two consecutive occasions separated by one month.
6. Two sighted eyes (sighted defined as best corrected visual acuity of 20/200 or better)
7. Willing to participate after being informed of and reading the patient information material explaining the study and the questionnaire.

Exclusion criteria

1. Evidence of secondary OAG (other than pigmentary or pseudoexfoliation) or narrow angle glaucoma (where anterior trabecular meshwork is not visible 360 degrees) as these patients would make the study population too heterogeneous.
2. Previous non-laser glaucoma surgery in the eye being considered for treatment due to possibly unpredictable changes in angle architecture.
3. Intraocular surgery anticipated in the 12 months after treatment.
4. Any corneal disease obscuring adequate visualization of anterior chamber trabecular meshwork or reliable applanation tonometry.
5. Present treatment with topical or systemic steroids or anticipated treatment with systemic steroids in the 6 months following treatment because of a high

probability condition (such as giant cell arteritis or a collagen vascular disease) as steroids themselves have a pressure increasing effect in an unpredictable fashion.

6. Previous ALT.

Starting medication status of patients

The most common treatment algorithm comprises the use of medication until failure, then laser and finally incisional surgery. There is, however, an increasing proportion of physicians who use laser first and eschew the use of medications until necessary (Katz et al. 2012, McIlraith et al. 2006). This trial admitted patients regardless of medication status (except for steroids) to reflect this changing clinical reality. The effects of varying the proportion of patients initially medicated will be examined as a series of scenarios in the model. From the Ministry perspective only the costs of medication for those over 65 will be considered. From the societal perspective, all medication costs will be considered.

3.2.6 - Cost collection and final measures of interest

Data record forms for the clinical trial, patient charts, staff interviews and patient questionnaires are used to estimate resource use for each patient and derive a patient-specific total cost for the intervention. The specific cost components and the methods for their calculation are expanded upon in section 3.4. The total cost for each patient is calculated as follows:

Let the intervention require *n* cost components for its production. Let the i^{th} cost component have unit cost *c* and let *q* be the quantity consumed (e.g. minutes of tech time, where time is valued in minutes). The total cost (TC) is the sum of the quantity of each resource used by its unit cost:

$$TC = \sum_{i=1}^{n} c_i \, q_i$$

The final measure is mean cost per patient for each of the two technologies. The mean cost is simply the arithmetic mean of total costs – let there be *N* patients and let the i^{th} patient have total cost TC_i. Then the average cost is:

$$Average\ cost = \frac{1}{N}\sum_{i=1}^{N} TC_i$$

3.3 – Model section

A decision tree was used to represent the possible clinical pathways that a patient would follow over the course a year, their probabilities and associated costs. The tree was implemented in TreeAge®. Given the short horizon of the model (1 year total), the relatively low number of possible states, no expectation of recurring states and lack of interaction between patients, a decision tree suffices to model the clinical situation and we may forego use of a Markov model. While some authors posit the superiority of discrete event simulation and microsimulation techniques (Caro et al. 2010), there is insufficient evidence to model this situation at the level of individual patients and a cohort approach is taken (Brennan et al. 2006).

The main model (henceforth the base tree – figure 1) is the same for both SLT and ALT, differing solely in the capital cost associated with each technology – as mentioned, the OHIP code for each is the same and the clinical pathways beyond the initial laser treatment are identical. Given the extensive evidence of their equivalence (Samples et al. 2011, Damji et al. 2006, Rolim de Moura et al. 2007), the two trees are identical and differ neither in overall structure nor constituent probabilities.

The only demographic characteristic on which patients are differentiated is age, where there are relevant differences in cost from the Ministry perspective for those over 65 and those under 65. In prognostic terms, only baseline IOP is a successful predictor of either ALT or SLT and age, gender and race have little prognostic value (Brooks and Gillies 1984, Martow et al. 2011, Mao et al. 2008, Bruen et al. 2012, Hodge et al. 2005) and so there are no separate branches by any of these demographic criteria. A second tree (the societal tree) has the same structure as the base tree but different payoffs, reflecting costs from the societal perspective instead of the Ministry perspective. To assess the importance of model formulation on costs, a third tree (the augmented tree – figure 2) was formulated.

3.3.1 – Structuring the tree

Overall structure was determined by consultation with a physician and a mapping of mutually exclusive states that are likely to characterize the possible pathways of patients undergoing repeat laser trabeculoplasty. In brief, patients (whether medicated or not) undergo laser. There is evidence that prior medication has no effects on success of laser surgery (Martow et al. 2011) and there is insufficient evidence to assess effects further downstream – furthermore, we assume that to the extent that such interactions occur, they occur after the 1 year of the model's horizon. Laser surgery may either be successful (using definitions in line with those of previous studies – either 3mmHg reduction in absolute pressure or a reduction of ≥20% from baseline IOP), in which case they undergo the initial normal standard of care (i.e. laser visit + 6 follow-up visits). If there is failure of the laser and IOP is uncontrolled, patients either have another medication added (which adds the costs of medication and a follow-up visit) or proceed to incisional surgery. In the augmented tree, all patients whose laser treatment failed proceed to the addition of medication. Patients may subsequently either respond favourably to the given medication or this medication may fail. At this point, either a further medication is added or surgery is indicated.

The first node is a chance node (as opposed to the more typical decision node) since we are computing expected cost for a single technology as opposed to an incremental cost. The entire tree can be viewed as the subtree to be entered into an ALT/SLT incremental analysis – the outcome is the expected cost for the single technology. The expected cost under this scenario functions analogously to average cost in the trial scenario. The same sort of model of cost would also be used for a single technology appraisal or budget projection (cf. Cantor et al.'s 2008 cost projection in Markov format, or Mar et al.'s 2008 projected burden of stroke costs).

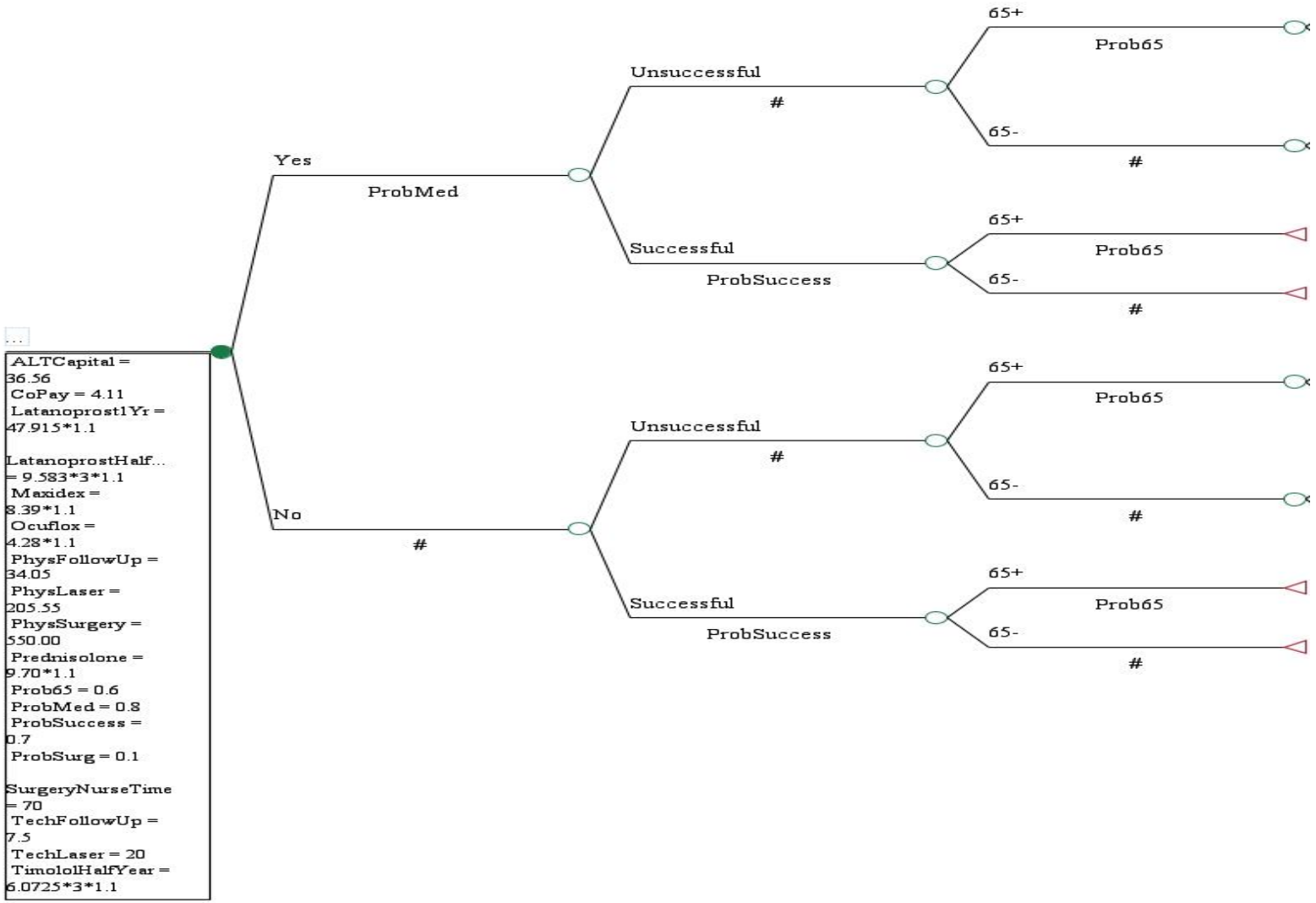
...
ALTCapital = 36.56
CoPay = 4.11
Latanoprost1Yr = 47.915*1.1
LatanoprostHalf... = 9.583*3*1.1
Maxidex = 8.39*1.1
Ocuflox = 4.28*1.1
PhysFollowUp = 34.05
PhysLaser = 205.55
PhysSurgery = 550.00
Prednisolone = 9.70*1.1
Prob65 = 0.6
ProbMed = 0.8
ProbSuccess = 0.7
ProbSurg = 0.1
SurgeryNurseTime = 70
TechFollowUp = 7.5
TechLaser = 20
TimololHalfYear = 6.0725*3*1.1
Yes
ProbMed
No
#
Unsuccessful
#
Successful
ProbSuccess
65+
Prob65
65-
#
Unsuccessful
#
Successful
ProbSuccess
65+
Prob65
65-
#

Figure 1 - Base tree model, ALT

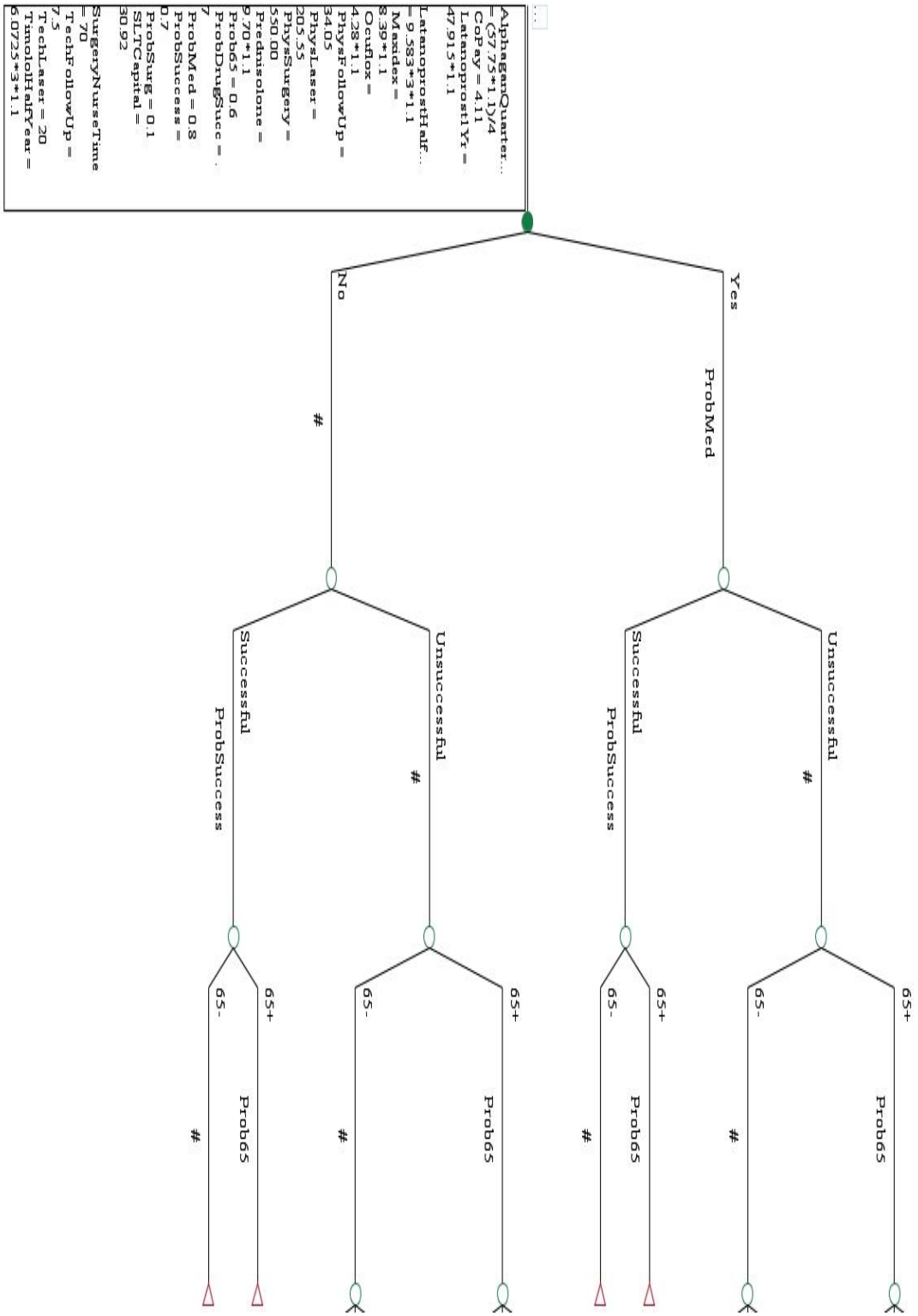
AlphaganQuarter...
= (57.75*1.1)/4
CoPay = 4.11
LatanoprostIYr =
47.915*1.1
LatenoprostHalf...
= 9.583*3*1.1
Maxidex =
8.39*1.1
Ocuflox =
4.28*1.1
PhysFollowUp =
34.05
PhysLaser =
205.55
PhysSurgery =
550.00
Prednisolone =
9.70*1.1
Prob65 = 0.6
ProbDrugSucc =
.7
ProbMed = 0.8
ProbSuccess =
0.7
ProbSurg = 0.1
SLTCapital =
30.92
SurgeryNurseTime
= 70
TechFollowUp =
7.5
TechLaser = 20
TimololHalfYear =
6.0725*3*1.1
Yes
No
ProbMed
#
Unsuccessful
Successful
ProbSuccess
65+
65-
Prob65
#

Figure 2 - Augmented tree model, ALT

3.3.2 - Descriptions of tree branches and parameters

Medicated vs. Unmedicated

A patient is assigned to a laser modality (ALT in the case of fig. 2), prior to which there is a probability *ProbMed* that they either are or are not on initial medications. If the patient is on medication, it is assumed they are on a standard dose (1x/d.) of generic Latanoprost, as Latanoprost remains the most widely prescribed first line treatment for OAG (McKee et al. 2005).

For the base case, *ProbMed* was set to 0.8, representing 80% of patients starting on medication and 20% starting without. Consultation with ophthalmologists in London and Toronto led to the conclusion that there are no reliable estimates of this probability, but that initial medication remains first-line treatment for the majority of physicians (Schwartz and Budenz 2004).

ProbMed represents our first planned sensitivity analysis, given the uncertainty around this parameter. *ProbMed* will be varied between 0 (a cohort entirely naïve to medication) and 0.8 (vast majority medicated – also the chosen parameter value in the model). In this manner we examine the effects of medication on overall expected cost.

Successful vs. Unsuccessful

A successful treatment is one in which IOP is satisfactory on all follow-up visits and the patient has no complications, no changes in medication and no unscheduled visits. Regardless of medication status, a patient has successful trabeculoplasty with probability *ProbSuccess*. In the base case, *ProbSuccess* was set to 0.7 in accordance with the few studies on repeat laser trabeculoplasty (Hong et al. 2009) as well as systematic reviews and large trials of laser trabeculoplasty (Wang et al. 2013, Damji et al. 2006). If the patient is successful then the pathway reaches a terminal node. This defines 3 payoffs, one for those who start on no medications and two for those who start on medication, depending on their age:

Payoff(no meds, successful) = Personnel + capital costs

Payoff(meds, successful, 65+) = Personnel + capital costs + costs of 1 year Latanoprost

Payoff(meds, successful, 65-)= Personnel + capital costs

The proportion of patients requiring extra medications or surgery is *1-ProbSuccess*. In the base model, patients either proceed to extra medication or immediately to surgery. In the augmented model, all patients with failed treatment proceed to medication that either works, requires still further medication or surgery.

ProbSuccess is a key parameter of uncertainty and, like *ProbMed*, will be a target for sensitivity analysis between *ProbSuccess*=0.30 (a majority of patients failing) to *ProbSuccess*=0.80 (a majority having successful laser).

Assumptions regarding medication

As indicated, patients who start on medications start on once daily generic Latanoprost. For any patients whose laser surgery fails and who proceed to medication, it is assumed that on average this occurs halfway through the year. Initially unmedicated patients will incur the costs of a half-year of Latanoprost. Patients who started on Latanoprost will continue on Latanoprost (incurring the cost of 1 year Latanoprost) and will add a half-year of Timolol maleate twice daily. The calculation of costs of medication is based on results from Rylander and Vold (2008) and is available in appendix A. Only the medication costs of those patients 65 years or older is included in the Ministry perspective as the Ministry pays for these patients.

In addition to the costs of medication, failure of laser and addition of medication is assumed to require an extra-follow up visit to gauge the acceptability and effectiveness of the new medication.

In the augmented tree the initial addition of medication is at half-way through the year as in the base tree. If further medication is required, it is assumed to occur on average at 9 months (halfway between the first added medication and the end of the trial), thus patients incur the costs of 3 months of medication of this additional medication. Among initially unmedicated patients, the first medication is Latanoprost and second medication is Timolol maleate. For those initially on Latanoprost, the second medication is Timolol and the third medication is Brimonidine (thrice daily).

Surgery

While not observed during the course of the trial at this centre, at other trial centres there have been patients who have proceeded to incisional surgery during the course of the year. Considering that these patients' glaucoma has progressed to the point of being uncontrolled by previous laser (and possibly medication) and given previous findings that patients proceed to surgery within one year of first laser (Damji et al. 1999, 2006), this is not implausible. In the base tree, upon failure of laser the patient is assumed to undergo incisional surgery half way through the year. Among initially medicated patients, Latanoprost is discontinued (thus patients incur the costs of half a year of Latanoprost). The surgery itself requires physician time and two hours of nurse time (two nurses for one hour each). Furthermore, patients are prescribed antibiotics (Ocuflox 4x/d. for 1 month) and prednisolone acetate (4x/d. for 1 month). Two follow-up visits are needed in addition to normal care – 1 on which surgery is indicated, 1 follow-up post-surgery.

In the augmented tree, surgery is assumed to occur at 9 months. Patients discontinue all glaucoma medications, thus initially medicated patients incur the costs of 9 months of Latanoprost and 3 months of Timolol. Initially unmedicated patients incur the costs of 3 months of Latanoprost. Additional visits, antibiotics and prednisolone costs are as above.

Other parameters and considerations

In the base tree, the probability of surgery is *ProbSurgery* and is assumed to be 0.1, indicating that 10% of failed patients will proceed to surgery immediately (cf. Damji et al. 1999, 2006). This will be varied in sensitivity analyses between 0.0 and 0.4.

From the Ministry's perspective it is relevant whether or not a patient is older than or less than 65 as the former have their medications paid for by ODB. This parameter is *Prob65* in the model and is set to 0.6. Data from the NIH[1] indicates that 60% of glaucoma patients are over 65 years old. The age distribution of the population in Canada is similar to that of the USA[2] and so this figure is used in the base case. Several studies have found that age is not a prognostic factor for laser success (Martow et al. 2011, Mao et al. 2008)

[1] https://www.nei.nih.gov/eyedata/glaucoma.asp
[2] http://www.statcan.gc.ca/pub/91-003-x/2007001/figures/4129875-eng.htm

and so probabilities are invariant by age. In practice, there is considerable variation in the average of participants by study – the individual studies analysed in Wang et al.'s meta-analysis of SLT trials (2013) had average participant ages that ranged from 50 to 73. As such, *Prob65* will be varied between 0.3 (a young cohort) to 0.8 (an older cohort).

There are contradictory findings regarding the increased or decreased need for adjunctive medications after laser surgery (Wang et al. 2013, Shi and Jia 2011), however the most typical model of care assumes that medications are continued after laser. We assume that medications are only discontinued in the case of incisional surgery.

The augmented tree has a further parameter – the probability that medication will succeed after initial failure of laser treatment (*ProbDrugSucc*). *ProbDrugSucc* and *ProbSurg* (proportion of those who fail laser treatment proceeding to surgery, *after* unsatisfactory response to additional medication) determine the proportion for whom medication fails and who proceed to further medication. *ProbSurg* is 0.1 as above and *ProbDrugSucc* is set at 0.7. These values were derived from expert opinion in the absence of other sources and are varied in sensitivity analyses.

3.4 - The treatment of direct costs

Labour - Physician time

Description – initial performance of laser surgery, follow-up visits consisting of partial assessment and tonometry at 1 hour, 1 week and 1, 3, 6 and 12 months post-laser for a total of 1 laser appointment and 6 scheduled follow-ups.

Unscheduled visits may occur due to uncontrolled IOP and have the same fee as the scheduled follow-up visits. While not observed during the trial, for the model it was assumed that patients may progress to trabeculectomy within the one-year post laser based on previous reports (Damji et al. 1999, 2006) and institutional experience.

Trial estimation:

- Quantity: patient charts were examined to determine whether patients underwent the normal, protocol-mandated course of appointments or whether there were any extra visits or missed visits (in which case the physician would not bill).
- Valuation: OHIP fee schedule.

- Unit cost: laser visit – $205.55 (OHIP fee code E134), each follow-up visit – $34.05 (OHIP code A234 – partial assessment $28.95 + G435 tonometry $5.10).

Model estimation:

- Quantity use: each branch of the tree terminates in a cost for that scenario. Standard care consisted of a single laser visit and 6 follow-up visits as in the trial. Branches of the decision tree where there was a failure of laser and the addition of medication required an extra follow-up visit. Branches with surgery required two follow-up visits and the performance of trabeculectomy.
- Valuation: OHIP fee schedule.
- Unit cost: As above, with addition of OHIP E132 (glaucoma filtering procedure) - $550.00.

Perspective:

- No difference between Ministry and societal perspective.

Labour - Ophthalmic technician time and nurse time

Description – an ophthalmic technician was present with the ophthalmologist to perform tonometry and other procedures. For the surgery scenario in the model, it was assumed that two hours of nurse time would be needed, comprising the one hour of surgery and involving two nurses.

Trial estimation:

- Quantity use: interviews with the trial ophthalmic technician were used to estimate the typical amount of time a technician would spend during a laser visit and during a follow-up visit. It was found that the technician spent an average of 40 minutes during the laser visit and 15 minutes at each follow-up visit.
- Valuation: the average wage of ophthalmic technicians at SJHC was obtained from Healthcare Materials Management Services payroll services. This was $30 per hour.
- Unit cost: $0.50/minute.

Model estimation:

- Quantity use: we assumed that the average time values from above were representative of the procedure as is performed in tertiary ophthalmology clinics in Ontario. In the absence of literature results to indicate otherwise, we were compelled to assume that this was so. For nurse time the average hourly wage was obtained from HMMS.
- Valuation: we assumed that the wage listed above was representative of ophthalmic technicians in tertiary ophthalmology clinics, as distinct from technicians in private practices or ophthalmic nurses. Interviews with payroll and the trial ophthalmic technician in question confirmed that this was likely a reasonable value, as contrasted with the average wages at smaller, private clinics. For nurses, we assumed that one hour was necessary for the surgery and that two nurses were required.
- Unit cost: $0.50/minute for technician, $31/hour for nurses.

Perspective:

- Same for Ministry and societal.

Capital costs

Description – capital costs reflect expenditures on the equipment needed to provide the intervention.

Trial estimation: Estimates were developed using values from the Healthcare Materials Management Services at St. Joseph's Healthcare.

- Quantity use: each patient has the same capital cost.
- Valuation: in conjunction with HMMS, the cost of each laser (L), a single tube replacement (TR), exam chair (EC), service contract (SC), annual lens replacement cost (LR), per patient medication and supplies cost (MS – comprises tonometry cleaning supplies, drops of Brimonidine, gel for lens application), number of patients (N) and laser lifetime in years (Y) were obtained, and the following scheme was used to assign a per patient capital cost (Drummond et al. 2005):

$$per\ patient\ capital = \frac{L + TR + EC + (SC * Y) + (LR * Y) + (MS * N * Y)}{(N * Y)}$$

Specific values were:

Table 2 - Capital cost calculations

Cost item	**ALT**	**SLT**
Laser (L)	$180,000	$70,000
Tube replacement (TR)	$25,000	N/A
Exam chair (EC)	$5,000	$5,000
Service contract (SC)	$8,800/year	$5,085/year
Lens replacement (LR)	$500/year	$500/year
Medications/supplies per patient (MS)	$1/patient	$1/patient
Lifetime of laser (Y)	8 years	8 years
Number of patients per year (N)	1,000	500
Cost per patient	$36.56	$30.92

- Unit cost – $36.56 for ALT, $30.92 for SLT.

Model estimation:

- Quantity use: a single capital charge for each patient.
- Valuation: it is difficult to estimate capital charges for other hospitals or for an 'average' tertiary ophthalmologic clinic. It was assumed that the above figures represented what any hospital in Ontario would pay and that differences would

arise primarily in annual patient volume, with higher numbers at large clinics like Toronto leading to a lower per patient capital cost and lower numbers at smaller clinics leading to higher per patient capital costs.

- Unit costs: as in the trial, with the value of *N* in the above equation varied in sensitivity analyses. As noted by Adam et al. (2003), capacity utilization is rarely considered in costing studies and could plausibly make a difference in the average cost of services, all else held constant. Patient volume is a key component of capacity utilization and we assess whether different annual patient visits affects expected costs. Capital costs were calculated for annual patient volume between 100 and 5000 patients annually. These capital costs were used in the model and the resultant expected costs were calculated.
- *Perspective:* Same unit cost for Ministry and societal perspectives.

Medications

It is in the treatment of medications that trial and model diverge and that the Ministry and societal perspectives differ. While in the trial there is individual patient-level data on actual use of medications, in the model we assume the most commonly observed procession of medications (McKee et al. 2005, Cantor et al. 2008). Furthermore, for the Ministry perspective, only drugs on the formulary are considered, and then only for those on the Ontario Drug Benefit (ODB) plan, comprising seniors 65+ and low-income persons. For the societal perspective, all drugs are considered regardless of their formulary status and the patient's ODB status. In the trial the patient's age is available to indicate ODB status. In the model the 65± distribution is modelled based on figures from the NIH and Statistics Canada.

There are medications which all patients receive as part of treatment – brimonidine post-laser (which is included in capital costs, as the hospital provides it), and a prescription for Maxidex (4x/day for 4 days). As indicated in section 3.2, there is variability in whether or not patients start the trial on medications or not. This is recorded directly in the trial costing. In the model we assume that a certain percentage begin on medication and vary this percentage in sensitivity analyses – assumptions viz. the procession of medication classes is listed in the model section. Unit costs are derived from the Ontario formulary.

Translating bottle volume into number of drops is done by making reference to studies by Rylander and Vold (2008) – unit costs and refill schedules are expanded upon in Appendix A.

It is assumed that patients are prescribed generics where available and that patients are prescribed the minimum commercially available volume for each prescription (considering the limited lifetime of some ophthalmic medications, cf. Frenkel et al. 2007, and the need for regular visits, it's unlikely that large volumes will be prescribed at any one visit). In the event of multiple medications, it is assumed that all medications are put onto one prescription and refilled at the rate of the medication that needs to be refilled most frequently. It was assumed that all medications were taken unilaterally, as was laser.

Trial estimation:

- Quantity use: all patients received Brimonidine and a prescription for Maxidex after first laser. Starting ophthalmic medications or the addition of adjunctive medications were determined by examining patient charts for medication type. Ophthalmic medication has standard dosages which were obtained from an ophthalmologist. Frequency of necessary refill was assessed by supposing that patients purchased the minimal available amount and there was 100% adherence. Each instance of filling a prescription by ODB patients was accompanied by the Ministry's payment of a dispensing fee to the pharmacy. Age was obtained from patient charts and only medications for patient 65 or older were included in the Ministry perspective.
- Unit cost: Brimonidine was included in the capital costs above. For Maxidex and all other medications, Ministry relevant prices were obtained from the Ontario formulary, schedule of refills and number of drops per bottle are available in Appendix A. A 10% markup was included on all drugs as the Ministry pays this markup. A $4.11 payment per prescription was added to the cost of drugs for those covered in the Ministry perspective, representing the Ministry payment of a dispensing fee for ODB patients. For the societal perspective, a full $6.11 additional cost per prescription was assumed for patients 65 or older, reflecting

the $4.11 Ministry payment and $2.00 patient copayment. For non-ODB patients formulary drug costs plus a 10% markup were used.

Model estimation:

- Quantity use – patients were assumed to start on Latanoprost and to proceed to Timolol maleate as needed. In the surgery situation, Ocuflox and prednisolone acetate are prescribed, both 4x/d. for 1 month. Specific assumptions regarding length of medication and costs incurred are available in the model section.
- Unit costs: as for the trial, listed in detail in Appendix A.

Perspectival issues:

This is an item on which perspectives diverge. From the Ministry perspective, all drugs given in hospital and all drugs issued to patients on the ODB are costs. Thus drugs that are not on the formulary or those given to patients under 65 are not costs – they are covered by private insurance or out-of-pocket payments.

For the societal perspective, the costs of all drugs are included regardless of patient age. A 10% pharmacy markup is assumed as is a full $6.11 for those 65 and older (representing Ministry payment of dispensing fee + $2 ODB patient co-payment) copayment for ODB patients. The price of drugs for those not on ODB is assumed to be the same price as on the formulary with the 10% markup.

Costs not considered

Administrative time was not considered as it was assumed to be minimal. The costs of buildings, overheads and infrastructure other than the laser equipment. These costs are difficult to ascertain and assigning them to specific procedures suffers from an irreducible arbitrariness and sensitivity to methods (Tan et al. 2009, Finkler et al. 2007, Barnett 2009).

3.5 - The treatment of indirect and patient travel costs

Indirect costs refer to the value of lost time and productivity as a result of morbidity, mortality or undergoing treatment (Drummond et al. 2005). Transportation costs are direct non-medical costs and are often grouped together with indirect costs as costs borne

by patients – furthermore, both costs are rarely considered in applied studies (Neumann 2009, Drummond et al. 2005). These costs are not considered from the Ministry perspective but are components of the societal perspective, which is a secondary perspective of interest in the Canadian context (CADTH 2006). There is enduring controversy about the relevance of the societal perspective (Currie et al. 1999). Previous studies on the costs of trabeculoplasty elected not to consider indirect costs due to the difficulty of estimation (Lee and Hutnik 2006, Stein et al. 2012). This study examines indirect costs and transportation costs using a patient questionnaire based on a modified version of a questionnaire by Thompson and Wordsworth (2011), developed in conjunction with an ophthalmologist to capture cost categories most relevant to this patient group and intervention. This questionnaire was administered verbally to patients at one of their follow-up visits by either the author or the ophthalmic technician after verbal consent was provided. In addition to providing an estimate of the difference between the societal and Ministry perspective for repeat laser trabeculoplasty, the present study contributes an estimate of average travel requirements for a tertiary ophthalmologic clinic in Southwestern Ontario and the demographic characteristics of patients which will be of value for future studies.

Overall approach to valuing lost time – theoretical preamble

The valuation of indirect costs is not straightforward (Liljas 1998). Three broad approaches exist – the human capital approach, friction costs and inclusion in QALY type measures. Since QALYs are unavailable for our problem and we are interested in monetary valuations, we will not discuss QALYs further – furthermore, there are conceptual difficulties in incorporating indirect costs into QALYs including the potential for double-counting (Jacobs and Fassbender 1997). The human capital approach assumes that the value of a person's working time is captured by their gross wage and that leisure time is valued at net wage (Drummond et al. 2005). The friction cost approach considers that the costs to society of a worker's incapacity due to illness is equal to the costs to replace that worker during a short 'friction' transitional period of adjustment and replacement. As such, the cost to society is the cost of replacing this work, or the cost of the 'friction' transitional period (Brouwer and Koopmanschap 2005).

In this study we opted for the human capital approach as outlined in Drummond et al (2005). Friction costs are associated with numerous theoretical problems and are not straightforward to compute (Liljas 1998). The human capital approach is more analytically tractable.

Glaucoma typically affects older people; unsurprisingly, a lot of patients are retirees. There is little guidance on how to value the time of retired persons or leisure time – indeed, to the extent that the value of time is considered at all in economic evaluations, time lost from work is usually the only component considered. In the absence of guidance otherwise, we followed the practice of Sharma et al. (2010) and valued both retiree and leisure time at 30% of gross wage.

The following cost components are considered for the societal perspective:

Patient time

Trial – a modified questionnaire based on Thompson and Wordsworth (2011) was used to ask patients about their employment status and what their use of time would have been had they not been at this appointment. Patient time at each visit was calculated as visit length (as from interviews with the ophthalmic tech regarding average visit length – 2 hours for initial laser visit and follow-up, 30 minutes for all subsequent visits) + 2*(time of 1-way trip). For each of the five following stand-alone follow-up visits it was assumed that the same stated amount of time taken off would obtain for all five visits.

Model – 12% of those over the age of 65 were assumed to be employed based on available 2010 figures[3]. Among those younger than 65, 7% unemployment (from the latest Statistics Canada figures)[4] was assumed.

Unit costs – average Ontario hourly wage for the age range among trial participants. Overall average hourly Ontario wage for model purposes. Retiree and leisure time were valued at 30% of the preceding values.

Transportation costs

[3] The Chief Public Health Officer's Report on The State of Public Health in Canada 2010
[4] http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/lfss01b-eng.htm

Trial – Patients were asked what their mode of transportation was, it was assumed that the same mode of transportation was used for all visits. Patients were asked to provide estimates of the one-way distance to the hospital and their travel time. For purposes of analysis, the shortest Google Maps™ distance from the patient's home address to the hospital was used after some glaring disparities between stated and actual distance. The total distance over the whole intervention was (number of individual visits*2) *one-way distance. Transportation time was included under patient time costs as above. The listed Google Maps™ time for a one-way journey was used for this purpose.

Trial unit cost – the CADTH (2006) guidelines do not list a preferred method of valuing transportation. We used Canada Revenue Agency's automobile allowance rates and assigned 54 cents per kilometre which captures the average costs of fuel, maintenance and vehicle depreciation.

Model – The trial average distance was used in the absence of available data for distances to tertiary ophthalmologic clinics in Ontario. Unit costs were the same.

The time of those accompanying patients

Trial – Patients were asked whether anybody accompanied them to their visit. If so, their employment status was ascertained. If they were gainfully employed, the amount of time taken off to accompany the patient was ascertained. It was assumed that the same amount of time would be taken off for all follow-up visits (unless otherwise stated).

Unit cost – average hourly wage for employment category if employed, 30% thereof if retired or not taking time off gainful employment.

Model – Based on expert opinion and the findings of Sharma et al. (2010), we assumed that 50% of patients were accompanied by somebody. We made the simplifying assumption that the accompanying person's employment status matched the patient's (e.g. a retired patient being accompanied by their retired spouse).

Informal caregiving

While this was included as a cost category in the questionnaire, it was found that nobody made use of informal caregiving (e.g. for watching children or housekeeping during the visit), as such this category was not considered.

3.6 – Final analyses and measures

Trial-based: demographic characteristics of patients, including information on indirect cost categories. Descriptive statistics of cost – disaggregated table of mean cost per resource category (± SD). Total mean cost (± SD) in 2014 Canadian dollars for each intervention under the Ministry perspective. Analysis of percentage of total cost contributed by each cost component, thus identifying the main drivers of cost.

Model-based: rollback analysis on the tree produces an expected cost for each laser modality. Expected costs are then listed for sensitivity analyses on *ProbMed, ProbSuccess, ProbSurgery* and *Prob65*, as well as for varying patient volume. Tornado diagrams are presented to ascertain those variables most responsible for changes in expected cost.

Comparative analysis: difference in absolute dollar terms and percentage difference between trial-based mean cost and model-based expected cost under the base case and Ministry perspective.

Secondary analyses: mean cost and expected cost for trial- and model-based societal perspective.

Chapter 4 - Results

4.1 – Ministry perspective

Data was available for 16 participants in total, 8 in the SLT arm and 8 in the ALT arm. 7 participants in the SLT arm and 6 participants in the ALT arm provided information on indirect costs. Demographic characteristics are listed in table 3 as are trial-derived costs in table 4. Tables 5 and 6 provide results from the model and sensitivity analyses. Table 7 examines the performance of the augmented model. Figures 3 and 4 consist of a tornado diagram showing relative sensitivity to key parameters and an examination of patient volume effects on expected costs, respectively. Finally, table 8 compares overall structure and parameter values from the model and trial.

Table 3 - Trial patient demographic characteristics

Characteristic	**ALT**	**SLT**
	n = 8	*n* = 8
Average Age (± SD)	67.8 (± 6.8)	63.7 (± 9.7)
Male/Female	5M, 3F	4M, 4F
Number starting on medication	1/8	2/8
Complications and additional medication	1 patient with extra follow-up visit and medication	No complications
Right/Left Eye	6/2	5/3

Table 4 - Trial-based costing, Ministry perspective

Cost category[5]	ALT	SLT	ALT % of Total	SLT % of Total
	n = 8	*n* = 8		
LASER VISIT				
Personnel[6]	225.55 (0)	225.55 (0)		
Capital	36.56 (0)	30.92 (0)	6.93%	5.73%
FOLLOW-UP VISITS				
Personnel	249.3 (22.21)	249.3 (0)		
Personnel total - physician	409.85 (18.20)	409.85 (0)	77.66%	75.96%
Personnel total – tech	65 (4.01)	65 (0)	12.32%	12.05%
Personnel total – TOTAL	474.85 (22.21)	474.85 (0)	89.98%	88.0%
DRUGS	16.34 (30.76)	33.81 (85.06)	3.10%	6.27%
TOTAL COST, MINISTRY PERSPECTIVE	**527.75** (37.94)	**539.58** (85.06)		
Minimum, maximum individual patient costs	469.86, 602.11	505.77, 749.55		

[5] All costs in 2014 Canadian dollars.
[6] Consisting of physician and ophthalmic technician time.

Table 5 - Model-based costs, Ministry perspective (2014 Canadian dollars)

	ALT	SLT
Expected value	568.52	562.88
Min, max[7]	491.41, 1259.86	485.77, 1254.22
Univariate Sensitivity Analyses:		
Prob65 (30%-90%)	546.12, 590.92	540.48, 585.28
ProbSuccess (30%-80%)	616.41, 556.55	610.77, 550.91
ProbMed (unmedicated-80% initial medication)	538.01, 568.52	532.37, 562.88
ProbSurg (0%-40% of those whose laser failed)	549.27-**626.27**[8]	543.63, **620.63**

Table 6 - Ministry perspective, scenario analyses that caused >10% deviation in expected value

	ALT	**SLT**
Bivariate 1: Low success, older cohort	641.22	635.58
Bivariate 2: High progression to surgery, older cohort	647.78	642.14
Bivariate 3: Low success, high rates of surgery	751.16	745.52
Bivariate 4: Highly medicated, highly surgeried	626.27	620.63
Trivariate 2[9]: Old, unsuccessful, surgery	773.88	768.24

[7] The minimum and maximum branch values for the reference case.

[8] Bolded entries result in over 10% deviation from initial expected value.

[9] All trivariate sensitivity analyses including ProbMed reduce to the bivariate case because the uppermost value of ProbMed is the same as the value in the base tree.

Table 7 – Augmented tree model, expected value and sensitivity analyses

		ALT	SLT
Augmented tree – base case		573.17 (8.6% deviation from trial, 0.8% from base model)	567.53 (5.2% deviation from trial, 0.8% from base model)
ProbDrugSucc	ProbSurg		
1	0	549.27	543.63
0	0	564.39	558.75
0	1	758.05	752.41
0.5	0.5	653.66	648.02
0.5	0.25	605.24	598.09

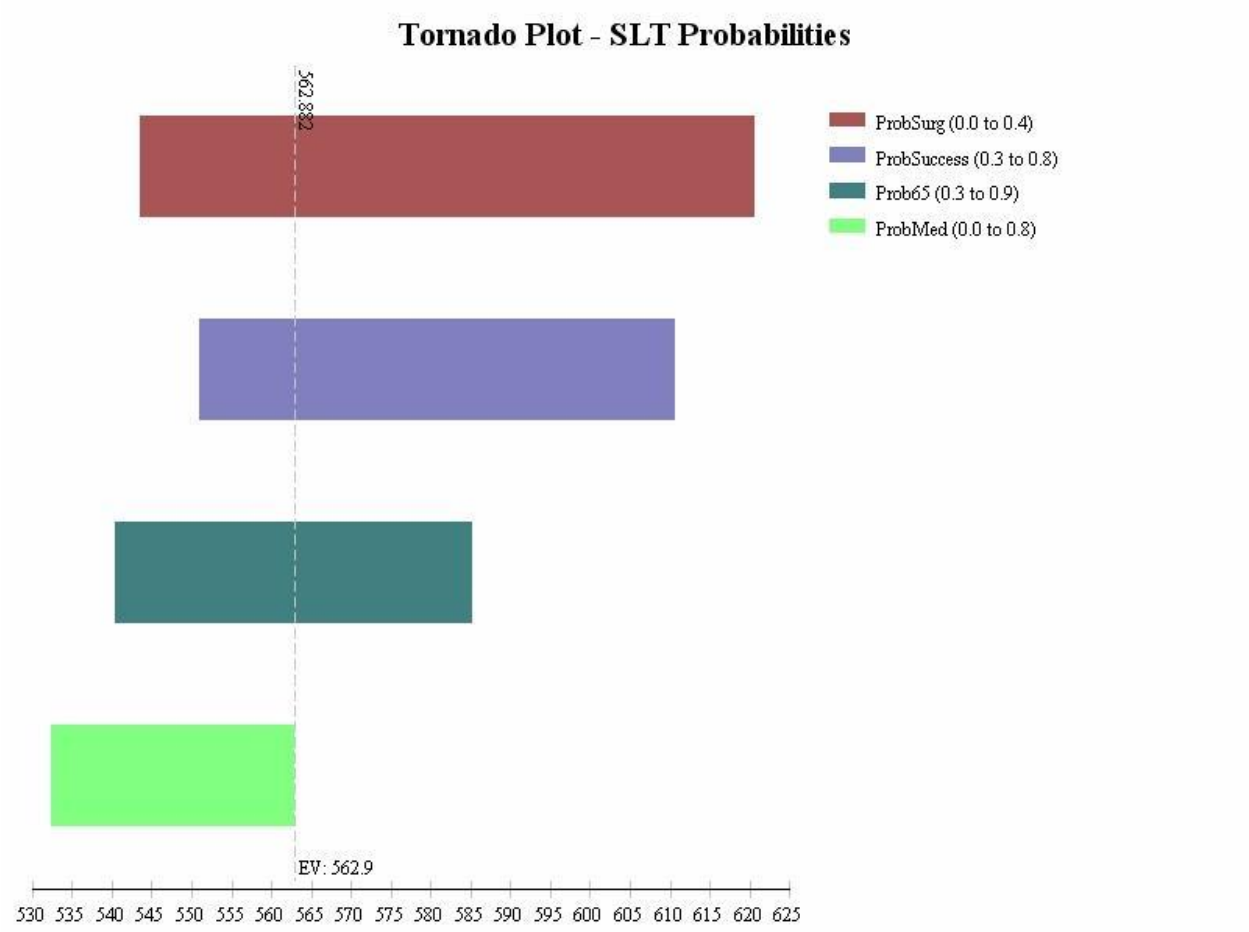

Figure 3 - Tornado diagram - Ministry perspective, base tree SLT

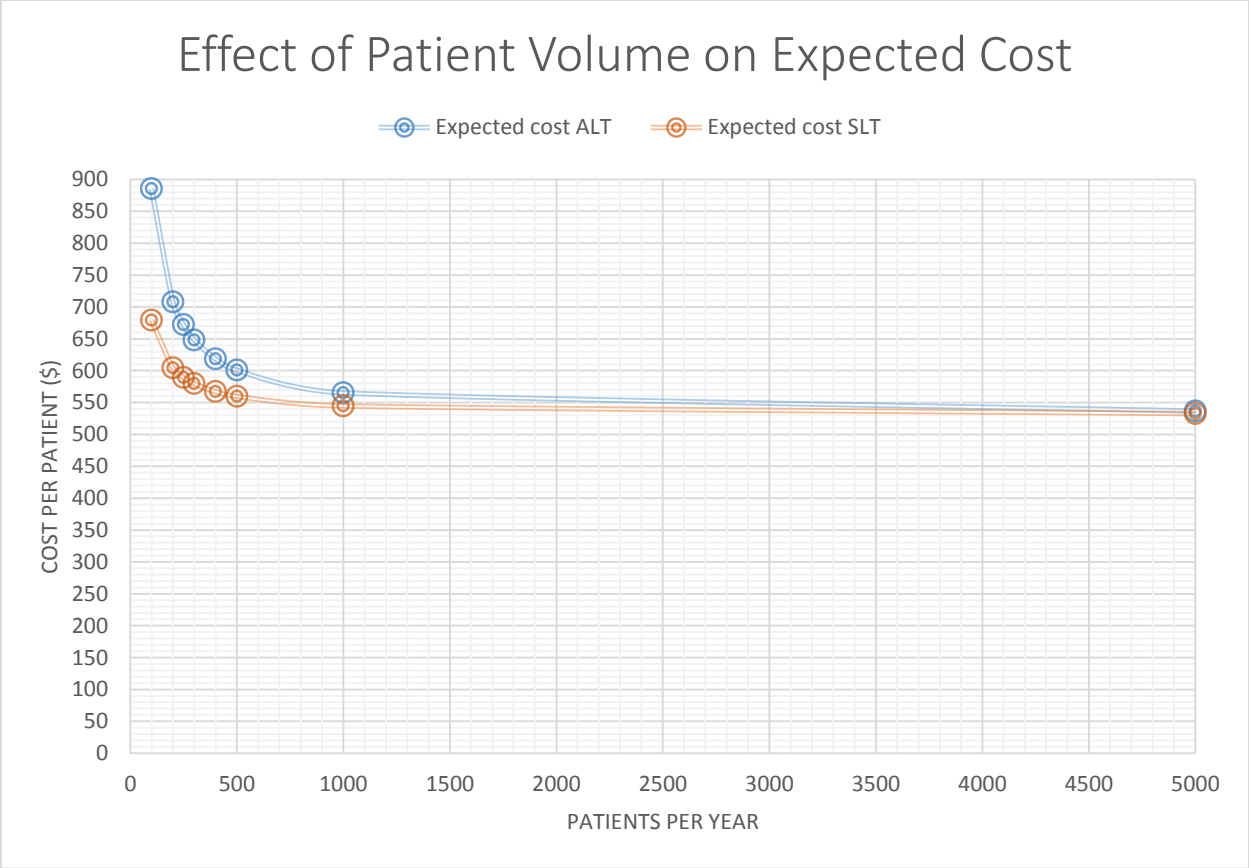

Figure 4 - Effects of patient volume on expected cost - ALT and SLT

Table 8 - Comparison of model (base tree) and trial parameters and characteristics

Variable	ALT Trial	SLT Trial	Model
Percent medicated	12.5%	25%	80% (reference case)
Types of adjunctive medication	Co-Dorzotimolol (1 patient under 65 on Travatoprost)	Latanoprost, Co-Dorzotimolol, Bimatoprost	Latanoprost, Timolol
Percent failure	12.5%	0%	30%
Surgery	0%	0%	20%
Mean/expected cost, model deviation from trial	$527.75	$539.58	568.52 (8% deviation – ALT), 562.88 (4% deviation, SLT)

4.2 – Societal perspective

Seven participants in the SLT arm and six participants in the ALT arm provided information on indirect costs. Obtained values for patient time use, accompanying persons and transportation are listed in table 9. Trial-based estimates of societal costs are in table 10. Table 11 presents results from modelling of societal costs and figure 5 shows sensitivity to key parameters in the societal model.

Table 9 – Patient time use and transportation characteristics

Characteristic	**ALT**	**SLT**
	n = 6	*n* = 7
Mode of transportation	100% Car	100% Car
Average one-way distance to SJHC (km ± SD)	38.7 (± 39.5)	38.6 (± 45.8)
Average one-way time to SJHC (min. ± SD)	37.75 (± 34.52)	35.4 (± 35.65)
Employment status/alternate use of time	4/6 retired, 2/6 working	5/7 retired, 2/7 working
Accompanied by anybody?	4/6 (spouse)	4/7 (3 spouse, 1 child)
Time use of accompanying person	3 retired, 1 working	2 retired, 2 working
Informal caregiving	0%	0%

Table 10 - Trial-based costs - societal perspective

Cost category[10]	ALT	SLT	ALT % of Total	SLT % of Total
	n = 8	*n* = 8		
Personnel total – TOTAL	474.85 (26.28)	474.85 (0)	44.92%	41.12%
Capital	36.56	30.92 (0)	3.46%	2.68%
DRUGS	40.64 (46.42)	51.84 (89.53)	3.84%	4.49%
Transportation	**251.64** (278.49)	**185.14** (257.09)	23.80%	16.03%
Parking	31 (2.53)	31 (0)	2.93%	2.68%
Patient time	148.76 (90.26)	138.98 (140.21)	14.07%	12.03%
Accompanying person time	73.72 (75.96)	241.98 (476.32)	6.97%	20.96%
Lost time, all persons	222.49 (136.37)	380.96 (608.03)	21.04%	32.99%
Total	1057.18 (383.2)	1154.71 (805.23)		

Table 11- Model analysis of societal costs

	ALT	SLT
Expected value	$1146.64 (8.5% deviation from trial)	$1141.00 (1.2% deviation from trial)
Univariate sensitivity analysis on *FuTime*[11] (1-4 hours)	1089.20, 1433.89	1083.56, 1428.25

[10] All costs in 2014 Canadian dollars.

[11] Average length of follow-up visit, increases may arise from increased transportation time, visit length or waiting time.

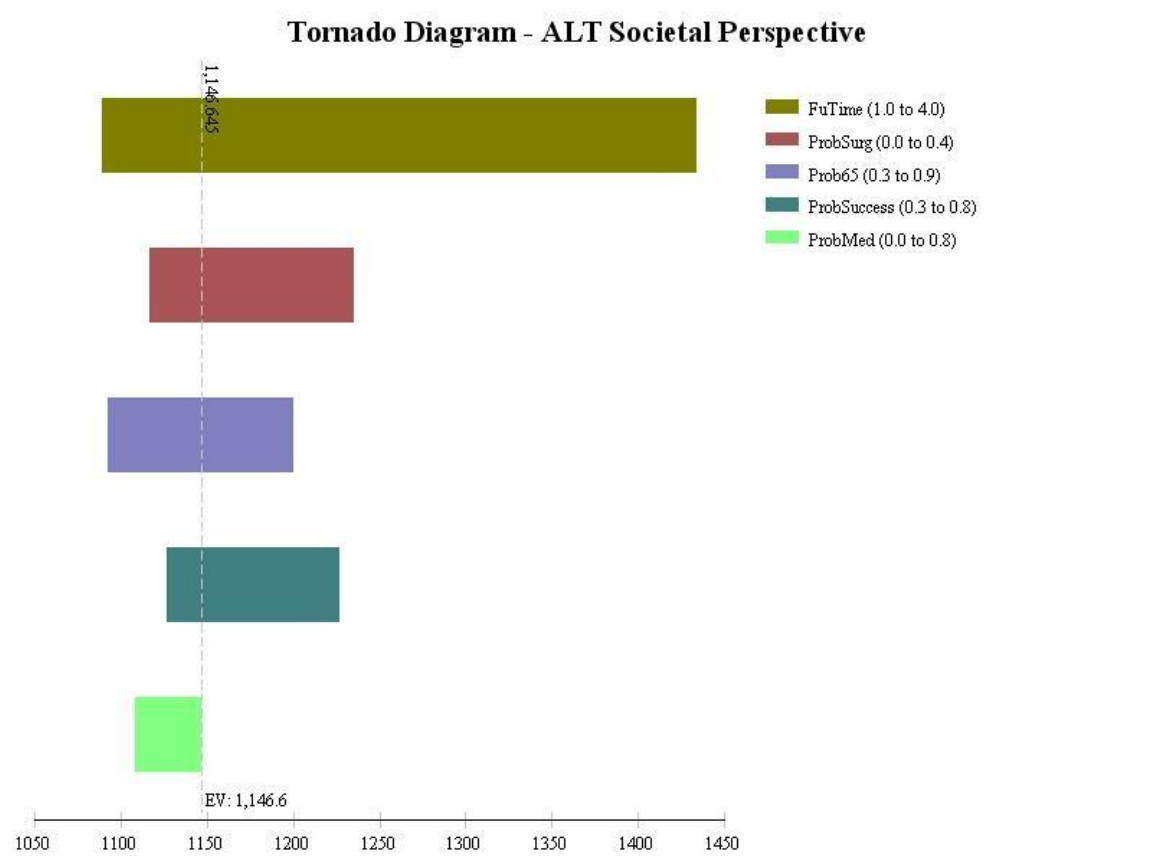

Figure 5- Tornado diagram – societal perspective, ALT

Chapter 5 – Discussion

5.1 – Results

5.1.1 – The Ministry perspective

In this thesis we examined the costs of repeat laser trabeculoplasty among glaucoma patients in Ontario from the Ministry perspective using two methods – empirical trial-based costing and model-based costing. In doing so, we aimed to take a representative glaucoma problem and determine whether less labour-intensive modelling methods provide a valid substitute for direct measurement of cost. Empirical costing undertaken alongside an effectiveness trial was used as the gold standard cost to which we compared model estimates. Secondary aims were assessing the impact of indirect costs on total costs (and thus the divergence of the societal and Ministry perspectives), determination of those variables to which costs were most sensitive, and to present a detailed profile of trabeculoplasty costs in Ontario using microcosting.

From the Ministry perspective, the trial and model estimates did not differ appreciably (ALT: $527.75 vs. $568.52 – an 8% difference, SLT: $539.58 vs. $562.88 – a 4% difference). Labour accounted for the vast majority of costs, comprising almost 90% of total costs. Physician fees alone accounted for nearly 80% of total costs – drugs and capital expenses accounted for slightly more than 10% of total costs in both cases.

We note that the model and trial estimates closely agreed even though they look very different in their structure and parameters. Firstly, while 80% of model patients began on medication, less than 20% of trial participants did. Secondly, not a single trial participant underwent the sequence of medications that obtained in the model. Thirdly, there was no surgery observed in the trial. Fourth, the rate of failure in the trial was far less than assumed in the model. If the trial was structured as a decision tree, it would differ in both structure (lacking a surgery arm) and parameter values from the model we produced. If the goal of the model was to present a high-fidelity rendering of the clinical situation at St. Joseph's, it failed.

Nonetheless, the costs from trial and model agreed for the Ministry perspective. If we accept Chumney's (2002) criterion of a 20% deviation in cost estimates as representing a policy-important difference, for the Ministry perspective our results are robust. This

likely reflects the fact that labour was such a large component of cost and, crucially, that it varied minimally between patients. In this respect, physician costs operate almost as a fixed cost – minor variations around this fixed core of labour costs barely make a difference. This is in contrast to the situation in inpatient care or intensive care where labour is a large component of cost and it varies largely between patients (Edbrooke et al. 1999, Tan 2009). The stability of our clinical scenario is likely aided by the availability of relatively cheap generic drugs, thus differences in drug regimen failed to substantially alter cost estimates.

Our conclusion regarding the stabilizing influences of a large, fixed base of labour is bolstered by sensitivity analyses undertaken on the model. Changing those variables that increased labour requirements made a large impact on expected cost, while non-labour related variables had negligible effect on costs. Costs were insensitive to large changes in cohort age and percentage starting on medication. Even an older, highly medicated cohort failed to raise costs as much as increasing the rate of progression to surgery. This indicates that demographic makeup of the local patient population and physician-specific preferences regarding drug regimens likely have negligible effects for Ministry costs. The extent to which initial drug use and demographic variables actually affect downstream effectiveness (and thus, presumably, added costs of complications) is an open question.

Costs were more sensitive to probability of treatment failure and risk of progression to incisional surgery – this is likely due to their effects on expanding labour costs. High rates of surgery and failure, when combined, altered the price by more than 30% from the base model value and more than 40% from trial estimates. It is worth noting, however, that the statement ‘high costs are associated with high probability of failure and progression to surgery’ reduces to ‘high costs are associated with poor effectiveness of the intervention’. The fact that costs are sensitive to these variables is thus, in a sense, superfluous information. High rates of failure and progression to surgery indicate that the intervention is not effective and may be without merit from an effectiveness viewpoint, thus rendering costing moot.

Adam et al. (2003) noted that the impact of capacity utilization on costs is understudied. The costs of delivering an intervention may differ based on patient load, all other factors

held equal. We address one aspect of capacity utilization, patient volume, on capital costs and final costs. We found that altering patient volume had a negligible effect on expected cost – a 10-fold annual increase in SLT patient visits results in less than 10% decrease in expected cost. Decreasing number of patients had a more pronounced effect in terms of increasing costs (cf. fig. 4). However, since these are tertiary clinics, we expect that such low patient volumes are unlikely – if patient volume was low enough, the clinic would presumably refer patients to a larger, tertiary clinic. The increased capital costs associated with low patient volume may be more relevant for rural settings or sparsely populated areas where such low-volume institutions may nonetheless be obliged to purchase a laser.

Our findings regarding the large component of labour concur broadly with those of Oostenbrink et al. (2001) and Kobelt-Nguyen (1998) who found outpatient encounters to be one of the largest components of cost for glaucoma treatment generally. These two studies also found a large contribution of drug costs, but it is worth noting that these studies were undertaken prior to generic Latanoprost becoming available (indeed, generic prostaglandin analogue costs are now so low that this is presented as a reason for a lack of interest on the part of pharmaceutical companies to seek drugs with different mechanisms for glaucoma (Karmel 2013) – such drugs will be seen as expensive when cheap, effective alternatives exist and sales are expected to suffer).

To conclude, model and trial-based costs agree for the Ministry perspective even though they differ in overall structure and parameter values. We speculate that the reason for this may be the large, invariant base of labour and the lack of high drug costs. This study provides the first detailed microcosting of trabeculoplasty in Ontario in the era after the introduction of generic Latanoprost. Further studies in other jurisdictions may determine whether this mix of inputs and cost profile is reflective of laser trabeculoplasty in general or whether patterns of delivery differ between locations.

This study was a rare opportunity to validate the sorts of models commonly used in CEAs of glaucoma interventions, specifically with regards to costs. We found that for laser treatment in glaucoma, simpler model-based costing may be an acceptable, valid substitute for empirical, bottom-up microcosting. Insofar as obtaining cost data by direct measurement is often tedious and expensive, our findings show that for at least some

clinical scenarios we may be assured that easier methods suffice and that we may be free to use our time and resources towards ends other than costing.

5.1.2 - Indirect costs and the societal perspective

The trial and model values for the societal perspective were as follows – ALT: $1057.18 vs. $1146.64 (8.5%), SLT: $1154.71 vs. $1141.00 (1.2%). Firstly, indirect costs contribute substantially to total costs. Indirect and patient-borne costs are at least equal to direct costs of treatment, more than doubling costs from the societal perspective as compared to the Ministry perspective. Secondly, while trial and model agree, there is sensitivity to assumptions considerably beyond that of the Ministry case.

Our results provide the first assessment of indirect costs for glaucoma treatment in Ontario. In comparing our results to those of other studies assessing indirect costs in glaucoma, dependence on local factors becomes apparent. Our results concur with those of Rouland et al. (2005) who found that indirect and patient-borne costs were higher than direct medical costs for glaucoma. Our results differ slightly from Sharma et al. (2010) who examined indirect costs for glaucoma clinics in London, UK and found a wider variety of methods of transportation (including the finding that twice as many patients used buses than cars) whereas all of the patients in this study used cars. This is unsurprising when comparing a tertiary centre with a large catchment area to a much denser metropolitan area where buses and taxis are more convenient. Our results also differ from those of Kobelt-Nguyen et al. (1998) who found that indirect costs were only 25% of total cost in the USA – however, this was for general practice as opposed to tertiary centres.

Costs from the societal perspective were much more variable than those from the Ministry perspective. For SLT costs ranged between $630 and close to $2750 from the societal perspective – from the Ministry perspective costs for SLT ranged from $506 and $750. This differs from the findings of Sharma et al. (2010) who found a much narrower range of societal costs. This may reflect the less transportation intensive requirements of the clinics in Sharma et al.'s study. Indeed, transportation accounted for close to 20% of costs in our study – this was only considering motoring costs and not lost time due to transportation (which we factored into calculations of lost time). Indirect costs were

evenly divided between transportation costs and the value of lost time. The large component of travel time was likely due to SJHC being a major tertiary centre for Southwestern Ontario and environs. Indeed, several patients had to travel a one-way distance of over 100km. At a minimum of six visits per year, this requires over 1200km of travel for these patients. The majority of patients were retired, as befits glaucoma's higher prevalence in older persons. Consideration of retiree time is likely to become a significant consideration as the population ages. If an intervention represents a significant time burden then patients may be less likely to make all appointments on account of the inconvenience involved. If this contributes to disease progression, then costs to the healthcare system become commensurately higher as visual impairment increases (Rouland et al. 2005).

The tornado diagram in figure 5 reflects the striking impact of assumed patient time loss relative to all other variables. As with the Ministry perspective, probability of surgery and rates of success had more pronounced effects on the variations in cost than proportion medicated or average age (true even assuming that the majority of those over 65 were retired). However, even these are dwarfed by assumptions regarding the amount of time given to follow-up visits. This variable functions as a catch-all for any increased source of patient time commitment, whether in increased travel, increased appointment length or waiting time. Assuming that average follow-up visit time went from 1.5 hours (half hour travel each way, half hour appointment) to 2.5 hours (reflecting a 20 minute further drive and 20 minute waiting time – not an implausible scenario), expected costs rose by over $100. Furthermore, given that we did not account for waiting times and the vicissitudes of weather (one patient noted that travel was significantly longer in winter), our estimates of societal costs are likely an underestimate.

While model and trial agreed for estimates of societal costs, the sensitivity of patient time commitment highlights the need to use institutional experience and plausible estimates when modelling. This study indicates that modelling may plausibly be used for estimation of societal costs. It also provides us with a feeling for the extent of patient and indirect time costs relative to direct costs. There are substantial differences between the societal and payer perspective, which is unsurprising given the chronic nature of the

disease, the number of visits per year and the time required to attend a possibly distant tertiary centre. This provides us with some feeling for patient inconvenience and time commitments which is of value, quite aside from the theoretical arguments in favour of the societal perspective. The use of the societal perspective as an aid for cross-sector comparisons of costs may be unlikely, especially given that methods are insufficiently standardized (Lensberg et al. 2013) and that there are theoretical arguments *against* the use of the societal perspective (Currie et al. 1999). Indirect costs in glaucoma may be sensitive to characteristics of the providing institution, as we noted in the comparison of our results to those of Sharma et al. (2010) and Kobelt-Nguyen et al. (1998), thus caution is advised when transporting indirect costs between settings. This is especially true of conditions like glaucoma where multiple visits per year mean that relatively minor differences in visit unit cost may add to substantial differences in total cost.

5.2 – Limitations

This research had several limitations. We note limitations in methods and execution here. A second class of difficulties lie with the explicitly preliminary nature of this work and the need for further studies – those we will discuss in the next section.

Firstly, we note the small sample size – eight patients in each arm. Small sample sizes are not uncommon in microcosting studies (e.g. Kinsella's 2008 costing of a single case of neonatal ICU care, Venkatnaryan et al.'s 2014 costing of 8 babies for the same scenario). While we are uninterested in inferential endeavours in this study (Claxton 1996), our sample is small and we recognize this. We witnessed sensitivity to vicissitudes of the patient sample. In the model ALT was more expensive than SLT – this result was reversed in the trial. This is likely due to one outlier of an SLT patient who started the trial on 2 branded medications and happened to be over 65 – all other patients were either unmedicated or on generic drugs. It's possible that there is more homogeneity in the provision of trabeculoplasty than inpatient procedures (e.g. the range of costs for cardiac intervention in Clement et al.'s 2009 study spans two orders of magnitude). If that happens to the case, we obtain a large amount of information from a small number of observations. However, more observations are needed to assess homogeneity of costs in this intervention, and for mere credibility.

A second potential weakness was the limited horizon considered in this study. The course of glaucoma is lifelong, ideally costing studies should reflect the lifetime course (Drummond et al. 2005). We demonstrated that model and trial agree over a short horizon, but important differences in resource use between alternatives is likely to occur downstream. Long-term effectiveness of SLT and its effects on downstream visual impairment, need for medication and progression to surgery remain empirical problems. Further data on SLT's repeatability will provide a more rigorous basis for modelling. We address the issue of whole treatment algorithm modelling in section 5.3.

Thirdly, other models are available. We assessed one model with sensitivity analyses on multiple parameters to represent a wide range of possible scenarios, and included an alternative model formulation to include the option for additional medication before surgery. However, the fact that multiple models are available for the same situation is to be expected (Simonella and Canfel 2014). If our model is a good representation of the scenario and costs are robust to minor variations, then observed costs should be similar whether techs or nurses are used and regardless of patient volume, as well as with different local medication regimens and age composition – as such the performance of our model may be assessed against empirical studies in other settings. As noted by Cantor et al. (2008), the model is best thought of a conceptual framework with which to think about the clinical scenario and identify areas of high variability. Furthermore, the presence of multiple models may not be a problem, but rather a fact of life based on different models of healthcare delivery and characteristics of the health system. The usefulness of any given model to a decision-maker is based on their needs.

We opted not to include certain costs, although we suspect they may have been minimally impactful and ultimately irrelevant. Given the lack of disposables, hotel, nutrition and laundry, overheads are expected to be minimal. A further problem was the lack of a medication adherence metric. With generic medication over the course of 1 year this may not represent substantial differences in costs although it becomes important in an incremental analysis or when calculating downstream differences in visual impairment attributable to medication adherence. For the trial in particular, it is difficult to assess adherence – previous methods include the inclusion of microchips in bottles of

medication (Kahook and Noecker 2007). Sensitivity analyses on the probability of initial medication functioned as a crude proxy for adherence (e.g. the costs of a 40% initially medicated cohort with full adherence is equivalent to an 80% initially medicated cohort with 50% adherence). The use of generic drugs and the finding of negligible impact of percentage initially medicated on estimated costs increases our confidence that adherence is unimportant over this horizon for cost purposes, although downstream effects of incomplete adherence on laser failure rates remains an open empirical question.

For patient-borne costs we interviewed patients at one visit and assumed that the same costs were present at all visits – this is likely insufficient for assessing the true extent of patient time costs. One patient interviewed during a snow storm noted that time to the hospital was double what it would normally be. The people accompanying patients were not present at every visit. Some patients were apt to take a half-day off on the day of an appointment, while others were able to visit the clinic on their lunch break. A more intensive approach would have interviewed patients at every visit, but this was not plausible within the time constraints of the study. Thus, while our estimates of indirect cost are better than speculation, they likely differ from more accurate estimates. This is especially likely to be true given the demonstrated sensitivity of indirect costs. Better capture of indirect costs is an area of future endeavour.

5.3 - Future directions, conclusion

We begin with the most pedestrian application of the trial-derived costing data - their use as an input to a full CEA pending trial completion. The answer of whether or not SLT is repeatable is of interest in and of itself and will doubtless inform further modelling studies, as well as providing a base for long-term SLT effectiveness data.

A second pedestrian extension is comparison of trial and model-based microcosting estimates and case-costing data in Ontario, whether for budget impact analysis or their effects on CEA outcomes. The shift to CMG-based tariffs coincides with Ontario's move to a prospective payment model of funding hospitals, replacing the older global budget system. The use of charges represents another method of bypassing full bottom-up microcosting and the ease of obtaining gross cost values means that they will doubtless be used in economic evaluations. Whether their use is sound for economic evaluations for

ophthalmology remains to be seen. Comparison of trial-based costing, decision-analytic modelling and gross costs will shed light on how all three methods impact cost estimates in CEAs.

A more interesting set of questions, and one towards which this research begins to contribute, is whether we are ever confident enough of a situation's amenability to modelling that we may bypass a trial or direct measurement of costs altogether. As has been noted, the sheer number of possible treatment comparisons possible in glaucoma precludes conducting trials on all but a miniscule number of them. Thus if certain sets of clinical scenarios admit modelling with confidence, we may choose to eschew trials or direct cost measurements for such comparisons.

We have shown agreement between trial and model estimates for a single centre and posit that agreement from the Ministry perspective is helped by large labour costs that are invariant. We thus suspect that for some clinical scenarios the use of simpler modelling methods in place of bottom-up microcosting is acceptable. By using data from the trial as it comes in as well as comparing these results with future studies, we may answer several further questions.

1. *Can we use results from the same effectiveness trial for all Ontario sites?* We note Adam's observation that the same procedure unit cost can vary by an order of magnitude within a jurisdiction (Adam 2006). Considering that physician costs are the same across Ontario, that the procedure seems to be essentially invariant, and that the minor demographic and drug-regimen variations fail to impact on costs, we may compare cost data from the Toronto trial site to London data and our model. If similar results obtain in all three scenarios, the implication is that for similar scenarios we can transfer ICERs or cost estimates between settings with minor adjustments. This may be especially true where differing demographic composition is unlikely to impact on cost, as may be the case for trabeculoplasty. As part of assessing those scenarios wherein modelling is useful, we may wish to quantify the degree of heterogeneity of costs. A salient issue in the costing of inpatient and ICU services is the heterogeneity in case mix and resource requirements. In this study we observed minor variations in costs incurred from

the Ministry perspective – the largest deviation from mean cost for SLT was $200 in absolute terms, or 37% from the mean. This is in comparison to Clement et al. (2009) who found that costs of cardiac inpatient procedures differed by two orders of magnitude. The idea of services that are homogeneous in their costs and those that vary greatly may be useful in determining the transferability of individual ICERs.

2. *Within country comparisons and open source models*. By the end of the trial we will have cost data from Alberta and Nova Scotia, in addition to multiple Ontario sites. Inter-provincial comparisons are complicated by the fact that healthcare costs are set at the provincial level as are drug costs. However, if there's homogeneity of service across different sites within the same country, then decision-makers may simply populate models with local cost data and parameters. In that sense, the final deliverable of a study is not just a raw cost estimate or ICER, but a file of the model and a technical report outlining assumptions and model construction. Goldhaber-Fiebert et al. (2010) stressed that improved dissemination and transparency will make models more impactful in decision-making. If a separate costing study has to be undertaken in every jurisdiction then some of the value as scientific information is lost – we are reinventing the wheel at each step. Sculpher and Drummond (2006) note that portability is desirable, but the needs of local decision-makers are paramount as they are represent the implementation step. The tension between cohort models based on a global literature and the needs of individual hospitals or governments may be bridged somewhat by the provision of the model as a conceptual framework and final deliverable (Cantor et al. 2008). Furthermore, as per Freedberg et al. (1996), an iterative process of model development and validation/updating with empirical results increases the credibility of models. There is a push to open data in clinical trials and it has been the case in other fields of scientific endeavour – for an applied field that aids decision-making, transparency of data and models is crucial. This is especially so with the burgeoning of multicentre trials where a single effectiveness value is available but there is no such aggregate, single cost (Goeree et al. 1999).

3. *Identifying aspects of clinical scenarios that admit 'grab and go' costing.* We have speculated that a fixed base of invariant costs and insensitivity to demographic variables results in stability of cost estimates, as evinced by divergence of model and trial structure/parameters but similarity in costs. This may be more formally assessed when comparing trial and model based cost estimates for a range of clinical scenarios. An exploratory metaregression of model-trial agreement on clinical scenario characteristics may further provide information on when modelling estimates are useful and reliable. One of the worries with the use of disparate sources is that they may reflect different underlying populations or the properties of the parent health system. If an intervention is relatively homogeneous and insensitive to demographic variables then we may be more confident that such disparate sources reflect the same problem and can be more fast and loose with our modelling.

While assessing the cost-effectiveness of single interventions is of interest, we are ultimately more interested in ascertaining the optimal glaucoma treatment algorithm. As noted, the chronicity of the disease (and lack of long-term effectiveness data) as well as the sheer number of potential treatment comparisons to be investigated preclude the use of trials for all but a few comparisons. This research attempts to begin delineating those treatment comparisons where we might be confident in foregoing a trial – not because of the insignificance of the comparison but because the gains in information from a trial would not offset the costs incurred in its conduct. This is, conceptually, a close relative of value of information analyses (Claxton and Sculpher 2006).

In order to determine the best combination of treatments for patient and cost considerations, it may be worth convening an expert panel to assess the state of the current treatment algorithm and to propose a list of candidate sequences to investigate. Such consensus would, presumably, reflect the best knowledge available of promising directions for investigation. Each treatment algorithm has nodes where different interventions are to be compared – we may formally assess uncertainty around cost and effectiveness values at each node using value of information analyses to identify where the information gained from trials will prove to be useful or otherwise (Claxton and

Sculpher 2006). We may assess whether the clinical scenario is amenable to modelling or not based on characteristics of the comparison. Thus we are able to identify important areas where research is needed, as well as those areas where trials are needed and where they are not. This would inform glaucoma research. A further role would be for simulation of clinical trials. There have already been some attempts in modelling whole glaucoma treatment algorithms (van Gestel et al. 2010, Crane et al. 2013). This would likely be an iterative process, wherein research priorities are shifted based on the results of studies, much as the Cochrane Collaboration regularly updates their systematic reviews. Part of this is developing some methods wherein we may assess the need for a trial, this research aims to begin that dialogue, especially since model and trial concurrence for 'grab and go' style modelling in glaucoma has not, hitherto, been studied. The state of modelling in health economics is rudimentary compared to other fields of scientific endeavour (Caro et al. 2010) and it is imperative to move beyond back of the envelope type exercises if we are serious about impacting policy. It would not be acceptable for effectiveness data, nor should it be acceptable for cost-effectiveness.

In conclusion, less laborious modelling methods for assessing cost, as are common in glaucoma, provide a valid substitute for empirically derived microcosting for the Ministry perspective, at least as pertains to laser therapy in glaucoma. The same is true of the societal perspective, with some caveats. The high patient time commitments in chronic disease as well as the impact of providing centre characteristics on transportation costs means that close attention must be paid to assumptions in the societal case as the results are more strongly influenced by assumptions regarding patient time commitments.

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Appendix A – Calculating Drug Costs

Drops per unit volume were obtained from Rylander and Vold (2008). Full adherence was assumed as was unilateral application of medication – comments regarding the adherence assumption are available in chapter 5. The assumption of unilateral medication was based on the fact that laser was applied unilaterally. Prices were obtained from the ODB formulary, generics were prescribed where available. The minimal commercially available amount was prescribed in all cases, except for Brimonidine where thrice daily administration meant that we assumed the second smallest size was used. Total cost (last column in the chart below, in 2014 Canadian dollars) plus 10% pharmacy markup was used for all analyses.

DRUG	Cost and vol.	Drops/mL, drops/bottle	Dosage	Bottles/year, cost	Total
Latanoprost	9.583/2.5 mL – 80 drops	30/mL – 75/bottle	1x/d	5	47.915
Bimatoprost/Lumigan (0.01%)	33.858/3 mL	33/mL, 99/bottle	1x/d	4	135.432
Travoprost/Travatan (0.004%)	28.76/2.5 mL	39/ml, 97 drops/bottle	1x/d	4	115.04
Timolol Maleate 0.5%	1.2145/ml – 6.0725 per 5ml bottle	28/ml, 140 ml/bottle	2x/d	6	36.435
Maxidex	1.6780/ml	5ml	4x/d for 4d	1	8.39
Ocuflox	0.8561/ml	5ml bottle	4x/d, 1mo.	1	4.28
Prednisolone acetate	1.9400/ml	Unavailable, 5ml bottle assumed to be sufficient for 1 month	4x/d, 1 mo.	1	9.70
Brimonidine/Alphagan	1.1550/ml	24 drops/ml, 240 drops/10ml bottle	3x/d	5	57.75
Cosopt/Dorzolamide HCL+Timolol Maleate	2.0951/ml	26 drops/ml, 260 drops/bottle	2x/d	3	62.853

Appendix B – Questionnaire

Based on a modified version of Thompson and Wordsworth's 2001 questionnaire.

Patient: _____

Treatment: _____

Date: _____

Section 1 - TRAVEL

1.1 - How did you get to your appointment?

(Place patient's verbal response into one of the following boxes. If bus/taxi, ask questions 1.2, 1.4 and 1.5. If car/motorbike – 1.3, 1.4 and 1.5. Else just 1.4 and 1.5)

Walked or cycled □ Bus □ Taxi □
Private car or motorbike □ Hospital or voluntary car services □
Other (please specify) □ _____

1.2 - If you travelled by bus or taxi for part or the entire journey, what was the cost of the one-way fare? $_____ - _____ cents

1.3 - If you travelled by car or motorbike for part or all of the journey and had to pay parking fees, how much did these amount to? $_____ - _____ cents

1.4 – What was the approximate one-way distance?

Number of kilometres: _____

1.5 - How long did it take to travel from your home to the hospital?

_____Hours - _____Minutes

Section 2 - PATIENT TIME COSTS

(At this point, hand them the sheet with the options for use of time. Ask question 2.1, check the appropriate box. If they are gainfully employed and would've been

working during the appointment time, ask questions 2.2, 2.3 and 2.4. Else just 2.4 – if they indicate that they're retired, occupation = retired).

2.1 - What would you have been doing otherwise as your **main** activity if you had not come to the hospital?

Retired ☐

Housework, childcare, caring for a relative/friend or volunteering ☐

Paid work ☐ Leisure activities ☐ Attending school/university ☐

On sick leave ☐ Unemployment and/or seeking work ☐

Other (please specify) ☐ _____

If you took time off from paid work (or business activity if self-employed) please continue with the next question. Otherwise go to **section 3**.

2.2 - If you took time off from paid work (or business activity if self-employed) to come to the hospital, approximately how much time did you take off work? Please write the number of hours and minutes below:

____Hours _____Minutes

2.3 - Did you lose earnings as a result?

Yes ☐ No ☐

2.4 - What is your **main** occupation/job?

Job: _____

<u>Section 3 - COMPANION COSTS:</u>

(Ask question 3.1 – if yes, continue with 3.2, else go to section 4).

3.1 - Did anyone accompany you to the hospital? Please circle the appropriate response:

1. Yes
2. No

3.2 - Who accompanied you to the hospital? ***(Place patient's verbal response into appropriate box – if more than one person, circle multiple if necessary and make note of who came).***

Partner/Spouse or Other Relative □ Child/children under 16 years □
Paid caregiver □
Other (please specify) □ _____

(Question 3.3 only if patient travelled by public transportation)

3.3 - If your main companion travelled with you by public transport for part or the entire journey how much did they pay one-way in fares (if anything)?

$_____ - _____ cents

(Give patient the possible uses of time sheet again, as for question 2.1. If their companion took time off paid work, ask questions 3.5 and 3.6 also. Otherwise, just questions 3.4 and 3.7).

3.4 - What would your companion otherwise have been doing as their **main** activity if you had not accompanied you to the hospital?

Retired ☐

Housework, childcare, caring for a relative/friend or volunteering ☐

Paid work ☐ Leisure activities ☐ Attending school/university ☐

On sick leave ☐ Unemployment and/or seeking work ☐

Other (please specify) ☐ _____

If your main companion took time off from paid work (or business activity if self-employed) please continue with the next question. Otherwise go to **section 4**.

3.5 - If your companion took time off from paid work (or business activity if self-employed) to come to the hospital, approximately how much time did they take off work? Please write the number of hours and minutes below:

____Hours _____Minutes

3.6 - What is your main companion's **main** occupation/job?

Job: _____

3.7 – How many people came with you to hospital today?

Number of people: _____

Section 4 – INFORMAL CAREGIVING

4.1 – As a result of attending this visit, did you have to accept help from relatives, friends or from professional services for work which you usually carry out yourself – e.g. house cleaning or care of children or dependents?

Yes (**CONTINUE WITH NEXT QUESTION**).....1
No (**GO TO SECTION 5**) 2

(If they did get help, which is unlikely in general for such short visits, ask from who, how long time-wise, and any costs).

KIND OF HELP	Number of hours and minutes	Cost
Help from relatives, friends or acquaintances		
Home help or professional aids (e.g. NCIB, Red Cross)		

4.2 – If friends or relatives provided help during your visit, what would they have been doing as their **main** activity if they had not been providing help: ***(Again with the use of time sheet).***

Retired ☐

Housework, childcare, caring for a relative/friend or volunteering ☐

Paid work ☐ Leisure activities ☐ Attending school/university ☐

On sick leave ☐ Unemployment and/or seeking work ☐

Other (please specify) ☐ _____

If friends/relatives who provided help took time off from paid work (or business activity if self-employed) please continue with the next question. Otherwise go to section 5.

4.3 - If your friends/relatives took time off from paid work (or business activity if self-employed) to provide help during your visit, approximately how much time did they take off work? Please write the number of hours and minutes below:

____Hours _____Minutes

4.4 - What is your the **main** occupation/job of the friends/relatives who were helping you?

Job: _____

Section 5 – Other

5.1 - Are there any other costs you have incurred as a result of coming for this visit or since you underwent the procedure that have not been covered? If so, please elaborate below and provide an estimate.

_____
_____
_____

Notes:

Curriculum Vitae

Name: Omar Akhtar

Education:

Western University — London, ON
MSc (Epidemiology and Biostatistics)
2012-2014

University of Toronto — Toronto, ON
Honours BSc (Psychology and Physiology)
2005-2009

Employment:

Ivey Eye Institute, St. Joseph's Health Care — London, ON
Graduate Research Student
Apr. 2013-Sept. 2013

Publications:

Akhtar O, Singh H, Si F, Hodge WG. A systematic review and cost-effectiveness analysis of tonometer disinfection methods. Can J Ophthalmol. 2014 49(4):345-50.

Conference presentations:

Akhtar O, Singh H, Si F, Hodge WG. Disinfecting Goldmann applanation tonometers against epidemic keratoconjunctivitis. *Ivey Eye Institute Ophthalmology Research Day, London, ON, Nov. 2013.* Podium presentation.

Akhtar O, Singh H, Si F, Hodge WG. A systematic review and cost-effectiveness analysis of disinfection methods for Goldmann applanation tonometry. *ARVO Annual Meeting, Orlando, FL, May 2014.*