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Cost-Effectiveness of Selective Laser Trabeculoplasty (SLT) versus Argon Laser Trabeculoplasty (ALT) in Uncontrolled Open Angle Glaucoma Patients having at least One Full Previous SLT: An Economic Evaluation Alongside an Ongoing Randomized Controlled Clinical Trial

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Abstract

Background and objective: ALT and SLT are both safe and effective for glaucoma treatment. We performed a cost-effectiveness analysis (CEA) of SLT versus ALT for a six-month follow-up period in uncontrolled open angle glaucoma patients having at least one full previous SLT from an ongoing RCT. **Methods:** Trial based treatment costing and IOP reduction at 6-month follow-up from baseline for both intervention arms were calculated. A decision tree model was developed considering possible clinical pathways of patients undergoing repeat laser trabeculoplasty. CEA among ALT and SLT was done, and ICERs were calculated from both societal and ministry perspective. One way sensitivity analysis was done for cost and effectiveness parameters. **Results:** From Societal perspective, expected cost/effectiveness for ALT and SLT was $458/0.143 mmHg vs $448/0.123 mmHg respectively and from ministry perspective, $467/0.154 mmHg vs $446/0.122 mmHg, respectively. To switch from SLT to ALT, it would cost $ 356.49 for each extra unit IOP reduction from societal perspective and from ministry perspective, the same would cost $ 649.71. This ICERs were much higher in comparison to ICERS of other IOP lowering medications in similar situations. **Conclusion:** Neither ALT nor SLT strategies were clearly dominated by any other. ALT is slightly more effective and slightly costly over SLT. Sensitivity analysis with effectiveness variables showed dominance of SLT over ALT for some instances. SLT has the theoretical plausibility of repeatability and is also easier to perform than ALT. All these factors should be considered when opting between ALT and SLT strategies.

KEYWORDS:

Argon laser trabeculoplasty, cost-effectiveness analysis, decision model tree, economic evaluation, glaucoma, incremental cost effectiveness ratio, intra-ocular pressure, selective laser trabeculoplasty.

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LIST OF ABBREVIATIONS

ACG: Angle Closure Glaucoma

ALT: Argon Laser Trabeculoplasty

C/E: Cost-Effectiveness Ratio

CAD: Canadian Dollar

CAIs: Carbonic Anhydrase Inhibitors

CBA: Cost-Benefit Analysis

CCT: Central Corneal Thickness

CDR: Cup:Disc Ratio

CEA: Cost-Effectiveness Analysis

CMA: Cost-Minimization Analysis

CSF: Cerebrospinal Fluid

CUA: Cost-Utility Analysis

DSMC: Data Safety and Monitoring Committee

GAT: Goldmann Applanation Tonometry

HMMS: Healthcare Materials Management Services

ICER: Incremental Cost-Effectiveness Ratio

ICG: Indocyanine Green

IOP: Intra Ocular Pressure

LTP: Laser Trabeculoplasty

OAG: Open Angle Glaucoma

OCT: Optical Coherence Tomography

OH: Ocular Hypertension

OHIP: Ontario Health Insurance Plan

PACG: Primary Angle Closure Glaucoma

PDS: Pigment Dispersion Syndrome

PG: Pigmentary Glaucoma

PGAs: Prostaglandin Analogues

POAG: Primary Open Angle Glaucoma

PXFG: Pseudoexfoliative Glaucoma

PXFS: Pseudoexfoliation Syndrome

QALY: Quality-Adjusted Life Year

QAYV: Quality Adjusted Year of Vision

RCT: Randomized Controlled Trial

RNFL: Retinal Nerve Fiber Layer

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

SLT: Selective Laser Trabeculoplasty

TM: Trabecular Meshwork

Chapter 1 - Introduction

Glaucoma, a progressive degeneration of the retinal ganglion cells, results in characteristic visual field defects (initially peripheral, then central loss of field of vision) (Gemenetzi et al. 2011). It may remain asymptomatic until becoming severe because of redundancy in the sensory system and the binocular nature of vision; one eye may compensate for early losses in the other (Weinreb et al. 2014). It is the second-leading cause of blindness and leading cause of irreversible blindness worldwide, having an estimation of 79.6 million glaucoma patients by 2020, and 74% of these will have open angle glaucoma (OAG) (Quigley et al. 2006). By 2040, an estimated 111.8 million people will suffer from glaucoma worldwide (Tham et al. 2014). Primary OAG (POAG) is the most common type; others include pigmentary OAG and pseudoexfoliative OAG (Musch et al. 2012). Increased intra ocular pressure (IOP) is considered as the most important modifiable factor for development and prognosis of POAG (Anderson et al. 1989). But the disease may occur in normal IOP also (Bahrami et al. 2006). Other important risk factors are thinner central corneal measurement, older age, and family history for glaucoma (Coleman et al. 2008, Friedman et al. 2004).

Along with age-related macular degeneration and diabetic retinopathy, glaucoma is the most important ocular public health problem in Canada with an annual economic burden close to $500 million (Hodge et al. 2004). It affects 1-2% of individuals over age 50. An estimated 400,000 Canadians are affected with over 10,000 blind (Hodge et al. 2004, Tielsh et al. 1991).). In 2008-2009, Statistics Canada reported that, more than 450,000 Canadians aged 45 years and above have been diagnosed with glaucoma by health professionals (Statistics Canada, 2010).

The quick accrual of medical information and rapidly evolving newer medical technologies results in several different management options even for a single medical condition. Thus, selection of treatment modalities becomes difficult at

both individual and policy level, warranting the development of guidelines for clinical practice and to set pragmatic funding priorities for policy on medical intervention directing what action should be done and paid for (Petitti. 2000).

Expensive health care, globally, includes a large and increasing share of private and public expenditure (CIHI 2013). Economic considerations for treatment options are getting more importance day by day as health systems are under enormous pressure to maximize the value for money. Consequently, clinical effectiveness alone is not the only criteria for adoption of an intervention nowadays. The value for money has to be considered equally along with the clinical effectiveness (Health Council of Canada. 2009). Economic evaluation measures and values explicitly to compare alternative courses of action in terms of both their costs and good or bad consequences. (Drummond et al. 2015; Hurley. 2010). Cost-Effectiveness Analysis (CEA), a method for economic evaluation, compares decision options in terms of their monetary costs and offers a framework where clinical effectiveness data along with costs are examined together and relevant issues on costs and clinical effectiveness of comparative alternative medical interventions can be addressed. A decision analytic model, especially in medical applications, is the usual conceptual basis for analysis of the effectiveness of the decision options. CEA, in addition, involves cost identification of the decision options and their valuation. In many instances, CEA also explores preferences of society or individuals of the decision option for the health outcomes (Petitti, 2000), termed utilities. The Incremental Cost-Effectiveness Ratio or ICER, which is the difference in cost divided by the difference in effectiveness of two or more competitive or alternative programs or interventions, represents the cost per additional unit of health effect (Petitti, 2000). Considering local context and decision rules, decision makers may use the ICER to determine whether or not a technology represents a good value for money.

Open angle glaucoma has a life-long progressive course. Once started, it is non-curable, only treatable. Its management requires careful selection of different combination of treatment modalities (mainly medications, laser therapy and surgery) on an individual patient at different time point and situation to achieve and maintain the target IOP to either halt or delay the disease progression. Otherwise, it may result in negative health consequences like increased blindness, falls, depression, and decrease in quality of life (Schmier et al. 2007). The mainstay of treating glaucoma is to halt or delay the deterioration of glaucomatous visual field defects, typically by reducing intraocular pressure.

Pharmacological treatment to lower increased IOP started nearly 150 years ago (Realini, et al. 2011). Currently, there are five major classes of drugs for the treatment of glaucoma: (i) Prostaglandin analogues (PGAs) ; (ii) Beta-adrenoceptor antagonists; (iii) Adrenoceptor agonists; (iv) Carbonic anhydrase inhibitors (CAIs); and (v) Cholinergics (acetylcholine receptor agonists) (Marquis and Whitson.2005), with at least 56,000 possible options for medication types, doses and schedules of glaucoma (Realini and Fetchner, 2002). They act by either decreasing aqueous humor production or by increasing aqueous outflow. Additional treatment modalities include stents, non-incisional surgery and incipient neuro-protective treatment (Wentz et al. 2014). A new emerging future treatment option for glaucoma is Rho kinase inhibitor (RKI), which inhibits the Rho-associated protein kinase (ROCK) signaling pathway (Bagnis et al.2011; Wang and Chang. 2014). Unfortunately, not all patients reach intra ocular pressure goals, despite efforts to treat with either medical monotherapy or combination of medical therapies. Use of anti-glaucomatous medications also carries the risk of ocular and systemic adverse effects. Non- compliance with instilling ocular medications on a regular basis is also a great barrier to the success of pharmacological therapy (Rotchford et al. 1998). Despite the government's funding for glaucoma medications for those aged 65 and over in Canada, the non-

adherence and non-compliance issues related to glaucoma medications remain a great challenge for optimal successful outcome of medical treatment (Kholdebarin et al. 2008).

Surgical therapy may be effective but carries the risk of sight threatening hemorrhage, infection, or hypotony (Vijaya et al. 2011).

Laser treatment of glaucoma guarantees patient compliance without any disastrous post-procedural complications. The results of Glaucoma Laser Trial (GLT) demonstrated that, laser trabeculoplasty (LTP) was at least as efficacious as anti-glaucomatous medications as the first-line treatment for POAG patients (The Glaucoma Laser Trial Research Group, 1990; The Glaucoma Laser Trial Research Group, 1995). Argon laser trabeculoplasty (ALT), introduced by Wise and Witter in 1979, is an effective way of lowering increased IOP by facilitating aqueous outflow through trabecular meshwork (TM) (Wise et al. 1979), but its effectiveness decreases with retreatment due to detrimental disruption to the microstructure of the TM, and this excessive TM damage often determines treatment failure (Hodge et al. 2005; Fink et al. 1988). In 1995, Latina introduced selective laser trabeculoplasty (SLT), an alternative laser treatment, by using a frequency doubled, Q switched Nd: YAG laser (532 nm) in lieu of an argon wave length (488 nm to 514 nm) (Latina et al. 1995, Latina et al. 1998). SLT targets the pigmented TM keeping the TM architecture more preserved, especially the long spacing collagen (Cvenkel et al.2003). This has the theoretical advantage of successful repeatability of SLT over ALT. The efficacy and safety of SLT are similar to ALT for first laser treatments (Damji et al. 1999; Hodge et al. 2005, Damji et al. 2006).

The outcome of glaucoma treatments, especially in terms of IOP lowering effects, varies widely from patient to patient. Medications have non-compliance issues and surgical options are tagged with complications, often sight and even life threatening. Laser treatments, are devoid of these drawbacks and are now used

widely with increasing popularity among patients and ophthalmologists. Laser treatments, especially SLT, are even considered by many ophthalmologists as a good choice for first-line treatment as studies support this claim (Waisbourd and Katz, 2014). SLT has the theoretical advantage for repeat treatment of glaucoma over ALT.

The aim of this thesis is to perform a cost-effectiveness analysis of SLT versus ALT in uncontrolled open angle glaucoma patients (including ocular hypertension, pigmentary dispersion syndrome and pseudoexfoliation syndrome) and at least one previous full SLT by examining the relevant data from an ongoing randomized clinical trial entitled ‘A randomized clinical trial of selective laser trabeculoplasty (SLT) in open angle glaucoma who had been previously treated with complete SLT’ on a short horizon (6-month) of follow-up. It will provide us important information and direction about the cost-effectiveness of ALT and SLT treatment for above-mentioned group of patients. We will also have a general impression of both cost and effectiveness (in term of IOP lowering effect) of ALT and SLT in a usual setting of such health care practice.

Chapter 2 - Background and Literature Review

2.1- Glaucoma: An overview

2.1.1 The sneak thief of vision

Glaucoma, a collective term for heterogeneous group of conditions having, in common, an irreversible, progressive optic neuropathy with distinctive patterns of structural changes in the optic nerve head (cupping) resulting in visual field loss (Rouland et al, 2005). The diversities of clinico-histopathological manifestations are not commonly appreciated by the general people (Allingham et al. 2011). The initial slow impairment of vision of the affected eye, starting usually in the peripheral field of vision and encroaches centrally in advance stage, is well compensated by the fellow healthy eye (Weinreb et al. 2014). As a result, when patient recognizes the visual field defect, progression of glaucoma usually causes severe and irreversible damage to the retinal ganglionic cell and visual field in the affected eye (Pan and Varma, 2011).

2.1.2 Historical Background

The description of glaucomatous condition can be found during the era of Hippocrates (Sorsby. 1932). The term 'Glaucoma' coined from the early Greek 'glaukos', a term to describe blue, green or light gray and possibly also used to indicate the color of the pupil in affected eyes (Leffler et al. 2015; Mark, 2010). Until 17th century, glaucoma was nearly indistinguishable from cataract and inflammatory condition of the eye (Frezzotti, 2000). After introduction of ophthalmoscope in 1851 by Hermann Vonn Helmholtz (Keeler, 2002), ophthalmologists could observe that excavated optic neuropathy was characteristic of patients having co-morbidity with mydriasis, an anteriorly prominent lens and a green pupil (glaucoma), albeit some patient with normal pupil (amaurosis) also had excavated optic neuropathy (Leffler et al. 2015). In the middle of the 19th century, Graefe thought ocular hypertension as a form of glaucoma. Donders called it "glaucoma simplex" shortly thereafter. Mackenzie, Jaeger, Weber and

Graefe emphasized that, the cupping viewed during ophthalmoscopic examination was due to the swelling of optic disc resulted from elevated aqueous pressure (Nathan, 2000; Frezzotti, 2000). The ciliary body as a source of aqueous humor secretion was discovered by Leber (Barnshaw, 1979). Graefe developed a transpalpebral tonometer in 1862, and Maklakoff and Fick developed applanation tonometers in 1880 (Kniestedt et al. 2008), both intended to measure intraocular pressure, a cornerstone diagnostic aspect of the disease.

2.1.3 Classification

Glaucoma is usually classified based on:

Etiological*

- Primary (No identifiable ocular or systemic disorders)
- Secondary (Identifiable ocular or systemic disorders)

Mechanism of IOP elevation*

- Open angle (No clinically visible anatomical obstruction to aqueous outflow in the iridocorneal drainage angle) with IOP elevation or without IOP elevation (Normal tension).
- Angle closure (Clinically visible anatomical obstruction to aqueous outflow in the iridocorneal drainage angle)

Based on severity*

- Early glaucoma
- Moderate glaucoma
- Advanced glaucoma

Developmental**

- Primary congenital glaucoma (from birth to 9 years)
- Primary juvenile glaucoma (from 9 years to 35 years)
- Axenfeld and Rieger anomaly (AXRA)

- Peters anomaly
- Anirida

*(Barton and Hitchings, 2013a); **(Auw-Haedrich et al. 2015).

2.1.3.1 Ocular Hypertension (OH)

In 1970, the term 'Ocular Hypertension' was introduced to separate persons having IOP greater than 21 mm Hg, who are at increased risk of developing POAG than persons with normal IOP (i.e., <21 mm Hg) (Allingham et al. 2011). Despite the similar flow pattern of aqueous humor of a person with normal IOP, patients with ocular hypertension exhibit higher IOP and resistance to aqueous outflow (Ziai et al. 1993).

2.1.3.2 Primary Open Angle Glaucoma (POAG)

It is the most prevalent form of glaucoma (aka Chronic Open-Angle Glaucoma). Damage of the optic nerve head is the ultimate result of the disease pathway due to all potential etiologies. As stated earlier, it has no warning signs until the development of advanced visual field loss. Elevated IOP (usually>21mm Hg before the start of treatment), due to aqueous outflow obstruction, is the most important modifiable risk factor (Allingham et al. 2011). When the pathway of aqueous humor is blocked, pressure inside eyeball raises due to excess accumulation of aqueous humor. This increased pressure causes slow and irreversible damage of optic nerve head leading to irreversible blindness.

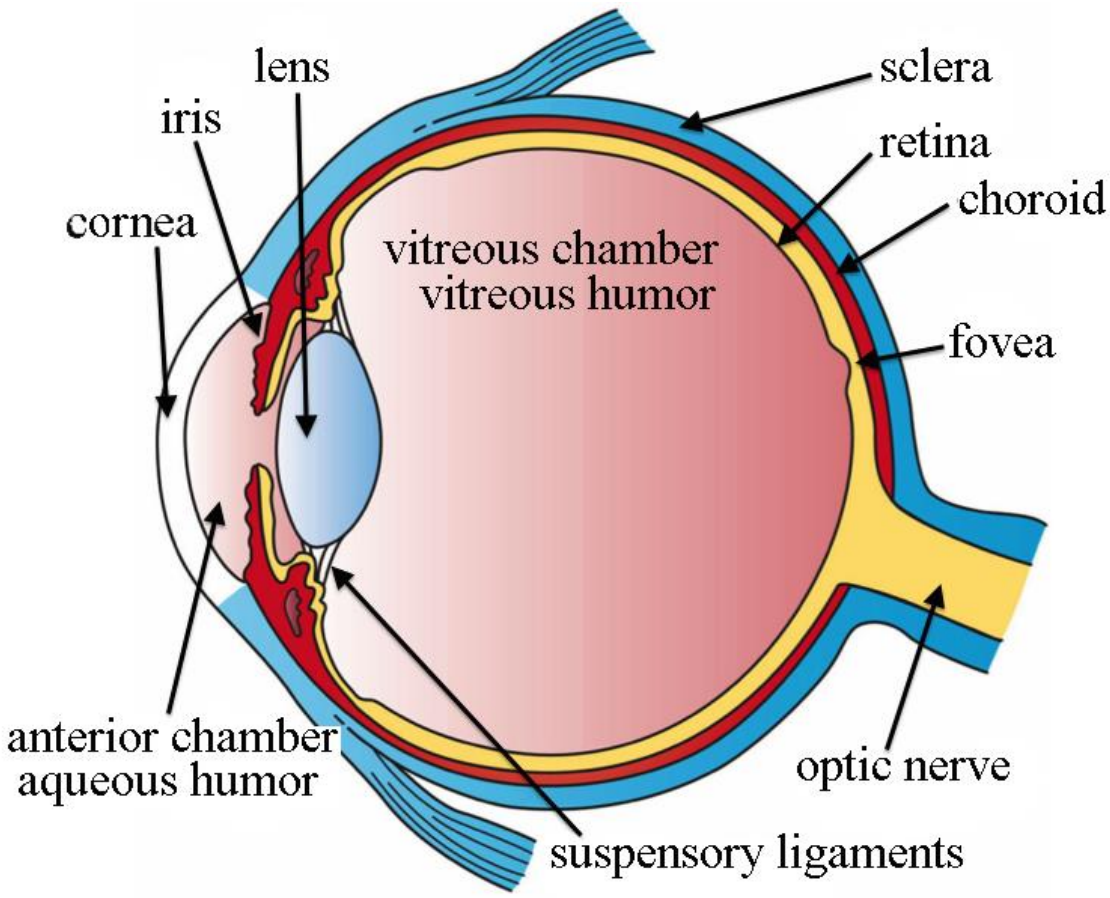

Figure 1: Different parts of eye

[Source: https://commons.wikimedia.org/wiki/File:Three_Main_Layers_of_the_Eye.png]

Transforming growth factor - β_2 (TGF- β_2), the predominant isoform of transforming growth factor - β in ocular tissue, is elevated in POAG patients than normal individuals. It may decrease the cellularity of the trabecular meshwork resulting in excessive amounts of extracellular matrix materials and formation of plaque from the thickened sheath of elastic fibers with eventual increased resistance to the aqueous outflow (Tamm and Fuchshofer, 2007; Agarwal et al. 2015). Narrowing of Schlemm's canal with collapse also results in increased resistance to the aqueous outflow (Johnson 2010). Attenuation of intrascleral

channels may also contribute to increased aqueous outflow resistance (Grieshaber et al. 2010). Many patients with POAG are unusually sensitive to corticosteroids that may also aggravate the situation (Allingham et al. 2011). Along with elevated IOP, additional factors like induction of fibrosis and capillary loss (with increased connective tissue in the septa and surrounding the central retinal vessels, including increased amounts of type IV and VI collagen) are involved in glaucomatous optic neuropathy (Gottanka et al. 2005). Low cerebrospinal fluid (CSF) pressure is often observed in POAG (Berdahl et al. 2008). The critical balance between neuroprotective and neurodegenerative roles of the immune system in glaucoma determines the ultimate fate of retinal ganglionic cells in response to various stressors (Allingham et al. 2011). In experimental glaucoma, apoptotic death of retinal ganglionic cells occurrs (Quigley, 1999). The Canadian Glaucoma Study reported an association of elevated anticardiolipin antibody (one of the antiphospholipid antibodies), with progression of POAG (Chauhan et al. 2008). In treatment of a patient with POAG, the target IOP range for both eyes in which there will presumably be no further optic nerve damage, has to be determined and would need to be reevaluated at each follow-up visit. Usually, target IOP is achieved with topical anti-glaucomatous medications. If not achieved despite maximum tolerated medical therapy, laser trabeculoplasty (argon or selective) is indicated followed by glaucoma filtration surgery or other appropriate incisional surgical therapeutic maneuvers (Allingham et al. 2011).

2.1.3.3 Pseudoexfoliation Syndrome (PXFS) and Pseudoexfoliative Glaucoma (PXFG)

A systemic disorder with important eye manifestations, pseudoexfoliation syndrome (aka exfoliation syndrome) is globally the most common identifiable cause (secondary) of open angle glaucoma; it is also associated with angle closure glaucoma and cataract with zonular instability (Ritch, 1994). When glaucoma is present with PXFS, it is called pseudoexfoliative glaucoma (aka exfoliative

glaucoma, capsular glaucoma). Due to rarity of true lens capsule delamination, the term ‘pseudo’ is most often used (Allingham et al. 2011). PXFS is more common in older age groups (Aström et al. 2007). Most eyes with PXFG follow an open angle mechanism, (a small number present with acute angle closure glaucoma), and control of IOP is difficult in open angle PXFG compared to similar IOP level of POAG (Allingham et al. 2011). When PXFS is fully developed, exfoliation material is seen on the anterior lens surface, and increased and uneven trabecular meshwork pigmentation due to excessive pigment dispersion is observed. In PXFG, elevated IOP and typical glaucomatous neuroretinal rim loss are present along with exfoliation material in the anterior lens surface and on the corneal endothelium and also on the pupillary margin of the iris (Allingham et al. 2011; Ritch and Schlötzer-Schrehardt, 2001). In PXFG, there is greater diurnal IOP fluctuation and treatment is challenging. Regarded as an inherited microfibrilopathy, development of PXFS and PXFG are strongly associated with polymorphism of lysyl oxidase-like protein 1 (LOXL1) gene, a member of a gene family that plays an important role in elastin metabolism (Allingham et al. 2011).

2.1.3.4 Pigment Dispersion Syndrome (PDS) and Pigmentary Glaucoma (PG)

These are two consecutive stages of the same disease process marked by disruption of the iris pigment epithelium and deposition of the dispersed pigment granules throughout the anterior segment. A concave iris contour allowing apposition of its posterior surface to the zonular bundles is responsible for PDS. Disruption of the iris pigment epithelium also releases pigment granules into the aqueous humor. The classic diagnostic triad are corneal endothelial pigmentation (Krukenberg spindle), slit-like, radial, mid-peripheral iris transillumination defects, and dense homogeneous pigmentation of the trabecular meshwork. Patients with PDS are usually myopic, so incidental diagnosis of PDS is often made at an early stage. Young males are at greater risk of developing PDS. It may

take years to develop PG from PDS and once established, PG is difficult to control. PXFS may be more common in PG (Tello et al. 2010).

2.1.3.5 Angle Closure Glaucoma (ACG)

Angle closure results from apposition of the peripheral iris to the trabecular meshwork leading to obstruction of aqueous outflow (Allingham et al. 2011). This results in a sudden (acute) or gradual (chronic) increase in intraocular pressure (Cyrlin, 2010). Two mechanisms of ACG are described as follows (Allingham et al. 2011):

- The Anterior Mechanism: The peripheral iris is pulled into the iridocorneal angle by contraction of an abnormal tissue (i.e., fibrovascular membrane, endothelial layer with a Descemet-like membrane, inflammatory precipitates) that bridges the anterior chamber angle.
- The Posterior Mechanism: Peripheral iris is pushed into the anterior chamber angle due to pressure behind the iris, lens, or vitreous, with or without pupillary block (see below). Posterior mechanism with pupillary block causes pupillary block glaucoma.

Primary angle closure glaucoma (PACG), most common variety of ACG, will have an estimated 21 million cases globally by 2020 (Quigley and Broman, 2006). Most cases of PACG are due to pupillary block, the most frequent cause of angle closure glaucoma (Nolan et al. 2000; Gazzard et al. 2003). Flow through the pupil is compromised and the peripheral iris bows forward against the trabecular meshwork. Increased pressure gradient between the posterior and anterior chamber eventually blocks the outflow. The symptoms of acute angle closure glaucoma are sudden and severe, with marked pain, blurred vision, elevated IOP, nausea and vomiting, minimal cell or flare, and a fixed or sluggish mid-dilated or irregular pupil. The initial treatment for an acute attack is to lower the IOP and relieve the pupillary block in the affected eye, including emergency paracentesis. In chronic angle closure glaucoma, the angle gradually narrows without precipitating an

acute attack and over time, a portion of the anterior chamber is permanently closed by peripheral anterior synechiae (scar tissue). Their corneas are usually clear and non-edematous, but may have more extensive optic disc and field of vision damage. These patients should be treated in a similar way as POAG (Allingham et al. 2011; Cyrlin, 2010).

2.1.4 Pathophysiology

The underlying pathophysiology of glaucoma is not yet fully understood. However, aqueous humor dynamics, optic nerve alterations and loss of visual functions are so far identified as key events for development of glaucoma. As already discussed, vascular, immunologic and cell signaling mechanisms may be involved.

2.1.4.1 Aqueous Humor Dynamics and IOP

Aqueous humor, a clear ultrafiltration fluid of plasma, fills and helps to form the anterior and posterior chambers of the eye. The ciliary body (site of aqueous humor production) and the trabecular meshwork and uveoscleral pathway (the principal site of aqueous humor outflow) are the main ocular structures related to aqueous humor dynamics (Goel et al. 2010). Aqueous leaves the eye through both conventional and unconventional pathways. The conventional or trabecular outflow pathway refers to exit of aqueous humor at the anterior chamber angle through trabecular meshwork, the Schlemm canal, intrascleral channels, episcleral and conjunctival veins. In the unconventional or uveoscleral pathway, it exits by passing through the suprachoroidal - scleral tissues. IOP is a function of the balance of aqueous humor inflow and outflow. A steady IOP is the result of equal inflow and outflow of aqueous humor (Allingham et al. 2011).

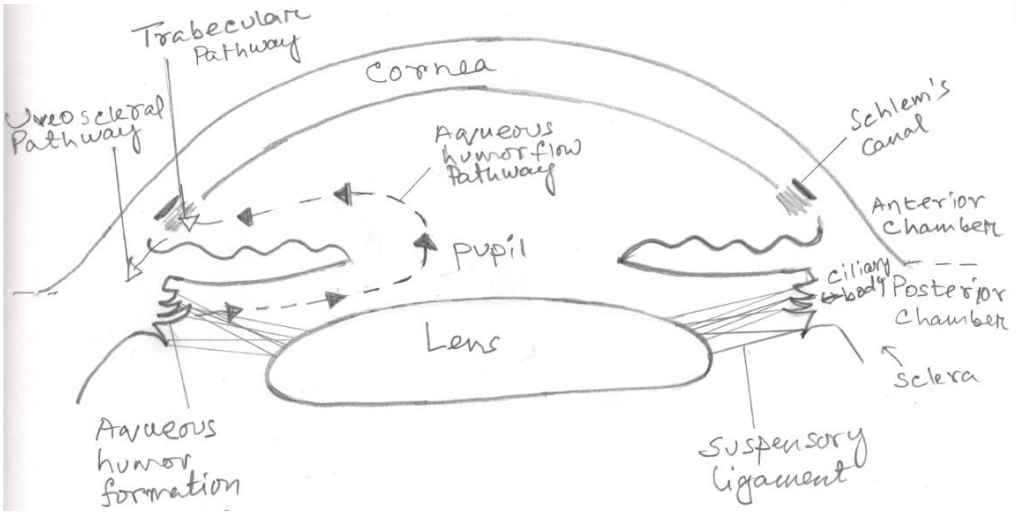

Figure 2: Outflow of aqueous humor

2.1.4.2 Glaucomatous Optic Nerve Damage

The optic nerve head is the distal portion of the optic nerve (2nd Cranial nerve). It encompasses the nerve fibers from the ganglionic cell layer of the retina and converges upon the nerve head into the fundus. The optic nerve head is directly susceptible to IOP elevations. The central area of depression in the optic head is known as the cup. The tissue between the cup and the disc margin is the neural rim, where the bulk of the axons are located. The nerve head may be arbitrarily divided into four portions from anterior to posterior:

- Surface nerve fiber layer: It is the innermost part composed mainly of nerve fibers.

- Prelaminar region: It is the anterior portion of the lamina cribrosa with predominance of nerve axons and astrocytes. Astrocytes are glial cells which provide a continuous layer between the nerve fibers and blood vessels in the optic nerve head.

• Lamina cribrosa region: It contains fenestrated sheet of scleral connective tissue and occasional elastic fibers. The sheets are separated from the fenestrae by the lining of astrocytes.

• Retrolaminar region: This area has less astrocytes and characterized by acquisition of myelin supplied by oligodendrocytes.

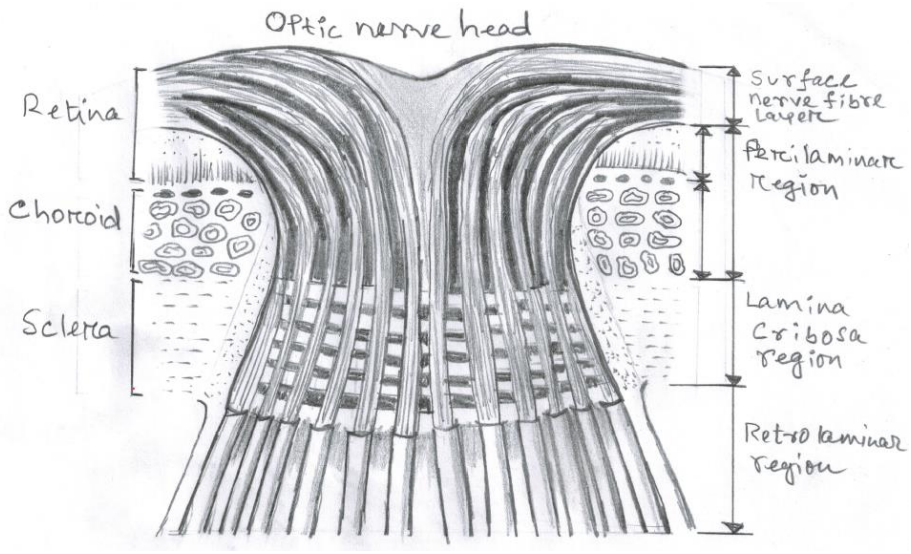

Figure 3: Optic nerve anatomy

Glaucomatous optic nerve damage involves progressive asymmetric loss (thinning) of neural rim tissue (manifested by an enlargement in the area of cupping and pallor), disc hemorrhages and peripapillary nerve fiber bundle damage that can be revealed by careful office examination and photographic documentation. Computed image analysis and blood-flow measures may provide more precise information. Cup to disc ratio (CDR) is only one of the measures of the amount of neural tissue in the optic nerve with Optical coherence tomography (OCT), now also an important part of the optic nerve assessment. (Allingham et al. 2011).

2.1.4.3 Visual Field Defect in Glaucoma

The normal boundary of field of vision is approximately 60 degrees above and nasal, 70 to 75 degrees below and 100 to 110 degrees temporal to fixation (Allingham et al. 2011). In early glaucoma, peripheral field defects, usually a nasal step, may be the only abnormality detected with perimetry (Caprioli and Spaeth, 1985). In advance stage central vision is also compromised. Some of the other visual field defects associated with glaucoma include temporal wedge, arcuate defects, - concentric contraction, and enlargement of the blind spot. Automated or manual perimetry can be used to measure visual field (Allingham et al. 2011).

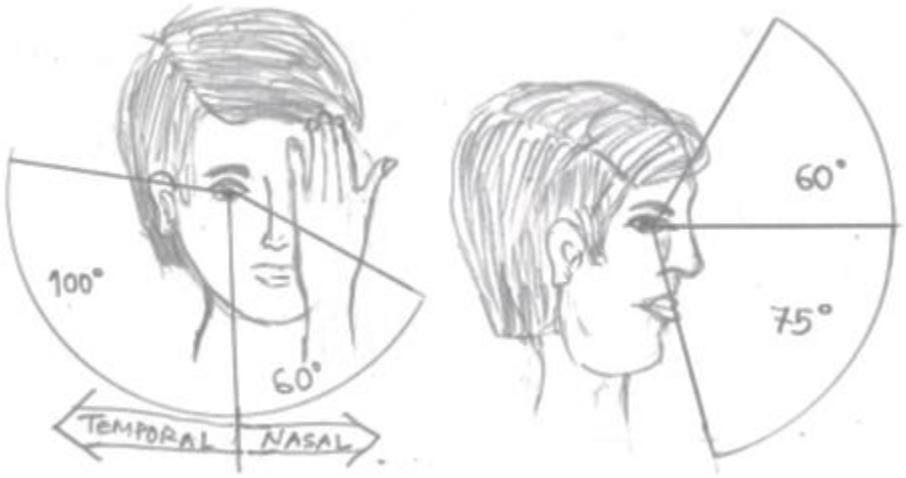

Figure 4: Normal boundary of field of vision

2.1.5 Natural History of Glaucoma

The natural history of glaucoma, in general, can be divided into five stages (Allingham et al. 2011):

- Stage 1- Initiating events: The series of conditions that initiate the chain of events responsible for favoring the onset of any pathologic or physiologic alterations pertinent to optic nerve function or aqueous humor dynamics.

- Stage 2 - Structural alterations: Changes in tissues that may ultimately lead to alterations in optic nerve function or aqueous humor dynamics.
- Stage 3 - Functional alterations: Physiologic abnormalities leading directly or indirectly to optic nerve damage.
- Stage 4 - Retinal ganglionic cell and optic nerve damage: Loss of retinal ganglionic cells and their associated axons.
- Stage 5 - Visual loss: Progressive loss of vision due to progressive optic nerve damage.

2.1.5.1 Natural History of POAG

The detection of slowly progressive POAG is delayed until in its advance stage due to lack of symptoms. The progression rate of visual defects and response to treatment to delay or halt the visual field damage is not uniform across all patients (Leske et al. 2004). Considering the clinical care of POAG, the natural history can be divided chronologically into following three phases (Allingham et al. 2011):

- The Latency Phase: It starts with the glaucomatous optic nerve damage extending up to the detection threshold, at which point the optic nerve damage can be accurately detected by the diagnostic procedure.
- Detectable Preclinical Phase: This is the lengthy asymptomatic phase during which, glaucoma can be detected with a diagnostic procedure. This phase continues until appearance of symptoms. However, detection of optic nerve damage in a single visit is often difficult.
- Clinical Phase: It is marked by the onset of symptoms, usually when the disease is advanced. It may take decades to reach this phase.

2.1.5.2 Natural History of ACG

ACG can be acute, sub-acute and chronic that can occur in same person at different time period and progression of ACG can be divided into following three stages (Pan and Verma, 2011):

- Anatomically narrow angle without elevated IOP, abnormal visual fields or peripheral anterior synechiae.
- Development of peripheral anterior synechiae or a closed angle with elevated IOP.
- Development of glaucomatous optic neuropathy and visual field changes along with an anatomical angle closure.

2.1.6 Descriptive Epidemiology

Glaucoma is the second-leading cause of blindness and leading cause of irreversible blindness worldwide, having an estimation of 79.6 million glaucoma patients by 2020 (Quigley et al. 2006) and by 2040, it will be 111.82 million (Tham et al. 2014). Worldwide, 13.5% of blindness is due to glaucoma (Thylefors et al. 1995). More than 50% of glaucoma patients are unaware of their disease at presentation (Reidy et al. 1998; Wensor et al. 1998; Mitchell et al. 1996). The case definition and clinical classification used in different glaucoma prevalence studies varies widely (Foster et al. 2002).These differences make it difficult for direct comparison of prevalence findings across studies. The global prevalence of glaucoma for 40-80 years age group is 3.54%; prevalence of POAG is highest in Africa (4.20%) and that of PACG is highest in Asia (1.09%). Men have 36% more chances to develop POAG than women. People of urban areas have 58% more risk of developing POAG than their rural counterpart. Glaucoma occurs more in elderly (Tham et al. 2014).

Prevalence of OAG among racial and ethnic groups varies greatly. The Baltimore Eye Survey revealed higher prevalence of POAG in blacks (4.3%) than white (1.3%) among age group 40 years and above (Sommer et al. 1991). For Hispanics in USA, it was 2% (Quigley et al.2001). Glaucoma rates in Asians ranges from 1 to 4% (Rudnicka et al. 2006). In 2007, it was estimated that 24,937 Canadians had severe vision loss due to glaucoma, corresponding to 3.1% of all vision loss. (Access Economics Pty Limited, 2009).

2.1.7 Risk factors

2.1.7.1 Increased IOP

The single most important modifiable risk factor for glaucoma is elevated IOP, though not all patients with elevated IOP develop glaucoma (Schmidl et al. 2015; Bahrami, 2006). The role of IOP in pathogenesis of glaucoma is supported from both clinical trials (Vass et al. 2007) and also from basic science research (Stammer et al. 2012; Tamm, 2009).

2.1.7.2 Age

Advancing age is a recognized risk factor for OAG, having a 4 to 10 times higher prevalence in the age group older than 40 years (Hollows and Graham 1966; Leibowitz et al.1980; Tielsch et al. 1991). A meta-analysis of multiple population-based studies of POAG or PACG concluded that, OR of prevalence of POAG was 1.73 with each decade increase of age (Tham et al. 2014).

2.1.7.3 Family history

Positive family history of glaucoma may increase the risk of developing glaucoma for individuals (Burr et al. 2007; Wolfs et al. 1998; Netland et al.1993). It is an important predictor for first-degree relative with glaucoma (Allingham et al. 2011). However, prospective studies that examined the progression of glaucoma and family history did not find any significant association between them (Leske et al. 2003; AGIS, 2002).

2.1.7.4 Ethnicity

Ethnicity can affect IOP and thus influences glaucoma prevalence and incidence. African descent has higher prevalence of OAG whereas prevalence of ACG is more in Asian and Inuit populations (Friedman and Vedula 2006; Hatt et al. 2006; Burr et al. 2007; Schmier et al. 2007). Black people have an estimated 2 to 5 times higher incidence of OAG than white people (Giangiacomo and Coleman, 2009).

2.1.7.5 Myopia

Patients with myopia have greater chance of developing OAG (Burr et al. 2007). Large population-based surveys (Quigley et al. 1999; Michell et al. 1999) and longitudinal studies (Phelps, 1982; Chihara et al.1997) also supported this fact.

2.1.7.6 Migraine and peripheral vasospasm

They may act as a risk factors for progressive glaucomatous optic nerve damage (Budenz et al. 2006; Mitchell et al. 1996). This supports some role for a vascular role in the pathogenesis of glaucoma.

2.1.7.7 Long-term use of corticosteroids

They are the main cause of drug induced glaucoma and associated with increased IOP (Adis International 2004; Tripathi et al. 2003).

2.1.7.8 Vascular aspects

Ocular vascular disturbance which may or may not be due to increased IOP or reduced ocular perfusion pressure may cause or contribute to glaucomatous damage as well as retinal ganglionic cell death (Cherecheanu et al. 2013; Flammer et al. 2002).

2.2 Management of Glaucoma

Glaucoma is generally a chronic, progressive life-long disease. Once diagnosed, the aim of management is to delay or halt the progression of optic nerve damage and visual field defect. The treatment plan needs assessing all risk factors for disease progression, access to healthcare, and lifestyle and life expectancy of patients (Allingham et al. 2011). The control of IOP, the most important modifiable risk factor, is the mainstay of treatment.

2.2.1 Diagnosis of Glaucoma

The diagnosis of glaucoma is a clinical one based on the collective evidence from a careful patient history, the essential elements of a comprehensive eye evaluation that includes assessment of IOP, central corneal thickness measurement,

gonioscopy. Optic nerve head and retinal nerve fiber layer examination, is important in clinical practice (Lester et al. 2013). In essence the diagnosis is made when there are characteristic anatomical (cupping, decreased NFLT) or physiologic (visual field defects) optic nerve changes.

2.2.1.1 Patient's History

As applicable for all other clinical scenarios, history of a new patient of glaucoma suspect (or referral) should include demographic information of the patient, chief complaints, ocular and non-ocular medical and surgical history, current and previous ocular and systematic medications, allergy history, as well as family history of ocular and non-ocular diseases.

2.2.1.2 Comprehensive eye examination

It is very important to obtain and document accurate baseline information of the comprehensive eye examination for assessing future progression of disease and response of treatment(s) initiated and modifications, as needed.

2.2.1.2(a) Intraocular Pressure (IOP) and Central Corneal Thickness (CCT)

Increased IOP is the most important modifiable risk factor for glaucoma and the main focus for the treatment. Goldmann applation tonometry (GAT), a contact method that needs corneal anesthesia, is the standard method for measuring IOP (Tonometry) with proper and regular calibration of the tonometer. Several readings should be obtained from each eye to get an average value of IOP. Serial measurement of IOP is also required due to diurnal variation of IOP. A number of non-contact devices (e.g., ocular response analyzer, ORA) are also available. Corneal biomechanics, most importantly CCT, substantially influence the results of tonometry. So, CCT should also be measured with a pachymeter (normal CCT: 530-545 nm). Increased or decreased CCT may lead to an overestimation or underestimation of IOP, respectively (Barton and Hitchings, 2013b).

2.2.1.2(b) Slit-lamp examination and Gonioscopy

To exclude primary angle closure glaucoma and secondary causes (e.g., angle recession, pigment dispersion and inflammatory forms of glaucoma), examinations of the cornea and anterior chamber are done with the slit-lamp. Gonioscopy, the gold standard for angle assessment (the outflow channels), is performed on slit-lamp examination. Grading of depth of angle is done during gonioscopy. A wide range of angle abnormalities may be found including peripheral anterior synechiae, pigmentation of the trabecular meshwork, signs of intermittent iridotrabecular contact, new vessels and traumatic damage to the drainage angle as well as congenital abnormalities like Axenfeld-Rieger syndrome (Barton and Hitchings, 2013b).

2.2.1.2(c) Dilated Fundus and Optic Disc Examination

These examinations are a must for exploring signs of glaucomatous changes in the optic disc (including cupping of optic disc, optic disc hemorrhage, and retinal nerve fiber layer defects) and to obtain a stereoscopic view of posterior segment to exclude any abnormalities causing secondary glaucoma (i.e., diabetic retinopathy, evidence of surgery for previous retinal detachment, lens abnormalities). The retinal nerve fiber layer, viewed with red-free illumination, should be studied carefully to detect any loss which strongly favors glaucomatous pathology. Meticulous examination for evidence of thinning of the neuroretinal rim should also be done (Barton and Hitchings, 2013b; Allingham et al. 2011).

2.2.1.2(d) Vertical Cup:Disc Ratio (CDR)

A large ratio suggests glaucoma or more rarely other pathology. Wide range of CDR values in normal population reduces its sensitivity for glaucoma diagnosis to less than perfect. (European Glaucoma Society, 2008).

2.2.1.2(e) Visual Field assessment and Perimetry

An integral part of a full ophthalmic examination, visual field assessment, performed with manual or automated perimetry, is essential for diagnosis of glaucoma and assessing baseline status and disease progression rate over time.

This test is subjective and needs patient cooperation and good response. Each eye should be tested separately and any refractive lens correction for the patient, if needed, should be in place. Abnormal visual field is a sign of a lesion anywhere in the visual system from the retina to the visual cortex of the brain. Therefore, visual field defect of glaucoma must be supported and co-related with other glaucomatous findings of retina and optic disc and tonometry. Kinetic (moving target) and Static (stationary target) perimetry are the two major types of perimetry. In static perimetry, a flashing dim light is used in one area of visual field with increasing intensity or size until the patient can recognize it. A complete visual profile is created by repeating the whole process. In kinetic perimetry, light intensity and size are fixed. The light is placed on the periphery of visual field and then gradually moves centrally until the patient visualizes it. A visual field boundary is then mapped by repeating the whole procedure (Cummings and Malouf, 2014). The present day accepted standard way of measuring the visual field is Automated Static Perimetry. Other automated perimetry include Short Wave Automated Perimetry, Frequency Double Technology (FDT) Perimetry, High-Pass Resolution Perimetry, Random Dot Motion Perimetry. Manual Perimetry includes Tangent Screens, Arc and Bowel Perimeters (Broadway, 2012; Barton and Hitchings, 2013b; Allingham et al. 2011).

2.2.1.2(f) Optic Nerve and Retinal Nerve Fiber Layer (RNFL) Imaging for Structural Evaluation

Numerous imaging methods to evaluate the structural changes of the optic disc and retina remain a mainstay for the diagnosis and management of glaucoma. Optical Coherence Tomography (OCT), developed in 1990 and available to ophthalmologists in 1996, provides quantitative and objective assessments of the optic disc, macula, RNFL in glaucoma by constructing cross sectional images and measuring the delay time of the echo of a backscattering low-coherence infrared (843-nm) diode light source. The light source is divided into reference and sample

path. Reflected sample light from patient's eye provides an interference signal with the reference beam detected and recorded by a fiber-optic interferometer. OCT is a non-contact method performed with the patient seating upright at a slit-lamp like headrest. Confocal Scanning Laser Polarimetry can be used to measure RNFL thickness as well. The retinal thickness can be measured by Retinal Thickness Analyzer. All these devices generate reproducible, quantitative measurements (Meira -Freitas et al. 2013; Barton and Hitchings, 2013b; Allingham et al. 2011) and have therefore become the gold standard for structural assessment of glaucoma nerve damage.

2.2.1.2(g) Ocular Perfusion

In patients with normal-tension glaucoma or Raynaud's phenomenon, ocular perfusion may be reduced (Barton and Hitchings, 2013b). Progressive worsening of glaucoma despite well controlled IOP may be due to ocular hypo perfusion. In such circumstances, ocular blood flow measurement may be of value. Several methods for quantitative, comprehensive study of retinal, choroidal, and retrobulbar circulations include vessel caliber assessment, pulsatile ocular blood-flow measurement, scanning laser fluorescein and indocyanine green (ICG) angiography of the peripapillary choroid and the retinal circulation. Laser Doppler flowmetry, confocal scanning laser Doppler flowmetry, and color Doppler imaging have been developed in the past two decades (Harris et al. 1999).

2.2.2 Planning of Treatment

As glaucoma is a chronic disease, long-term planning supplemented by a holistic approach to the individual patient, including education of the condition is needed. The aim of treatment for a glaucoma patient is to halt or delay the glaucomatous progression and damage to the visual function, mostly by lowering the IOP to a target pressure set for individual patients based on the status of the optic nerve head and other risk factors for progression like CCT, increased age, positive family history, African heritage and myopia for POAG; Asian heritage and

hyperopia are considered risk factors for ACG. In general, a target of 20% to 30% reduction from baseline IOP is recommended. Establishing the target IOP is one of the most important decisions to preserve the visual function and best possible quality of life for the patient. It needs careful assessment and modification of target IOP, if warranted, at each follow-up visit. Elevated IOP without glaucomatous damage (i.e., ocular hypertension) may need careful follow-up only without initiation of treatment (Allingham et al. 2011). Proper treatments delay the progression in early glaucoma patients (Leske et al. 2003; Leske et al. 1999). In advanced glaucoma, low IOP with minimal variation after treatment delays further progression of glaucomatous visual function defects (AGIS, 2000).

2.2.3 Treatment Options for Glaucoma

Currently available treatment option for glaucoma are:

- Medication therapy, usually eye drops
- Laser therapy
- Surgery

2.2.3.1 Medication therapy

The field of glaucoma pharmacology was introduced by Sir Thomas Fraser when he mentioned the physiological action of the calabar bean (a source of physostigmine) in his publication (Realini, 2011; Fraser, 1867). The basic pharmacokinetics of topical glaucoma medications that include absorption, distribution, metabolism and elimination of an administered drug should be taken into consideration while prescribing (Mishima, 1981). Currently available major classes of topical medications for glaucoma treatment are as follows:

- Prostaglandin analogues (PGAs)
- Beta-adrenoceptor antagonists
- Adrenoceptor agonists
- Carbonic anhydrase inhibitors (CAIs)

- Cholinergics (acetylcholine receptor agonists)

(Marquis and Whitson.2005; Allingham et al. 2011)

2.2.3.1(a) Prostaglandin analogues (PGAs)

Since their introduction in 1996, PGAs have changed the scenario of glaucoma therapeutics and become the choice of first-line pharmacotherapy for lowering increased IOP (Realini, 2011; Soltau and Zimmerman, 2002). In 1982, Hungarian physiologist Lazlo Bito developed the prototype molecule latanotoprost at Columbia University, after he and Carl Camras revealed that, in both healthy and glaucomatous monkeys, PGF2α (Prostaglandin F2α, a naturally-occurring prostaglandin) lowers the IOP (Camras and Bito, 1981). It took 14 years to develop an approvable formulation of latanotoprost (0.005%). In 2001, two other PGAs, travoprost (0.004%) and bimatoprost (0.03%) came into the market (Realini, 2011). They are administered once daily before bedtime and control diurnal fluctuation of IOP. (Asrani et al. 2000; Bergea et al; 1999).

The PGAs are lipophilic, multi-carbon chain molecules derived from arachidonic acid. They lower IOP by increasing outflow of aqueous humor, primarily through the uveoscleral pathway (Mishima et al. 1997) and also through the TM pathway (Ziai et al. 1993). They also relax the ciliary muscle (Crawford and Kaufman).

Patients tolerate PGAs well. Fewer topical applications with fewer severe side effects rank PGAs as most commonly prescribed glaucoma medication. Ocular adverse effects include conjunctival hyperemia, eyelash growth, and increased iris pigmentation (due to increased melanin production within iris melanocytes after long-term use (Marquis and Whitson, 2005; Watson and Stjernschantz, 1996; Netland et al. 2001; Sherwood and Brandt, 2001). Systemic adverse effects include headache and upper respiratory tract symptoms. Exacerbation of anterior uveitis (Fechtner et al. 1998), cystoid macular oedema (CMO) after complicated cataract surgery (Ayyala et al. 1998; Callanan et al. 1998) have been reported with latanotoprost use.

2.2.3.1(b) Beta-adrenoceptor antagonists

Tonic sympathetic stimulation mediates the formation of aqueous humor in the ciliary body (Wax and Molinoff, 1987). Most of the β-adrenoceptor antagonists block both β1 and β_2 receptors and decrease the production of aqueous humor (Alward, 1998). They are used as a component in many fixed-combination preparations as well as adjuncts and initial monotherapy (Barton and Hitchings, 2013c). The topical use of propranolol, the first β-adrenoceptor antagonists found to decrease IOP, caused corneal anesthesia preventing its further use. Timolol (0.25% and 0.5%), the most popular topical non-selective β_1 and β_2 adrenergic antagonist, was introduced in 1978 in the USA**.** It is used twice a day. The US FDA considers timolol as 'gold standard' for glaucoma pharmacotherapy. All-new glaucoma medications are compared against timolol for FDA approval. Levobunolol (0.25% and 0.5%), carteolol (1.0%), metipranolol (0.3%) are also used twice daily (Marquis and Whitson, 2005). Reported ocular adverse effects include conjunctival hyperemia, stinging, superficial punctate keratitis and worsening dry eye symptoms (Coakes et al. 1981). Bradycardia, arrhythmia, cardiac block, congestive heart failure and bronchospasm are known systemic adverse effects. CNS adverse effects like depression, anxiety, fatigue, impotence and hallucinations have also been reported (McMahon et al. 1979; Van Buskirk, 1980; Fraunfelder, 1980).

Betaxolol (0.25% and 0.5%), applied twice daily, is a cardioselective B_1-adrenoceptor antagonist. It is a less effective IOP lowering agent than timolol and other non-selective agents, but has shown to be more effective in preserving visual field than timolol (Collignon-Brach, 1992; Messmaer et al. 1991). Other than occasional stinging after instillation, there are almost no ocular adverse effects. Systemic adverse effects, if any, are also less pronounced than the non- selective agents (Schoene et al. 1984).

2.2.3.1(c) Adrenoceptor agonists

As part of the sympathetic nervous system, α-adrenergic receptors have an important role to regulate aqueous humor dynamics. Drugs in this class lower IOP by increasing aqueous outflow through trabecular meshwork and uveoscleral pathway or decreasing production, or both. Epinephrine is a non-selective adrenergic agent that stimulates both α- and β- adrenoceptors within the eye. It was commercially available in 1950s as topical glaucoma medication and is rarely used now (Realini, 2011; Marquis and Whitson, 2005; Townsend and Brubaker, 1980). Ocular adverse events of epinephrine include pupillary dilatation, conjunctival hyperemia and ocular irritation (van Alphen, 1976). Systemic adverse events include headache, palpitation, high blood pressure and anxiety.

Clonidine, a highly lipophilic molecule with α_2- and some α_1- adrenoceptor agonistic activity, readily crosses the blood-brain barrier having systemic hypotension as an adverse effect when instilled topically into eyes. It is still in use in part of Europe (Marquis and Whitson, 2005). Apraclonidine or para-aminoclonidine (available in 0.5% and 1.0% concentration), a serendipity derivative of clonidine, is a highly hydrophobic molecule (less likely crosses the blood-brain barrier with relatively selective α_2-adrenoceptor agonistic activity. It is not used for a prolonged period due to high rate of blepharoconjunctivitis **(**Butler et al. 1995**)**. Tearing and foreign body sensation may occur with ocular instillation (Wilkerson et al. 1991).

Brimonidine, a highly selective α_2-adrenoceptor agonist, is used more commonly as adjunctive therapy for long-term use, though monotherapy is not unusual. It is also used to prevent post-operative IOP spike following anterior segment laser therapy. Brimonidine 0.2% (with benzalkonium chloride as a preservative) is used for two or three times a day (Marquis and Whitson, 2005). Allergic blepharoconjunctivitis is seen in 12%-15% of patients after several months use (Schuman, 1996; Schuman et al.1997). Dry mouth, fatigue and headache may

occur with use of brimonidine. A new formulation of 0.15% brimonidine with stabilized oxychlorocomplex as a preservative shows lower rate of fatigue, dry mouth, and conjunctival hyperemia (Katz, 2002). Brominidine should not be used in children due to chance of CNS and respiratory depression (Marquis and Whitson, 2005). Concomitant use of brimonidine and/or apraclonidine with mono-amino oxidase inhibitors (MAOIs) is contra-indicated (Barton and Hitchings, 2013c).

2.2.3.1(d) Carbonic anhydrase inhibitors (CAIs)

Belonging to the sulphonamide group of drugs, CAIs are available in both oral and topical form. They inhibit the catalyst carbonic anhydrase isoenzyme II in the ciliary epithelium to suppress the conversion of CO_2 and H_2O to HCO_3^- and H^+, thus decrease aqueous humor formation (Marquis and Whitson, 2005).

Acetazolamide, the first systemic CAI introduced in 1954, is available in 125 mg and 250 mg and a sustained-release capsule form of 500 mg with twice daily dosing. Methazolamide (25 mg and 50 mg), weaker and slightly less effective than acetazolamide, is often better tolerated by patients with twice or thrice daily dosing. Despite effectiveness in lowering IOP, their clinical use is limited due to several and often very bothersome adverse effects, including hands and feet paresthesia, nausea, vomiting, fatigue, weight loss, metabolic acidosis, low serum potassium (hypokalemia), low serum sodium (hyponatremia). They are reserved for short term use in a patient with maximally tolerated medical therapy and often before ocular surgery to control raised IOP (Realini, 2011; Marquis and Whitson, 2005).

Dorzolamide (2.0%) was the first topical CAI introduced in 1994. In 1998, another topical CAI, brinzolamide (1.0%) became available. Both are used three times a day. Topical CAIs have much fewer adverse events than systemic CAIs. Ocular adverse effects include stinging, burning and itching (Realini, 2011; Marquis and Whitson, 2005). In patients with marked endothelial compromise, irreversible

corneal decompensation may occur (Konowal et al. 1999). Brinzolamide has better patient tolerability than dorzolamide (Silver, 1998). All forms of CAIs should be avoided in patients with sulfonamide hypersensitivity (Marquis and Whitson, 2005). Unfortunately topical CAIs are much less effective than oral CAIs thus relegating them to third or fourth line agents.

2.2.3.1(e) Cholinergics (acetylcholine receptor agonists, parasympathomimetic)

Also known as miotics, they are the oldest glaucoma drugs introduced in the 1870s (Alward, 1998). At neuromuscular junction, they stimulate parasympathetic receptors. As a result, there is contraction of the longitudinal muscle of the ciliary body that pulls on the scleral spur and opens the trabecular meshwork and schlemm canal causing increased aqueous outflow (Kaufman et al. 1976) and subsequent reduction in IOP. They are of two types: direct-acting cholinergics, work on the parasympathetic receptors in the eye and indirect-acting cholinergics, work by inhibiting acetylcholinesterase enzyme and results in decrease degradation of acetylcholine (Marquis and Whitson.2005).

Pilocarpine, the most commonly prescribed topical short direct-acting cholinergic compound, is available in a range of 0.5% to 4.0 % concentration with four times a day dosing. A topical gel form to be applied at bedtime is also available. Diminished visual acuity, fixed small pupil and induced myopia are often and retinal detachment is rarely reported ocular adverse effects. Frontal headaches above the eye can be very bothersome. Systemic adverse effects are uncommon and include increased salivation and sweating, diarrhea, vomiting and tachycardia. Although effective and inexpensive, it is not used that much today because of its ocular adverse effects and multiple dosing requirements and availability of alternatives. Ecothiophate iodide and demecarium bromide are indirect-acting cholinergics. As like pilocarpine, they are available in multiple concentrations and are used twice a day. They deplete systemic cholinesterase and pseudocholinesterase. They are used for treatment of glaucomas in aphakia and

pseudoaphakia in many parts of Europe and Latin America (Marquis and Whitson.2005). Chronic use of ecothiophate iodide may predispose tocataract formation (Thoft, 1968).

2.2.3.2 Laser Therapy

A significant advancement in the treatment of glaucoma was the introduction of light amplification by stimulated emission of radiation or laser during the second half of the 20th century. Lasers are now commonly used to treat various forms of glaucoma including open angle glaucoma, pseudoexfoliative syndrome and pigmentary glaucoma (Mainster et al. 1983; Peyman et al. 1984, Allingham et al. 2011).

2.2.3.2(a) Basics and Properties of Laser Energy

The basis of laser technology is based on the Quantum Theory of Radiation by Albert Einstein, where he hypothesized that the photon, the tiny packets or particles of light, has discrete quantum of energy proportional to its wavelength (Einstein, 1917). Laser energy has distinct properties. Light emitted by lasers causes the photons to be synchronized (coherence). A small focal spot can be created when the laser is delivered through an optical system (commonly a slit-lamp biomicroscope) resulting in a nearly parallel beam with limited divergence (collimation), with only one discrete wavelength (monochromacy) and high intensity (Allingham et al. 2011).

2.2.3.2(b) Laser effects on target tissue.

Laser therapy for glaucoma causes photocoagulation (local inflammation and scarring) of target tissue or photovaporization (vaporization of intracellular and extracellular fluids), facilitated by short exposure time and high-energy level and an area of exposure that reduce heat conduction and creates a noninvasive incision in the tissue. Thermal effect depends on wavelength of the light, duration of exposure and amount of light energy per area of exposure. Lasers with wavelengths between 400 to 600 nm are most useful for these procedures as

Melanin, the pigment of most target tissues, has a peak absorption in the blue-green portion of the visible spectrum. High intense energy of laser in a very small area of target tissue for an ultra-short period of time causes ionizing reaction resulting in photodisruption, a technique in ophthalmology utilizing lasers to form a gaseous state called plasma, which then causes acoustic shock waves that can disrupt both pigmented and non-pigmented structures. The most common application of this technology being excimer laser technology to treat refractive errors. Thermal effects also play a role in photodisruption mechanism (Mainster et al. 1983; Allingham et al. 2011).

2.2.3.2(c) Laser Delivery Units and Laser Types for Glaucoma Treatment

A slit-lamp biomicroscope is used by most laser units. In an articulated arm, a system of fiber optics or mirrors guide the laser beam from the laser tube, through the slit-lamp, into the patient's eye. Other laser delivery systems use contact probes attached to the fiber optics. For positioning and focusing of the laser beam in the visual spectrum, an aiming laser beam of attenuated energy can be used. For laser beams with wavelengths outside the visual spectrum, an additional laser (e.g., helium-neon), or semiconductor diode, with wavelength of 633 and 640 nm, respectively, is used. The control unit of most laser systems include spot size (in microns), exposure duration (milliseconds, microseconds or nanoseconds), and energy (joules or millijoules) or power (watts or milliwatts). Most commonly used lasers for glaucoma are argon, Nd: YAG, and semiconductor diode. They primarily differ by the medium in which the atom exists that causes the stimulated emission of photons (Allingham et al. 2011).

2.2.3.2(d) Argon Laser Trabeculoplasty (ALT)

Since Krasnov reported a temporary control of IOP in open -angle glaucoma in 1973 by using ultra-short ruby laser pulses (Krasnov, 1973), control of open angle glaucoma by treating trabecular meshwork with laser has been a common treatment in the field of ophthalmology. Wise and Witter first reported a series of

56 eyes of diagnosed open angle glaucoma patients treated with argon lasers applied 360 degree to the trabecular meshwork and concluded that, treatment of open angle glaucoma with argon laser (laser trabeculoplasty) was an effective alternative to filtration surgery in phakic eyes (Wise and Witter, 1979). Argon gas is the medium in the argon laser delivery system. The wavelength is in the blue (488nm) and green (514 nm) portions of visible spectrum and is optimum for absorption by melanin. Green only argon light may be safer for the ophthalmologist with equivalent efficacy of lowering IOP. The procedure is performed at the slit lamp with gonioprism placing evenly spaced 50-100 nonpenetrating argon laser spots to the TM over 180° - 360° of the angle to produce thermal burns around the circumference of the TM. Commonly used parameters are spot size (50μ), pulse duration (0.1 sec) and power (400-800 mW) (Marqquis and Whitson, 2005). The precise mechanism of improved aqueous outflow and IOP reduction by ALT is still unclear. Heat-induced shrinkage and tightening of treated trabecular meshwork cells may contribute to the mechanism (Babizhayev et al. 1990). It has also been postulated that ALT reduces the trabecular cell density by eliminating them partially, and the remaining cells produce a different composition of the extracellular matrix with improved outflow properties (Van Buskirk et al.1984; Kimpel and Johnson, 1992). The cellular response and the tissue remodeling after initial mechanical injury by ALT probably result in an improved aqueous outflow and IOP reduction (Van Buskirk, 1989). In the histopathological study of autopsy eye, Kramer and Noecker (2001) found coagulative damage with ablation craters at the base and edge within the uveal meshwork following ALT. Due to the initial damage to the targeted tissues, repeat ALT is not effective in lowering IOP. (Feldman et al. 1991; Weber et al. 1989). However, efficacy of ALT in lowering IOP is equivalent compared to medications (The Glaucoma Laser Trial Research Group, 1990). Complications of ALT include transient IOP elevation (Frucht et al. 1985), iritis (Thomas et al. 1982) and PAS (scar) formation (Hoskins et al. 1983).

2.2.3.2(e) Selective Laser Trabeculoplasty (SLT)

Latina and Park reported that, when the energy of a Q-switched (to allow photodisruption), frequency doubled, 532 nm Nd: YAG lasers (neodymium atoms are embedded in a crystal of yttrium-aluminium-garner) with pulse durations ranged from 10 nsec to 0.1 sec was used in a mixed cell culture of pigmented and nonpigmented TM cells, it selectively targeted pigmented trabecular meshwork cells without causing structural damage to non-pigmented cells (Latina and Park, 1995). The mechanism is based on the principle of selective photothermolysis, whereby absorption of a suitable brief optical radiation with inherent optical and thermal properties causes selective damage to target cells and destroys melanosomes within melanocytes that minimize thermal injury to surrounding structures (Anderson and Parrish, 1983). The desired target cell must have an intracellular chromophore with greater optical absorption at the laser wavelength than its surrounding tissues and the duration of laser must not exceed the time required for thermal diffusion into the tissue (thermal relaxation time) (Kagan, et al. 2014). The precise mechanism of action of IOP lowering effect of SLT is not fully understood, but several potential biological and mechanical mechanisms, particularly cytokine secretion, matrix metalloproteinase induction, increased cell division, repopulation of burn sites and macrophage recruitment may be vital. Clinically, the energy level of SLT is titrated until the appearance of microbubbles (Latina and de Deon, 2005).

In the same histopathological study by Kramer and Noecker (2001), those human autopsy eyes having SLT showed only disruption of trabecular endothelial cells, possibly resulted from the cracking of intracytoplasmic pigment granules. Coagulative damage or disruptions of the corneoscleral or uveal trabecular endothelial beams were not observed. This finding suggests, at least theoretically, SLT may be a potential repeatable procedure.

SLT is now a widely used and acceptable procedure for treatment of glaucoma at both patient and ophthalmologist level. Many ophthalmologists suggest SLT even as first line of treatment for OAG (Melamed et al. 2003; Nagar et al. 2005; McIlraith et al. 2006). SLT as initial treatment of glaucoma results in fewer treatment steps to maintain the target IOP and slower progression to blindness or invasive surgery when compared to medications as initial treatment (Katz et al. 2012). SLT is also effective in lowering IOP when previous ALT failed (Latina et al. 1998; Birt, 2007). As like ALT, SLT produces equivalent IOP reduction to medications (Melamed et al. 2003; McIlraith et al. 2006). SLT success is significantly predicted by baseline IOP. (Hodge et al. 2005).

There is a paucity of well designed, especially prospective studies for assessing the safety and efficacy of SLT (Ayala and Chen, 2011). Study of safety and efficacy of repeatability of SLT is even less studied. A few retrospective studies have demonstrated that, repeat SLT in POAG patients had similar efficacy to initial SLT (Avery et al. 2013; Hong et al. 2009). Another retrospective study revealed successful IOP lowering effect of repeat SLT in eyes that did not achieve desired IOP reduction after initial SLT (Khuri et al. 2014). A prospective study demonstrated an 86% (26 out of 30 eyes) success rate of repeat SLT (Lai and Bournias, 2005). The fact that this repeatability issue has not been well studied prospectively is the cornerstone issue for this clinical trial.

IOP spike immediately after SLT may be a potential complication that can be prevented by using topical α-agonist in the perilaser period and ensuring titration of energy to just produce microbubbles in the target tissue. (Waisbourd and Katz, 2014). Other complications include uveitis (Kim and Singh, 2008), corneal edema (White et al. 2013), hyphema (Shihadeh et al. 2006), macular burn (Liyanage et al. 2014), and irreversible IOP spike, especially with heavily pigmented TM (Harasymowycz et al. 2005).

Comparison of ALT and SLT

The first clinical trial comparing IOP lowering effect of ALT and SLT was conducted by Damji et al. (1999) that revealed equivalent reduction in IOP at 1-year follow up. In their review of 145 articles, Sample et al. (2011) concluded that, Laser trabeculoplasty is successful in lowering intraocular pressure for patients with open-angle glaucoma, but they did not find any literature establishing the superiority of any particular form of laser trabeculoplasty. The efficacy of both lasers compared to each other and also to different pharmacotherapies are equivalent. Their complications are also similar (Marquis and Whitson). SLT has the theoretical advantage of repeatability that has yet to be established with a sufficiently powered randomized prospective clinical trial-which is what we are doing in this clinical trial.

2.2.3.2(f) Surgical Options

When medical or laser therapy fails to control glaucoma, surgical options have to be considered. The glaucoma surgery aims to either increases the outflow or decreases the production of aqueous humor (Razeghinejad and Spaeth, 2011). As such, glaucoma surgery has two basic approaches-

(a) Aqueous humor outflow increasing surgery:

In 1856, Graefe observed that glaucoma, particularly acute attack, could be controlled with iridectomy. In 1867, De Wecker did anterior sclerotomy, the first filtration surgery to make a ‘filtration cicatrix’ with a full-thickness scleral incision 1 mm posterior to the limbus, through which intraocular fluid might escape the anterior chamber. This formed the basis of ocular filtration surgery (Hirschberg, 1994). Modern trabeculectomy techniques started over 30 years ago (Cairns, 1968). It involves making a fistula underneath the scleral flap into the anterior chamber to allow the aqueous humor to pass through it into the bleb in the subconjunctival space, thus reducing the IOP. Surgical scar formation is a potential limiting factor for long-term success (Marquis and Whitson, 2005), that

can be delayed or halted to some extent by post-operative use of anti-fibrotic agents (fluorouracil, mitomycin), thus extending the duration of trabeculectomy success (Ruderman et al. 1987; Palmer, 1991). Complications of trabeculectomy include hypotony, cataract formation, choroidal effusion or hemorrhage, and endophthalmitis (Marquis and Whitson, 2005). In non-penetrating trabeculectomy (NPT), the innermost layer of trabecular meshwork is kept intact, so the aqueous humor can gradually pass through under the scleral flap (Zimmerman et al. 1984). Although NPT has fewer early post-operative complications, its effectiveness, when compared to standard trabeculectomy, is also less. (Chiselita, 2001).

When trabeculectomy fails, drainage device implant surgery can be performed. Usually, a silicone drainage tube is implanted from the anterior chamber to a plate or disc below the subconjunctival space (Marquis and Whitson, 2005). A number of valved (Krupin and Ahmed) and non-valved (Baerveldt, Molteno, Schocker, Ex-PRESS) devices are available (Razeghinejad and Spaeth, 2011).

The Ex-PRESS shunt, introduced in 1998, is a biocompatible, stainless steel device, placed under a partial thickness scleral flap. It is often used in conditions such as aphakia, uveitic glaucoma, and pseudoaphakia (Nyska et.al. 2003).

The iStent, is a heparin coated, non-ferromagnetic, 1 mm long L-shaped stent, introduced in 2001 for trabecular meshwork micro-bypass procedures, that reroutes the aqueous from the anterior chamber directly into the Schlemn's canal (Razeghinejad and Spaeth, 2011). Preliminary result of this procedure is encouraging, but studies with long term follow-ups are warranted for further evaluation (Nichamin, 2009; Fea, 2010).

(b) Surgery for decreasing aqueous humor inflow:

These are cyclodestructive procedures, the last resort to control glaucoma refractory to medical and other surgical therapies, involving destruction of part of the ciliary body, thus decreases the production of aqueous humor and reduces IOP

(Marquis and Whitson, 2005). These procedures include cyclocryotherapy (deRoetth, 1966), cyclodiathermy (Dunphy and Albaugh, 1941), and laser cyclophotocoagulation (Peyman et al. 1990).

2.3 Economic Evaluation of Healthcare: An Overview

In every corner of life, scarcity of resources prevails. There are no exceptions. Hence a series of pragmatic decisions in a systematic manner for optimum use of limited resources for the maximum benefit of stakeholders is needed (Hurley, 2000). The decision of resource allocation for healthcare is even more difficult. Rapid accumulation of medical information and availability of different technologies for the same medical condition often offers complicated situations to decide which treatment option for the given condition would carry the best results at both individual and policy level (Petitti, 2000). Mounting pressure on healthcare budgets in every country force policy makers to consider the costing aspect of a given treatment modality along with its clinical effectiveness to maximize outcome and minimize costs. Economic evaluation is the comparative analysis of alternative course of action in terms of both their costs (input) and consequences (outcomes, effects). It provides a framework to make the best use of clinical evidence through organized analysis of effects of all available alternatives on health, healthcare cost and other issues deemed valuable. Economic and clinical evaluations for a given medical condition are complementary to each other. (Drummond et al. 2015).

Some key aspects of a good economic evaluation are as follows:

Formation of a Clear Evaluation Question:

As with any good research analysis, the carefully articulated question of an economic analysis should clearly reflect the goals and objectives of the interventions under consideration with outcome measures to judge the interventions (Seflon, 2000).

Defining Effectiveness of Intervention and Measuring and Valuing Outcome:

For linkage of cost to effect in an economic evaluation, assessment of effectiveness of the interventions along with value of outcomes or benefits are vital. Conclusion about the effectiveness is often more criticized than costing of interventions (Clyne and Edwards, 2002).

Comparison of Competing Alternatives:

This is, perhaps, the most central feature of an economic evaluation. Within a specific context, costs and effectiveness of specific interventions or programs in comparison should be made (Clyne and Edwards, 2002).

- ***Defining the Perspective:***

  The costs and consequences of an economic evaluation are determined critically by its perspective. The cost can be estimated from the perspective of society. This societal perspective includes all the accrued costs and consequences for a given situation. In perspective from government, a sector, or even individuals, cost will be calculated according to the interest of the party involved (Drummond et al. 2015; Clyne and Edwards, 2002).

- ***Assessing Costs:***

  Careful cost assessment is a pivotal component of economic evaluation. Conducting a cost assessment not only includes the identification of alternatives and measurements of relevant cost items after establishing the perspective, discounting and monetary evaluation of benefits, but also the opportunity cost (relative to benefit) of the alternative uses (Shiell et al. 2002). Often, “Do Nothing” alternative is used to establish a baseline comparator for resource use (Palmer and Reftery, 1999). The former may be more costly than the latter option, as individuals may inefficiently utilize a wide range of publicly provided alternatives (Browne, 1998). Costs may be calculated item by item (microcosting) or based on an average or modeled estimate (macrocosting)

- ***Valuing Cost Items in Monetary Terms:***
  Albeit cost estimates in economic evaluation should reflect the opportunity cost. In practice, direct costs are usually valued at the price paid for each item, termed as the market value (Clyne and Edwards, 2002).
- ***Time Preferences and Discounting:***
  Most interventions and programs, particularly in medical fields, continues over a long period of time. In such scenario, it is necessary to consider the time preference for money that measures the extent to which individuals prefer to have dollar or resources today rather in future (Hurley, 2000). Discounting reflects the loss in economic value due to delay in incurring cost or realizing benefit. So in health economic evaluation, a discount rate (usually 3% to 8%) is applied over all the number of years to be considered over all the accumulated expenditure and anticipated benefits to discount the future costs and benefits to the present (Petitti, 2000; Hurley, 2000).

Although costs estimation across most economic evaluations, in monetary units, has a common format, the approach of consequences or benefits estimation varies substantially (Hurley, 2000; Drummond et al. 2015). Four types of economic evaluations are most commonly used:

- In ***Cost Effectiveness Analysis (CEA)***, consequences or benefits of different interventions are measured in natural units (e.g., life years gained, cases prevented, deaths avoided). Alternative interventions are then compared in terms of costs per unit effect achieved (Hurley, 2000) in the same outcome units. For evaluating the relative efficiency of two (or more) programs, the incremental cost-effectiveness ratio (ICER) that expresses the additional cost needed per additional unit of effect, is determined. For a comparison of competing programs P1 and P2, the ICER is calculated as follows:

$$\text{ICER} = \frac{\text{Difference in costs between programs P1 and P2}}{\text{Difference in health effects between programs P1 and P2}}$$

CEA may identify the intervention with dominant position that achieves the desired outcome with lower costs over the other options considered (Drummond et al. 2015; Clyne and Edwards, 2002; Hurley 2000).

- In ***Cost-Utility Analysis (CUA)***, the outcomes of the interventions are measured in terms of Quality-Adjusted Life Year (QALY) keeping all other structures the same as CEA. QALY is a measure that assesses the effect of a health intervention on both the quantity (length) and quality (as indicated by people's subjective rating of the health state between 0 or immediate death and 1 or full health) of life. CUA is often addressed as an adaptation of CEA (Hurley 2000; Palmer et al. 1999). Its main use is to compare costs on outcomes that may be similar enough to compare but do not have the same exact outcomes (e.g. death from breast cancer with morbidity from severe eczema).

- In ***Cost-Benefit Analysis (CBA)***, outcomes of interventions are valued in monetary terms by either human capital approach or willingness to pay. In human capital approach, health gain is valued against accompanying increase of a person's wage rate (market productivity). In willingness to pay, health gain is valued against the amount the person is willing to pay to achieve the health gain. For programs P1 and P2, net benefit can be calculated from CBA as follows:

  Net Benefit = (Benefit P1- Benefit P2) - (Cost P1-Cost P2).
  If the net benefit is positive, implementation of the program P1 would increase welfare of society and vice versa (Hurley, 2000). CBA is not used nearly as much as CEA or CUA.

- In ***Cost-Minimization Analysis (CMA)***, the interventions are compared only on their costs to determine the least-expensive option, as the effectiveness (or outcome) of the interventions is the same qualitatively and quantitatively. This condition is not often met in real situations (Clyne and Edwards, 2002; Petitti, 2000).

Several types of uncertainty are associated with method of analysis of economic models. Sensitivity analysis can help the reviewer to determine which parameters are the key drivers s of a model's output. One-way sensitivity analysis assesses the impact of changes of certain parameters, one at a time, on the model's conclusion. Probabilistic sensitivity analysis quantifies the level of confidence to the conclusions of an economic evaluation (Taylor, 2009; Petitti, 2000).

2.4 Trial Based Economic Evaluation

When economic data are collected in a randomized control trial (RCT), it can serve as the basis for an economic evaluation study and can be termed as 'Trial Based Economic Evaluation' (Ramsey et al. 2015). When randomization is proper in different study arms, RCT provides high internal validity with good effectiveness data of interventions among different arms. Patient-specific data on both costs and consequences (outcomes) are used to estimate mean cost and mean health outcomes for an incremental analysis. However, there are some issues and problems needed to be addressed by the researchers in such a setting of economic evaluation. Some RCTs may lack generalizability to the target population of interest. Effectiveness or outcome measurement in an explanatory RCT may not mimic the real practicing intervention scenario and thus may over-estimate or under-estimate the cost-effectiveness analysis. Inadequate patient follow-up may adversely affect the economic evaluation (Drummond et al. 2015). Schwartzand and Lellouch (1967), introduced 'pragmatic approach' along with 'explanatory approach' of RCT. A compromise between the goals of internal validity and generalizability with the aim to evaluate the effectiveness or cost-effectiveness of

the intervention to reflect the 'real world' condition when the intervention will be in routine use, may support an economic evaluation (Drummond et al. 2015). Thorpe et al. (2009) developed the Pragmatic-Explanatory Continuum indicator Summary (PRECIS) to assess and display the position of any given trial within this continuum to help trialists to assess the degree to which design decisions align with the trial's stated purpose of either supporting pragmatic approach (decision making) or explanatory approach.

2.5 Markov Modelling

Markov modeling allows presentation and analysis of random and repetitive process over time in a decision tree. It is particularly suitable for chronic disease with recursive nature. The disease in question is divided into distinct states, known as Markov states over a series of discrete time period with the transition probabilities of occupying a given state known as Markov cycle. During each cycle, the patient may move from one state to another. The length of the cycle should represent a clinically meaningful time-interval. During the modelling process, a patient may stay to the same state or may transit to another state at the end of the cycle. A Markov process ultimately needs the 'absorbing state' when it is impossible for patient to move from the state or the patient dies. Two other less applied but useful Markov states are temporary state and tunnel state. Temporary state is used for a short event when a patient can stay at that state for a maximum of one cycle. When a temporary state lasts for more than one cycle and can transit in a fixed sequence, it is known as tunnel state. The Markov state should also represent a clinically and economically important event over a period of time. The transition probabilities of a Markov chain model are assumed constant over time. However, transition probabilities in health care are time dependent and may change with age, sex and other relevant characteristics of patients. Costs are typically assigned to each Markov cycle in line with the state of the patient. Health utility or effect and cost are calculated independently from each cycle. Costs and

health outcomes from all cycles are then added up. The expected costs and values of health outcomes of each Markov state are weighted by the time a patient spends in that state. The final expected values of cost and health outcome are derived from summing up weighted values of each cycle. Discounting for cost and health outcome (when appropriate) should be done using the defined formula of discounting. For survival duration, proportion of all alive patient in each state per cycle should be weighted by 1 and those who died should be weighted by 0. Adding the result would give the expected number of life -year of the cohort of the Markov model. To examine the robustness of the results of a Markov model, sensitivity analysis under variability of parameter uncertainty, analytical uncertainty, generalizability of results and structure uncertainty are performed. (Drummond et al.2015; Xin, 2007; Briggs and Sculpher, 1998; Sonnenberg and Beck, 1993).

2.6 Economic Evaluation of Glaucoma

Studies on the economic evaluation of glaucoma are limited with the majority addressing costs only (Rouland et al. 2005; Kobelt, 2002; Coyle and Drummond, 1995). Several studies on the cost-effectiveness of glaucoma screening have been conducted. Gottlieb et al. (1983) introduced a measure of Quality Adjusted Year of Vision (QAYV) and performed a cost-effectiveness analysis of various screening methods of glaucoma in 40-79 years age group. They concluded that screening of age group 55-70 years were most cost-effective, tonometry was more cost-effective in younger groups and screening of the high-risk group for glaucoma was more cost-effective compared to general population. Boivin et al. (1996) did a cost-effectiveness analysis of glaucoma screening using opinion based estimates of the effectiveness of glaucoma for a three yearly screening of subjects 40-79 years, where perimetry was done if any abnormality was detected on fundoscopy and tonometry. Scenarios with different screening frequency, age, participation in screening, compliances with treatment, treatment efficacy, and

diagnostic tests were also examined. They did not find any proof that treatment of glaucoma or of high intraocular pressure from a screening standpoint would arrest the progression of glaucoma to blindness, even when treatment efficacy was assumed to be as high as 50%. They also concluded that, the cost-effectiveness of most glaucoma screening programs considered would not be competitive. Tuck and Crick (1997), in their cost-effectiveness study of different modes of screening/case-finding for glaucoma, concluded that glaucoma screening for people aged 40 years or more could be justifiable and likely to be economically beneficial when conducted with overall eye examinations.

In their review of the economic burden of glaucoma, Rouland et al. (2005) found that, most costs were associated with direct medical costs, although non-medical costs were also substantial. Treatment costs were directly proportional to severity of disease and number of medications used and negatively correlated with treatment efficacy in reducing IOP. With introduction of costly but more potent and better tolerated medications, treatment costs also increased greatly.

Using a Markov model with a 25-year time horizon, Stein et al (2012) compared the incremental cost-effectiveness of treating newly diagnosed mild OAG with PGAs, LTP, or observation only. They concluded, both PGAs and LTP were cost-efficient options and if the assumption of optimal medical adherence was made, PGAs were more cost-efficient. However, they commented that, more realistic assumption of medical adherence (considering 25% less effective than the documented effectiveness reported in the clinical trial) might prove the other way round.

Lee and Hutnik (2006) projected cost comparison of SLT (repeat treatment every 2 or 3 years) versus glaucoma medication (mono-, di-, and tri-drug therapy groups) over the period of 6 years for OAG patients of Ontario aged 65 years or more. They found, at per-patient level, SLT offered a modest potential cost saving over primary medication regimens. However, the cost of surgery for failed SLT or

medical therapy and the cost for medical therapy in conjunction with SLT were not considered in this study.

Seider et al. (2012) compared cost analysis of topical medications versus SLT assuming a societal perspective. SLT was less costly than most brand-name medications within 1 year and less costly than generic latanoprost and generic timolol after 13 and 40 months, respectively. However, they did not include complications after SLT, need for subsequent surgery, or transportation costs for patients in their analysis.

Cantor et al. (2008) developed a Markov model to stimulate the transition of treatment progression and to compute and compare costs of glaucoma treatment for LTP, surgery and medication over a period of five years. They concluded that, laser trabeculoplasty was associated with the lowest total costs compared to treatment by medication alone or by filtering surgery for patients who were not adequately controlled by two medications. However, they mentioned that, due to limited availability of the transition probabilities in published literature, the model results needed to be validated by prospective or retrospective observational studies.

At the time of writing this thesis, we did not find any study that computed and compared cost-effectiveness of ALT and SLT for treatment of OAG. This study aims to compute and compare the cost-effectiveness analysis of ALT versus SLT among uncontrolled open angle glaucoma patients (including ocular hypertension, pigmentary dispersion syndrome and pseudoexfoliation syndrome) who have had at least one previous full SLT, and are recruited in an ongoing clinical trial entitled ‘A randomized clinical trial of laser trabeculoplasty (SLT) in open angle glaucoma who had been previously treated with complete SLT’.

Chapter 3 – Methods

The objective of this study is to compute and compare the cost-effectiveness of repeat laser treatments (ALT versus SLT) among uncontrolled open angle glaucoma patients (including ocular hypertension, pigmentary dispersion syndrome and pseudoexfoliation syndrome) following previous full 360 degree SLT, who are recruited in an ongoing clinical trial entitled 'A randomized clinical trial of laser trabeculoplasty (SLT) in open angle glaucoma who had been previously treated with complete SLT'.

In section 3.1, a thorough description of the ongoing clinical trial is provided. Section 3.2 elaborates the decision model tree with calculation of ratios of success and failure of each intervention arm. Section 3.3 depicts the cost calculation of the trial components and in section 3.4, final analysis and measures are outlined.

3.1 - Trial section

3.1.1 - Ethics statement

This RCT received approval from The University of Western Ontario Health Science Research Ethics Board (REB# - 103028).

3.1.2 The Hypothesis and the Design of the Trial

The trial hypothesis is that, SLT will be equivalent to ALT for laser treatment of open angle glaucoma. So, an active equivalence parallel armed randomized multi-centered clinical trial based on the results of earlier clinical trial work with SLT and ALT was undertaken in an attempt to demonstrate expected equivalence between the two laser treatments SLT and ALT with respect to intraocular pressure lowering in patients who had previous full SLT. There is no indication that either laser modality would be superior to 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 the events of the post-laser clinical pathways between the two are same. In keeping with an "effectiveness" type

clinical trial, a generalizable study population, permissive eligibility criterion, an easily administered treatment protocol and outcomes that are relevant to patient care were chosen. 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.

When performing a hypothesis testing such as an active equivalence trial like this one, two types of basic error can occur namely type I and type II. Type I error occurs when we reject null hypothesis when it is true. For example, when a researcher claim based on his experiment and statistical analysis of data that, the experimental drug is effective in reducing the morbidity of a specific disease than the placebo, when, in fact, there is no such difference between them, a type I error has occurred. The probability of committing type I error is known as the level of significance, denoted by α. In practice, the standard type I error rate is 5% or α=0.05. Type II error occurs when null hypothesis is not rejected when it is false. When a researcher concludes that there is no difference between the experimental drug and the placebo in reducing the morbidity of a specific disease, but in fact, there is a difference. The probability of committing type II error is denoted as β. The power of a test, which is denoted as 1-β, is the ability to reject a null hypothesis when it is false. There is an inverse relationship between power and β. Increase of power requires a larger sample size (Chow and Liu, 2004).

3.1.3 Trial Interventions

The intervention is to apply one setting of complete SLT or one setting of complete ALT. On the day of laser trabeculoplasty, intraocular pressure is checked and one drop of 0.15% brimonidine is instilled in the study eye before and after laser treatment to decrease the chance of post-laser IOP spike at the one hour measuring point. Patients are then treated with either SLT or ALT according to the randomization schedule.

3.1.4 Study Center

There are sites in London, Toronto, Hamilton, Edmonton, Calgary, Halifax and Montreal of Canada. The present study considers data from all sites.

3.1.5 Randomization and Allocation

The ophthalmologist assessed eligibility criteria and verbally explained the study to the potential patient. Once a patient has decided to participate, they are asked to sign the informed consent. Then they are randomized.

At each center, a blocked randomization was performed to recruit participants alternately in order to force reasonably equal number of eyes in both treatment and control arms. . The allocation schedule, done by computer (e.g. STATA, College Station Texas) from the conditional uniform distribution, is generated by the study coordinating center at the Ivey Eye Institute, University of Western Ontario with the help of the Lawson Research Kidney Research Unit, LHSC, London, Ontario.

3.1.6 Treatment Masking

The patient, not the clinician, is masked to intervention (either one complete setting of SLT or one complete setting of ALT).

3.1.7 Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Study base: From one of the practices participating in this study.
2. More than or equal to 18 years of age.
3. Open angle glaucoma, including ocular hypertension, pigmentary dispersion syndrome and pseudoexfoliation syndrome, as long as the angle is open, to increase the generalizability of the study.
4. Previous 360 degree SLT (one time of 360 degree or two 180 degree).
5. Intraocular pressure greater than 16 mm Hg on at least two consecutive occasions separated by one month. From previous SLT vs ALT clinical

work by Damj et al. (2006), mean IOP of diagnosed OAG patients for one year follow-up period was as low as 17.88 mmHg with a SD of 3.92.

6. Two sighted eyes (best corrected visual acuity of 20/200 or better)
7. Willing to participate after being informed and reading the patient information material that explains the study.

Exclusion Criteria:

1. Any evidence of secondary open angle glaucoma (other than pigmentary and pseudoexfoliation) or narrow angle glaucoma (where the anterior trabecular meshwork is not visible 360 degrees). As they would make the study population too heterogeneous.
2. Advanced visual field defect in the eye being considered for treatment (defined as a scotoma within 10 degrees of fixation or split fixation on Humphrey's visual field 24-2, full threshold program) as they would be too close to central visual loss to be considered ethically feasible to include.
3. Previous non laser glaucoma surgery in the eye being considered for treatment as this would change the angle architecture too unpredictably to be included.
4. Intraocular surgery anticipated in the 12 months after treatment.
5. Any corneal disease obscuring adequate visualization of the anterior chamber trabecular meshwork or reliable applanation tonometry.
6. 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 had a pressure increasing effect in an unpredictable fashion.
7. Previous ALT.

3.1.8 Starting medication status of patients

Common treatment algorithms comprise the use of medication until failure followed by laser and finally incisional surgery. However, recent trends have shown an increasing proportion of physicians using laser first and avoiding the use of medications until necessary (Katz et al. 2012, Mcilraith et al. 2006). To reflect this changing clinical practice, this trial recruited patients regardless of medication status (except for steroids).

3.1.9 Duration of Intervention

The laser session for each group takes approximately 5 minutes.

3.1.10 Baseline data, Frequency and Duration of Follow-Up

After patients are screened for eligibility and provide their informed consent, baseline data (demographic variables and baseline IOP) are collected. There is a follow-up visit at 1-hour post-laser, and patients are prescribed topical steroid (1drops 4x/day). They are then evaluated at approximately the same time of day as the baseline examination (to minimize diurnal variation in pressure), at the end of week 1, and at 1, 3, 6 and 12 months post-operatively. At all follow-up examinations, the IOP, best corrected vision acuity, the anterior chamber reactions (cells/flare) are recorded. For this thesis, patients with 6-month follow -up data are considered.

3.1.11 Primary and Secondary Outcomes

The primary outcome for the clinical trial is the change in intraocular pressure from the baseline visit to the twelve-month visit (a continuous variable). The Goldman applanation tonometer, calibrated weekly, is used at approximately same time of the day (±1-hour) at baseline visit and during each follow-up. This thesis will use data obtained at 6 months.

Secondary outcomes include, exclusion of pseudoexfoliation or pigment dispersion syndrome and repeating the primary analysis. Status of anterior

chamber inflammation (graded from 0 to +4, based on standard criteria), Snellen visual acuity (in LOGMAR units, a continuous variable), trabecular meshwork pigmentation (graded from 0 to + 4, an ordinal variable, compared to a standard photograph) and number of glaucoma medications needed per patient in each group are recorded at every post-operative visit for subgroup analysis.

For this thesis, intraocular pressure change from the baseline visit to the follow-up visit up to 6-months have been considered. The effectiveness of each intervention (ALT and SLT) for outcomes (treatment success or failure) and relevant cost components of the laser treatment modalities have been compiled and computed and a cost-effectiveness analysis of repeat laser treatment (ALT vs SLT) following at least one full previous SLT has been carried out.

3.1.12 Sample size:

In an active control equivalence trial, the formula for sample size for a continuous outcome for each group is:

$$N=2v^2(Z_\alpha+Z_ß)^2/d^2$$

(Chow and Lee, 2004Blackwater and Chang, 1984)

Where, N = Sample size for each group.

v^2 = Variance of the continuous variable.

Z_α= Type I error.

$Z_ß$= Type II error.

d^2= The squared difference in the equivalence study that would be clinically meaningful.

- v^2: From previous SLT vs ALT clinical work (Damji et al. 2006), the standard deviation of the difference in IOP between the two groups at

different times varied between 3.4 and 5.8 mm Hg. The median standard deviation from all pressures recorded was 5.0 mm Hg, which is used for v^2.

- Z_α: This value is 1.96 for the standard acceptable type I error rate of 0.05, two sided test, in an active controlled equivalence trial.

- $Z_ß$: To reduce the chance of a type II error, which is central to an equivalence study, 90% power is used. This value is therefore 1.282.

- d^2: A meaningful clinical difference (squared) that would change the management of OAG had been chosen to be 3 mm Hg by the expert group.

As we have an active control group (ALT) and a comparator group (SLT), the total sample size (for both active control and comparator group) would be

$$2N=4v^2(Z_\alpha+Z_ß)^2/d^2$$

Plugging the value of the formula, the total sample size

$$2N=4(5.0)^2(1.96+1.282)^2/3^2$$

$$2N=117 \text{ eyes.}$$

Assuming a 10% drop out rate would require to increase the sample size by (1-d) where d is 0.1 in this case. The sample size would be:

$$2N=117/(1-0.1)$$

$$2N=130 \text{ eyes}$$

When cluster sampling would be done, the sample size estimate must be increased by the factor:

$$1 + (m-1)\,\rho$$

Where m = Average cluster size

ρ = The intra-class correlation coefficient (Friedman et al. 1996).

Based on previous work, it is estimated that 15% of individuals might be randomized from any one center from a cluster (Damjii et al. 2006). With this assumption, the average cluster size is 1.15. As the cluster would be within fairly homogenous practices, the ρ might be as high as 0.7. If ρ = 0, then each individual in one clusters responds same as individual in any other cluster. If ρ = 1, then all individuals in a cluster responds the same (Friedman et al. 1996).

So adjustment factor $1 + (m-1)\rho = 1 + (.15)0.7 = 1.105$.

Multiplying this correction factor by 130 eyes resulted a final sample size of 144 eyes.

At the time of writing this thesis, a total of 91 eyes has completed the 6-month follow-up. In this study, analysis is based on this sample size (91 eyes). Based on this reduced sample size, the recalculated power of the study would be 81% instead of 90% (See Appendix C for details).

3.1.13 Trial Management

Data, recorded on a standardized form by the research assistant, are entered in a web based data uptake system, checked for completeness, errors and inconsistencies by the coordinating center at located at the clinical research unit, Ivey Eye Institute, University of Western Ontario. Any data discrepancy is fixed accordingly. A double data entry protocol, that require the data entry personnel to re-enter all data a second time using identical error verification parameters, is used to ensure data integrity and accuracy for all key variables. Patient confidentiality is guarded with stringent security procedures.

The executive committee oversees all aspects of the trial. The Data Safety and Monitoring Committee (DSMC), independent of the trial functioning participants,

consists of two glaucoma expert physicians and one epidemiologist/biostatistician, with provision to invite ad hoc expert consultancies as required. The DSMC ensures that that study participants are not exposed to unnecessary or unreasonable risks and that the study is being conducted according to the highest scientific and ethical standards. Based on the review of both primary and secondary interim analysis, the DSMC has the right to recommend whether the study needs to be changed or terminated. In the event that the Study PI and/or the Executive Committee disagree with the DSMC recommendation to modify or to terminate the trial, a third party arbitrator from the University of Western Ontario Research Ethics Board, who possesses the knowledge and experience to make a final decision in the matter, will be called upon.

3.2 Decision Tree Model

For this thesis, a decision tree model was created using TreeAge Pro 2009 to represent the possible treatment outcome for a patient over a period of 6-month after intervention. Due to the short span of follow-up time and few treatment outcomes, this decision tree model would be sufficient to model the clinical scenario without the need of Markov modeling.

The model was built using the data from the ongoing clinical trial cohort of adults aged 18 years or more suffering from uncontrolled open angle glaucoma patients (including ocular hypertension, pigmentary dispersion syndrome and pseudoexfoliation syndrome) with maximally tolerated medical therapy and at least one previous full SLT. The outcome of interest is the IOP lowering effect of each intervention.

Our focus of interest was to evaluate the cost-effectiveness of the laser treatments (SLT versus ALT) following previous full SLT based on the treatment outcome at 6-month post -laser follow-up.

3.2.1 Structuring the decision tree model

The overall structure was determined after consultation with ophthalmology experts by identifying possible clinical pathways of patients undergoing repeat laser trabeculoplasty. In our trial, patients underwent laser (either ALT or SLT). . Presence or absence of an IOP spike at 1-hour post-laser (defined as rise of IOP ≥ 5 mm after 1-hourlaser intervention from baseline for this study) is considered a possibility consistent with previous published studies (Kara et al. 2013; Johnson et al. 2006; Nagar et al. 2005). Laser surgery might either be successful (using definitions in line with similar previous studies - either 3mmHg reduction in absolute intra ocular pressure from baseline or a reduction of ≥ 20% from baseline IOP at 6-month follow-up), in which case they would follow the initial normal standard of care (i.e. laser visit + 4 follow-up visits). Based on standard of care, it was decided that for the failure cases of the laser treatments at 6-month visit (v6), patients either would have another SLT (if IOP at v6 is <= 5 mm from baseline) or proceed to incisional surgery (if IOP at v6 > 5mm from baseline), which would add the costs of another SLT or surgery, respectively, and also cost of additional 4 follow-up visits for each scenario.

3.2.2 Societal and Ministry perspective of the decision model tree

For societal perspective, data from all participants are included to calculate the ratio of outcome and IOP spike in the decision tree. For ministry perspective, only data from participants having age 65 years or more are considered. The reason being that all drug costs are covered by the ministry when patients are 65 years or older. Ideally, from societal perspective, indirect medical costs that may include wage loss, travel costs for treatment purposes, wage loss of accompanying persons etc., should be included in the cost analysis of any medical situation. However, indirect treatment cost has more impact in chronic disease of young population leading to disability and significant loss of economic contribution to the society. Disease like glaucoma, which mainly affects elderly population, comparatively

has less economic impact in terms of indirect medical cost. Moreover, laser treatments for glaucoma is a short outpatient medical procedure without any significant disastrous post-procedural adverse events. It does not need hospital admission. So for this specific study, exclusion of indirect medical cost would not have any substantial cost-impact that may affect the cost-effectiveness outcome.

3.2.3 Calculation of success and failure ratio of each intervention for the decision tree model

Based on the definition of success of treatment, ratio of success is calculated from the proportion of patients in each intervention arm with a successful outcome. The ratio of failure is calculated from (1-ratio of success). Success of treatment is defined as either 3mmHg reduction in absolute IOP from baseline IOP or a reduction of ≥20% from baseline IOP to follow-up visit at 6-month, as defined in the Manual of Procedure (MOP) of the clinical trial. Similar definition of success has also been used previously. (Akhtar 2014; Martow et al. 2011; Mao et al. 2008; Hodge et al. 2005).

3.2.4 Determining effectiveness of each intervention

Each intervention arm (ALT and SLT) is stratified based on outcome (success or failure) at 6-month post-intervention follow-up visit (v6). So there are a total of 4 groups as follows:

- ALT Success group
- ALT failure group
- SLT success group
- SLT failure group

For each group, baseline mean IOP and mean IOP reduction from baseline at 6-month post-laser follow-up periods (v6) are determined. The effectiveness of ALT and SLT for each group is calculated considering the reduction of mean IOP at v6.

The following general formula is used:

- Effectiveness of Intervention at v6 = (Mean IOP reduction at v6)/Mean Baseline IOP

Considering societal (all participants considered) and ministry perspective (participants aged 65 years and above), there are 2 separate decision model trees. Expected costs and effectiveness of each intervention are calculated from them. The incremental cost-effectiveness ratio (ICER) is calculated as the extra cost needed to lower one additional unit of IOP in mmHg from baseline for each decision model tree.

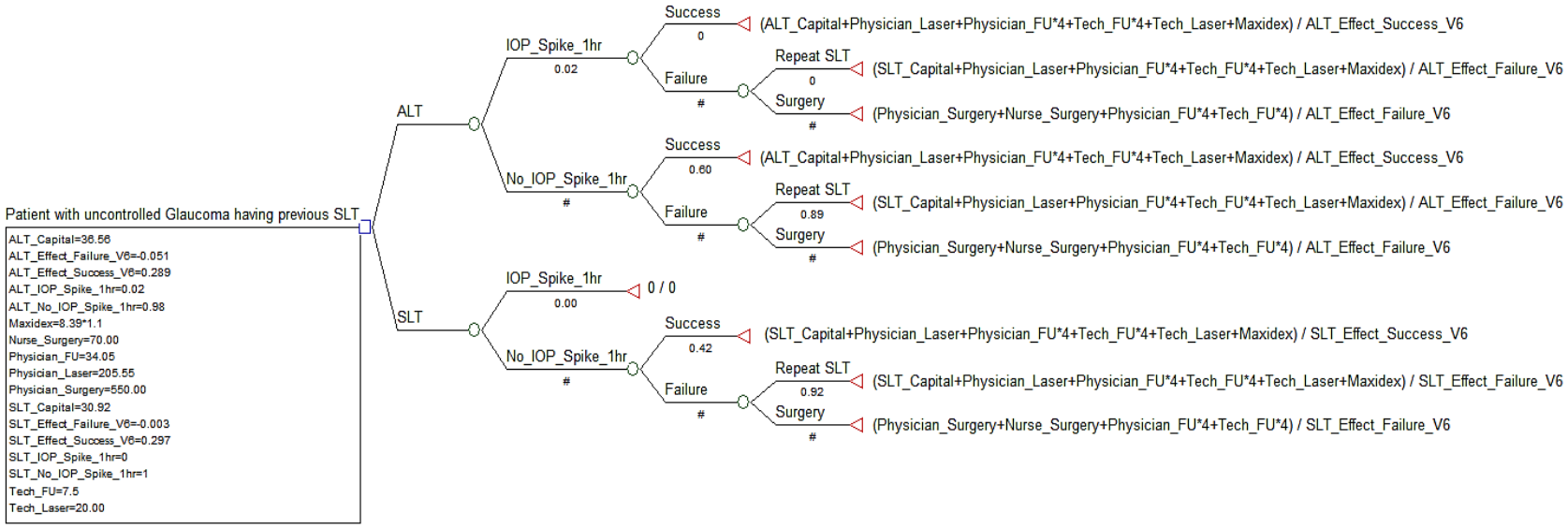

Figure 5: Decision Tree Model of ALT and SLT intervention: Societal perspective

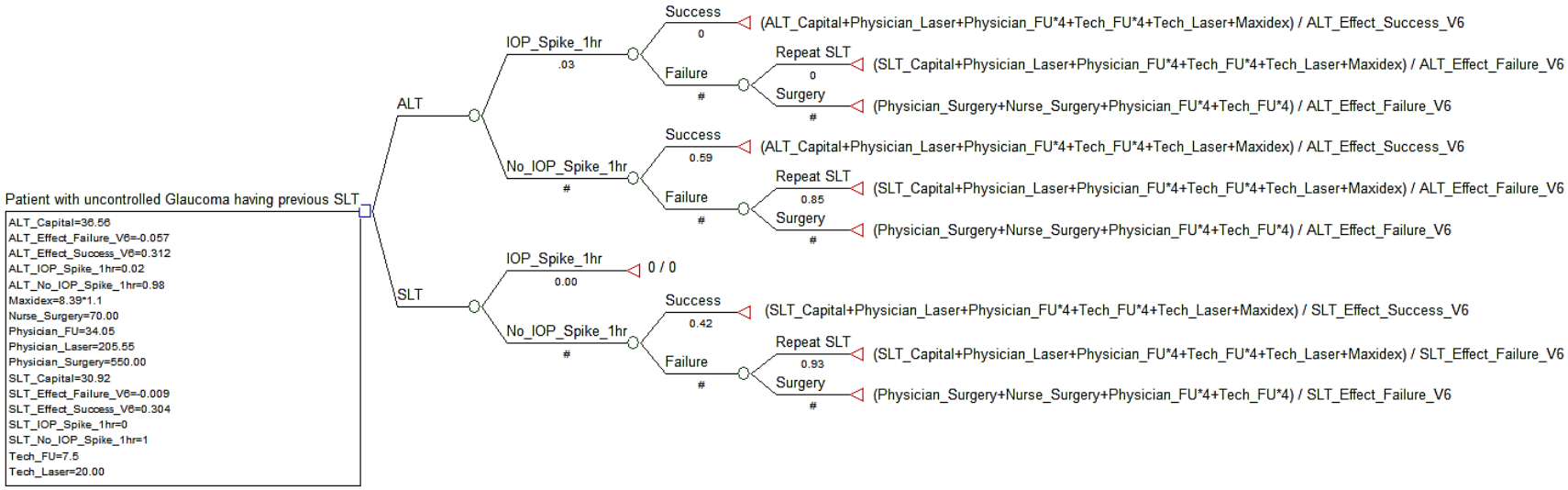

Figure 6: Decision Tree Model of ALT and SLT intervention: Ministry Perspective

3.2.5 Calculation of expected values of costs and effectiveness

From the decision tree model of societal and ministry perspective, we have calculated the expected values of costs and effectiveness for both ALT and SLT interventions.

3.2.6 Calculation of incremental cost-effectiveness ratios (ICERS)

From the expected values of costs and effectiveness of ALT and SLT interventions, we have calculated the ICERs for reduction of 1 mmHg IOP from baseline at 6-month post-intervention period from both societal and ministry perspective.

3.2.7 Willingness to pay (WTP)

We compare ICERs from previous economic studies with similar clinical scenarios of treating OAG with IOP lowering medications for 6-month follow-up period.

3.2.8 Sensitivity analysis

Sensitivity analysis is an essential component of both decision tree and cost-effectiveness analysis. It is a well-accepted, method to evaluate and address the uncertainty on the conclusion of a decision analysis (Petitti, 2000). We consider IOP lowering effect of ALT and SLT intervention and Capital Cost of ALT and SLT to be potential drivers of the decision tree model for generating the expected values of costs and effectiveness for both ALT and SLT interventions. We would perform one way sensitivity analysis to investigate the extent to which the uncertainty of these variables would affect the decision model tree results. We would assign plausible ranges based on upper and lower 25% limits for the base case value. This would provide substantial evidence to address the uncertainty of base case ICERs value for both interventions (ALT vs SLT) from societal and ministry perspective. Moreover, the statistical and quasi-statistical methods (e.g., probability density function, the Bayesian approach) for estimating the uncertainty

of expected outcome from the decision analytic model has not been widely applied (Petitti, 2000).

3.3 Calculation of intervention costs

Many parts of costing of the trial had been calculated previously (Akhter, 2015). We have updated these costing as needed and calculated costing of new items.

3.3.1 Calculation of direct costs

Direct costs in health care problems are agreed generally as opportunity costs of formal health-care goods and services like hospital and nursing-home care expenses, health care personnel fee schedules, drugs and so on (Ernst R, 2006). For this thesis, direct costs have been calculated considering charges of health care delivery personnel, procedural costs, post-operative medication costs and per-patient capital costs of interventions.

3.3.1.1 Physician time and follow-up schedule:

It includes baseline assessment, 1laser intervention appointment and 5 scheduled follow-up visits of partial assessment and tonometry at one hour, one week and 1, 3, and 6-month post-laser procedure. For failure cases at 6months, additional costs of either a repeat SLT or incisional surgery and 4 follow-up visits are added.

For monetary valuation of unit cost, as nearly half the participants are from Ontario and fee schedules for similar services are nearly same across Canada, we use the OHIP fee schedule, in general as follows:

- Laser visit: $205.55 (OHIP fee code: E134)
- Follow-up visit: $34.05 (OHIP code A234-partial assessment $28.95 + OHIP code G435-tonometry $5.10).
- Glaucoma filtration surgery: $550.00 (OHIP code E132)

3.3.1.2 Ophthalmic technician time and nurse time:

An ophthalmic technician assists the ophthalmologist to perform tonometry and other examination procedures. Interviews with the trial ophthalmic technicians revealed that they spent an average of 40 minutes during the laser visit and 15 minutes at each follow-up visit. The average wage of an ophthalmic technician is determined $30/hour. We took the information from St. Joseph's Health Care (SJHC), London, Ontario from payroll services of Healthcare Materials Management Services (HMMS). Unit cost for an ophthalmic technician is $0.50/min.

For nurses, an average of 1-hour is necessary for laser intervention, and two nurses are required. The average hourly wedge of nurse time of $31/hour is obtained from HMMS.

We assume that, these costs are similar across Canada.

3.3.1.3 Capital costs:

Capital costs are investments as an asset which is used over time (Drummond et al. 2015). Costs of equipment needed for the intervention using monetary values from the HMMS at SJHC are calculated. Capital cost is the same for each patient of the same arm. The following schema is used to calculate per patient capital cost (Drummond et al. 2015):

- Per patient capital cost =
  ((L+TR+EC+(SC*Y)+(LR*Y)+(MS*N*Y))/(N*Y)
  Where, L=Laser

  TR=Tube Replacement

  EC=Exam chair

  SC=Service Contract

  LR=Annual Lens Replacement Cost

MS= Medications/Supplies per Patient (includes tonometry cleaning supplies, brimonidine drops, Gel for lens application)

N=Number of patients (Based on expert opinion)

Y=Laser lifetime in years

Table 1: Capital cost calculation

Item	Cost for ALT (CAD)	Cost for SLT (CAD)
Laser	180,000	70,000
Tube Replacement	25,000	N/A
Exam chair	5,000	5,000
Service Contract	8,800	5,085
Lens Replacement per year	500	500
Laser lifetime in years	8	8
Medications/Supplies per Patient	1	1
Number of patients	1000	500
Per patient capital cost (Unit Cost)	36.56	30.92

3.3.1.4 Medications:

As hospitals provided post-laser use of brimonidine, it is included in the capital cost. Maxidex eye drop (4x/day for 4 days) is prescribed for each patient post-laser ($8.39 for 1 bottle of 5ml with 10% pharmacy mark up, included in direct cost).

Baseline medications and their costs have not been considered for this thesis with the assumption that, appropriate randomization would result in a homogenous distribution of participants across the two intervention groups based on disease severity and baseline IOP lowering drug consumption (mean number of medications used in each group).

3.3.2 Costs not included:

Other than the laser equipment, the cost of hospital infrastructures, overheads and buildings is not considered as they are difficult to assess and assigning them to the specific procedure usually results in irreducible capriciousness and sensitivity to methods (Tan et al. 2009, Finkler et al. 2007, Barnett, 2009).

Indirect costs, often termed as direct non-health care costs, refers to productivity costs associated with lost or impaired ability of work or lost productivity due to death or disability (Neumann, 2009). This is more concern for a societal perspective. According to the Panel on Cost-Effectiveness Analysis of US Public Health Service, productivity costs should not be valued monetarily. It should be encompassed as health effects from the intervention (Gold et al. 1996). However, for highly disabling illness of young patients, exclusion of productivity costs from the numerator of CEA may have a large effect (Petitti, 2000). As laser trabeculoplasty is an outpatient procedure, that usually does not require long term absence from normal daily tasks, wage loss due to the intervention procedure of patients and their accompanying personnel, where applicable, is ignored in this thesis. Travel costs are also not included assuming that, they would be similar in both intervention arms, thus nullifying each other and would not influence the CEA if not included.

3.4 Final Analyses and measures

Our main purpose is to perform a cost-effectiveness analysis for this thesis. Demographic characteristics of participants after stratification based on intervention arms are done. Expected costs on all decision model trees are performed and ICER for each decision model tree is calculated and compared. One way sensitivity analysis is done considering the IOP lowering effect and capital cost of ALT and SLT as the potential drivers for changes is expected cost of laser modalities. Treatment outcomes (success and failure) of both arms are presented considering different parameters.

Chapter 4 - Results

4.1 Descriptive Statistics

Data was available for 91 participants for a 6-month follow-up period, 46 in ALT arm and 45 in SLT arm. Mean age of ALT arm was slightly higher than SLT (69.28±8.72 vs 65.97±11.81). In both arms, number of male participants were slightly higher than females. More right eyes were treated in ALT group and for SLT group, it was reversed. Caucasian race ranked highest among both arms (82.6% in ALT vs 82.2%). (Table 2).

Table 2: Descriptive statistics of participants

Demographics	ALT	SLT
Age(Yrs)±(SD)	69.28±8.72	65.97±11.81
Male	28	25
Female	18	20
Treated Eye-Right (OD)	26	18
Treated Eye- Left (OS)	20	27
Race/Ethnicity		
Caucasian	38	37
African	4	2
Asian	2	2
Middle East	0	3
Aboriginal	1	1
Self-Defined	1	0

4.2 Number of IOP lowering Medications at Baseline:

The mean of number of IOP lowering medications at baseline for ALT group was 1.22 (95% CI, 0.90 to 1.53) and for SLT group was 1.36 (95% CI, 0.97 to 1.74). (Table 3).

Table 3: Number of IOP lowering medications at baseline

	Number of Medications							
Intervention Arm	0	1	2	3	4	Mean	95% CI	Total
ALT	15	13	11	7	0	1.22	0.90, 1.53	46
SLT	16	10	8	9	2	1.36	0.97, 1.74	45

4.3 Baseline and Follow-up Mean IOP at different time point:

Mean Baseline IOP for ALT and SLT arm were similar (21.65±4.08 vs 22.13±4.21, respectively). ALT arm showed a steady decrease over 6-month duration. However, for SLT arm, there was a rise in Mean IOP at 6-month compared to IOP reduction at 3-month from baseline (19.11±4.29 vs 17.54±3.71, respectively). (Table 4).

Table 4: Mean IOP (in mmHg) at baseline and different time points

Timeline	ALT	SLT
Baseline	21.65±4.08 (Min:12, Max:33)	22.13±4.21 (Min: 16, Max: 30)
1-hour	14.76±4.83 (Min:5.5, Max:33.5)	15.86±5.17 (Min: 8, Max: 28)
1-week	20.14±4.83(Min:11.5, Max:33)	17.92±4.27 (Min: 11.5, Max: 28.5)
1-month	18.71±4.20(Min:11, Max:29)	17.43±3.91 (Min: 11, Max: 26)
3-month	18.43±5.42(Min:6, Max:41)	17.54±3.71 (Min: 12, Max: 25.5)
6-month	18.22±4.37(Min:9, Max:31)	19.11±4.29 (Min: 13.5, Max: 32)

4.4 Mean IOP Reduction from Baseline at different time points:

While ALT arm showed a steady and sustained reduction in IOP from baseline to 6-month follow-up, SLT arm demonstrated a more mean IOP reduction up to 3-month follow-up than ALT arm, but at 6-month, had less mean IOP reduction than ALT. (Table 5).

Table 5: Mean IOP reduction (in mmHg) from baseline at different time points

Timeline	ALT	SLT
Baseline	21.65±4.08	22.13±4.21
1-week	1.51±3.88	4.22±4.42
1-month	2.94±4.42	4.70±4.44
3-month	3.22±5.44	4.59±3.80
6-month	3.43±5.17	3.02±4.59

4.5 Eyes achieving 20% IOP reduction from Baseline to different time points:

ALT arm had gradual increase of number of eyes achieving 20% reduction of IOP from baseline for the 6-month time horizon. For SLT arm, up to 1-month, almost half of the eyes (48.8%) had achieved this, but at 3-month and 6-month follow-up, there was substantial drop (44.4% and 35.5%, respectively). (Table 6).

Table 6: Eyes with 20% IOP reduction from baseline at different time points

Timeline	ALT (n=46)	SLT (n=45)
1-week	23.9% (11/46)	48.8% (22/45)
1-month	39.1% (18/46)	48.8% (22/45)
3-month	36.9%(17/46)	44.4% (20 /45)
6-month	41.3% (19/46)	35.5% (16/45)

4.6 Outcome of treatment (success or failure) at 6-month follow-up

We defined success of treatment as either 20% reduction of IOP from baseline or absolute reduction of IOP of 3mmHg or more from baseline, or both. ALT arm had higher success outcome at 6-month follow-up. (Table 7).

Table 7: Outcome of treatment at 6-month follow-up

Outcome	ALT (n=46)	SLT (n=45)
Success	58.7% (27/46)	42.2% (19/45)
Failure	41.3% (19/46)	57.8% (26/45)

Majority of the patients in both arms had previous SLT done twice. Only 1 patient, in ALT arm, had previous SLT done three times. (Table 8).

Table 8: Previous SLT history and outcome at 6-month follow-up

	ALT (n=46)		SLT (n=45)	
Previous SLT	Success	Failure	Success	Failure
Once	19.6% (9/46)	13.0% (6/46)	8.9% (4/45)	20.0% (9/45)
Twice	39.1% (18/46)	26.1% (12/46)	33.3% (15/45)	37.8% (17/45)
Thrice	0.0% (0/46)	2.2% (1/46)	0.0% (0/45 eyes)	0.0% (0/45)

In ALT arm, 23 out of 38 eyes of Caucasians had successful outcome at 6-month, compared to 14 out of 37 eyes in SLT arm. (Table 9).

Table 9: Outcome among race/ethnicity at 6-month follow-up

Race/Ethnicity	ALT(Success/Failure)	SLT (Success/Failure)
Caucasian	23/15	14/23
African	1/3	1/1
Asian	2/0	2/0
Middle East	0/0	2/1
Aboriginal	1/0	0/1
Self-Defined	0/1	0/0

Only 1 patient in ALT arm had an IOP spike at 1-hour post-laser. (Table 10).

Table 10: IOP Spike at 1-hour post-laser

	ALT	SLT
IOP Spike	1	0
No IOP Spike	45	45

For failure cases at 6-month, either repeat SLT or surgery had been designed based on IOP of that visit. Repeat SLT was planned for patients with IOP 5 mmHg or

less from baseline. Surgery was planned for those having IOP greater than 5 mmHg from baseline. ALT arm had a total of 19 failure cases and SLT arm had 26. (Table 11).

Table 11: Further treatment plan for failure cases at 6-month follow-up

Treatment Plan	ALT	SLT
Repeat SLT	16	24
Surgery	3	2

4.7: Obtaining Ratio of Treatment outcome for the Decision Model Tree

4.7.1 Societal perspective

For societal perspective, all data, irrespective of age were considered. Ratio for IOP spike at 1-hour post-laser for ALT and SLT group were 0.02 and 0, respectively and that for No IOP spike were 0.98 and 1, respectively. (Table 12).

Table 12: One-hour post-laser IOP spike for ALT and SLT group: Societal perspective

Intervention Arm	IOP Spike	No IOP Spike	IOP Spike Ratio	No IOP Spike Ratio
ALT (n=46)	1	45	0.02 (1/46)	0.98 (45/46)
SLT (n=45)	0	45	0 (0/45)	1 (45/45)

Success ratio of IOP spike and no IOP spike group at 6-month post-laser follow up for ALT arm were 0 and 0.6, respectively. (Table 13).

Table 13: IOP Spike at 1-hour post-laser and treatment outcome at 6-month for ALT: Societal perspective

Treatment Outcome	IOP Spike at 1-hr post-laser		IOP Spike	No IOP Spike
At 6-month	Yes (n=1)	No (n=45)	Outcome Ratio	Outcome Ratio
Success	0	27	0 (0/1)	0.6 (27/45)
Failure	1	18	1 (1/1)	0.4(18/45)

Success ratio of IOP spike and no IOP spike group at 6-month post-laser follow up for SLT arm were 0 and 0.42, respectively. (Table 14).

Table 14: IOP Spike at 1-hour post-laser and treatment outcome at 6-month for SLT group: Societal perspective

Treatment Outcome	IOP Spike at 1-hr post-laser		IOP Spike	No IOP Spike
At 6-month	Yes (n=0)	No (n=45)	Outcome Ratio	Outcome Ratio
Success	0	19	0	0.42 (19/45)
Failure	0	26	0	0.58 (26/45)

For 19 failure cases of ALT, the ratio of repeat SLT and surgery for IOP spike group were 0 and 1, respectively and for no IOP spike group were 0.89 and 0.11, respectively. (Table 15).

Table 15: Treatment (Rx) plan for failure cases (at 6-month follow-up) of ALT group: Societal perspective

Future Rx Plan	IOP Spike at 1-hr post-laser		IOP Spike	No IOP Spike
for Failure Cases	Yes (n=1)	No (n=18)	Outcome Ratio	Outcome Ratio
Repeat SLT	0	16	0 (0/1)	0.89 (16/18)
Surgery	1	2	1 (1/1)	0.11 (2/18)

For 26 failure cases of SLT, there was no case in IOP spike group. For no IOP spike group, ratio of repeat SLT and surgery were 0.92 and 0.08, respectively. (Table 16).

Table 16: Treatment (Rx) plan for failure cases (at 6-month follow-up) of SLT group: Societal perspective

Future Rx Plan for Failure Cases	IOP Spike at 1-hr post-laser		IOP Spike Outcome Ratio	No IOP Spike Outcome Ratio
	Yes (n=0)	No (n=26)		
Repeat SLT	0	24	0	0.92 (24/26)
Surgery	0	2	0	0.08 (2/26)

4.7.2 Ministry Perspective

For ministry perspective, data from participants aged greater than or equal to 65 years were considered. Ratio for IOP spike at 1-hour post-laser for ALT and SLT arms were 0.03 and 0, respectively and that for No IOP spike group were 0.97 and 1, respectively. (Table 17).

Table 17: One hour post-laser IOP spike for ALT and SLT group: Ministry perspective

Intervention Arm	IOP Spike	No IOP Spike	IOP Spike Ratio	No IOP Spike Ratio
ALT (n=33)	1	32	0.03 (1/33)	0.97 (32/33)
SLT (n=24)	0	24	0 (0/24)	1 (24/24)

Success ratio of IOP spike and no IOP spike at 6-month post laser follow up for ALT arm was 0 and 0.59, respectively and that of failure group were 1 and 0.41, respectively. (Table 18).

Table 18: IOP Spike at 1-hour post-laser and treatment outcome at 6-month for ALT group: Ministry perspective

Treatment Outcome	IOP Spike at 1-hr post-laser		IOP Spike	No IOP Spike
At 6-month	Yes (n=1)	No (n=32)	Outcome Ratio	Outcome Ratio
Success	0	19	0 (0/1)	0.59 (19/32)
Failure	1	13	1 (1/1)	0.41(13/32)

Success ratio of IOP spike and no IOP spike at 6-month post laser follow up for SLT arm were 0 and 0.42, respectively and that of failure group were 0 and 0.58, respectively. (Table 19).

Table 19: IOP spike at 1-hour post-laser and treatment outcome at 6-month for SLT group: Ministry perspective

Treatment Outcome	IOP Spike at 1-hr post-laser		IOP Spike	No IOP Spike
At 6-month	Yes (n=0)	No (n=24)	Outcome Ratio	Outcome Ratio
Success	0	10	0	0.42 (10/24)
Failure	0	14	0	0.58 (14/24)

For 14 failure cases of ALT arm, the ratio of repeat SLT and surgery for IOP spike group were 0 and 1, respectively and for no IOP spike group were 0.85 and 0.15, respectively. (Table 20).

Table 20: Treatment plan for failure cases (at 6-month follow-up) of ALT group: Ministry perspective

Future Treatment Plan	IOP Spike at 1-hr post-laser		IOP Spike	No IOP Spike
for Failure Cases	Yes (n=1)	No (n=13)	Outcome Ratio	Outcome Ratio
Repeat SLT	0	11	0 (0/1)	0.85 (11/13)
Surgery	1	2	1 (1/1)	0.15 (2/13)

For 14 failure cases of SLT arm, there was no case in IOP spike group and for no IOP spike group, ratio of repeat SLT and surgery were 0.93 and 0.07, respectively. (Table 21).

Table 21: Treatment plan for failure cases (at 6-month follow-up) of SLT group: Ministry perspective

Future Treatment Plan for Failure Cases	IOP Spike at 1-hr post-laser		IOP Spike Outcome Ratio	No IOP Spike Outcome Ratio
	Yes (n=0)	No (n=14)		
Repeat SLT	0	13	0	0.93 (13/14)
Surgery	0	1	0	0.07 (2/26)

4.8 Cost of the intervention arms

Capital cost of ALT and SLT per patient were 36.56 and 30.92 CAD, respectively. Health personnel charges and drug costs were included in the costing. (Table 22).

Table 22: Cost-Calculations of the interventions

Item	Cost (In Canadian Dollar)
ALT Capital (Per Patient)	36.56
SLT Capital (Per Patient)	30.92
Maxidex Eye drop with 10% pharmacy mark up	9.23
Laser Charge for Ophthalmologist	205.55
Laser Charge for Technician	20.00
Surgery Charge for Ophthalmologist	550.00
Surgery Charge for Nurse	70.00
Follow-up Charge for Ophthalmologist	34.05
Follow-up Charge for Technician	7.50

4.9 Mean IOP reduction at 6-Month Follow-up

4.9.1 Societal perspective:

Mean IOP reduction of ALT and SLT arms from the societal perspective were 3.435 mmHg (95% CI: 1.898 to 4.971) and 3.027 mmHg (95% CI: 1.648 to 4.405) from baseline. This difference was not statistically significant (p=0.69).

(Table 23).

Table 23: Baseline IOP and IOP reduction at 6-month: Societal perspective

Intervention Arm	n	Mean IOP reduction at 6-month	95% CI
ALT	46	3.435	1.898, 4.971
SLT	45	3.027	1.648, 4.405
*p-Value		0.69	

*By non-paired t-test

4.9.2 Ministry Perspective:

Mean IOP reduction of ALT and SLT arms from the ministry perspective were 3.697 mmHg and 2.883 mmHg from baseline. This difference was not statistically significant (p=0.56). (Table 24).

Table 24: Baseline IOP and IOP reduction at 6-month: Ministry perspective

Intervention Arm	n	Mean IOP reduction at 6-month	95% CI
ALT	33	3.697	1.649, 5.744
SLT	24	2.883	0.926, 4.841
*p-Value		0.56	

*By non-paired t-test

4.10 Determination of Effectiveness for Intervention Arms

4.10.1 Societal perspective

IOP lowering effectiveness for each success and failure group for ALT and SLT arms were calculated for societal perspectives. For failure group, effectiveness were negative. Success group of both arms had higher Baseline IOP. (Table 25).

Table 25: IOP lowering effectiveness at 6-month follow-up for ALT and SLT: Societal perspective

Intervention Arm	Outcome of Intervention at 6-month Follow-Up	(n)	Baseline Mean IOP	Mean IOP reduction from Baseline at 6-month Follow-Up (v6)	Effectiveness: Mean IOP reduction at v6 from Baseline / Mean Baseline IOP
ALT	ALT Success	27	22.741	6.574	0.289
ALT	ALT Failure	19	20.105	-1.026	-0.051
SLT	SLT Success	19	24.421	7.263	0.297
SLT	SLT Failure	26	20.461	-0.069	-0.003

4.10.2 Ministry Perspective

IOP lowering effectiveness for each success and failure group for ALT and SLT arms were calculated for ministry perspective also and revealed similar results as that of societal perspective. (Table 26).

Table 26: IOP lowering effectiveness at 6-month follow-up (v6) for ALT and SLT group: Ministry perspective

Intervention Arm	Outcome of Intervention at 6-month Follow-Up	(n)	Baseline mean IOP	Mean IOP reduction from Baseline at 6-month (v6)	Effectiveness: Mean IOP reduction at v6 from Baseline / Mean Baseline IOP
ALT	ALT Success	19	23.263	7.263	0.312
ALT	ALT Failure	14	20	-1.143	-0.057
SLT	SLT Success	10	23.7	7.2	0.304
SLT	SLT Failure	14	21.5	-0.199	-0.009

4.11 Expected Values (Cost/Effectiveness) from the Decision Model Tree

4.11.1 Societal perspective

From societal perspective, the expected value of cost and effectiveness derived from the decision tree model for ALT arm was CAD 458/0.149 mmHg of IOP reduction from baseline IOP and that for SLT arm was CAD 448/0.123 mmHg of IOP reduction from baseline IOP. (Figure 9).

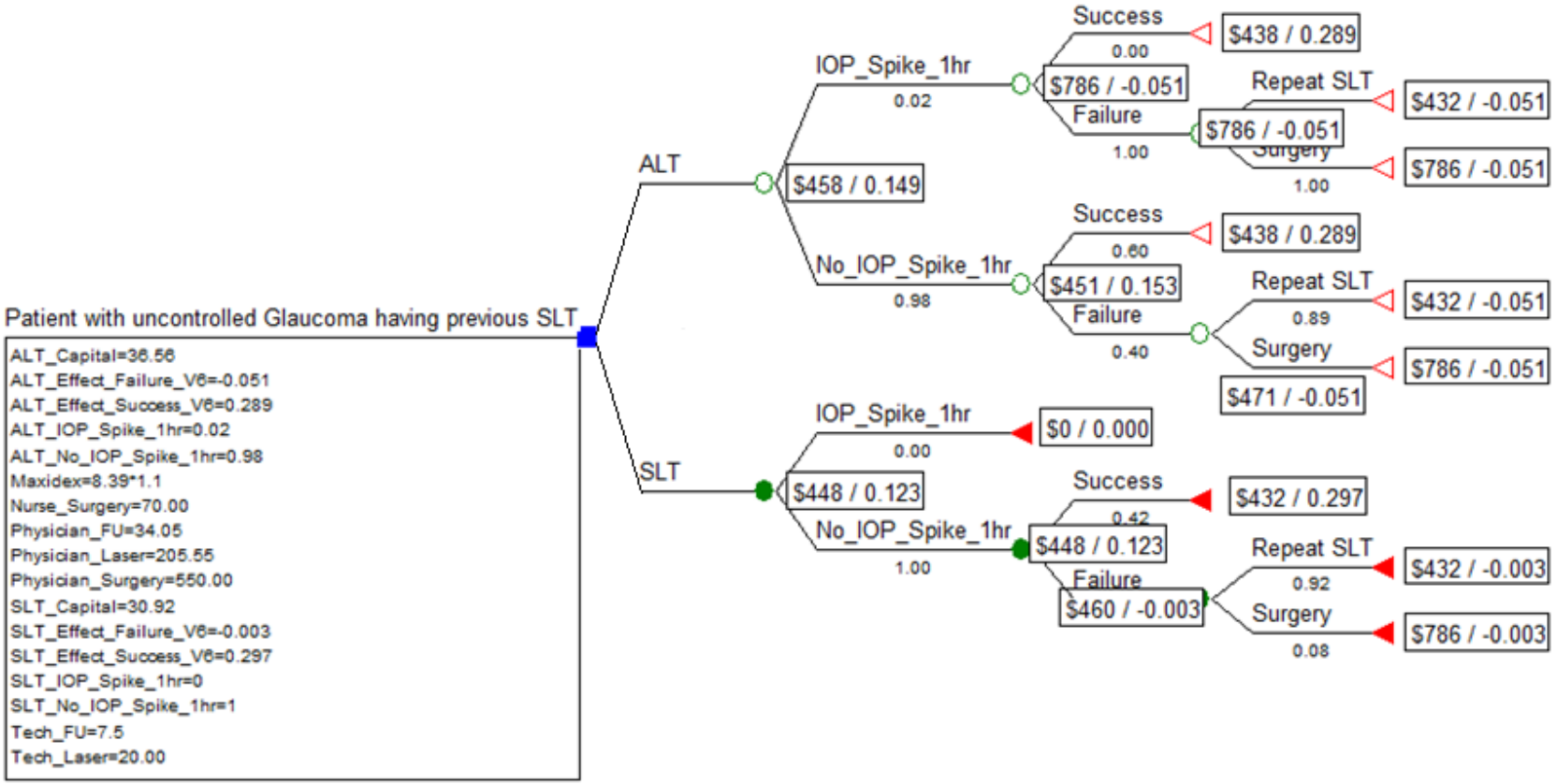

Figure 7: Expected Values of Cost/Effectiveness from Decision Model Tree: Societal perspective

4.11.2 Ministry Perspective

From ministry perspective, the expected value of cost and effectiveness derived from the decision tree model for ALT arm was CAD 467/0.154 mmHg of IOP reduction from baseline IOP and that for SLT arm was CAD 446/0.122 mmHg of IOP reduction from baseline IOP. (Figure 10)

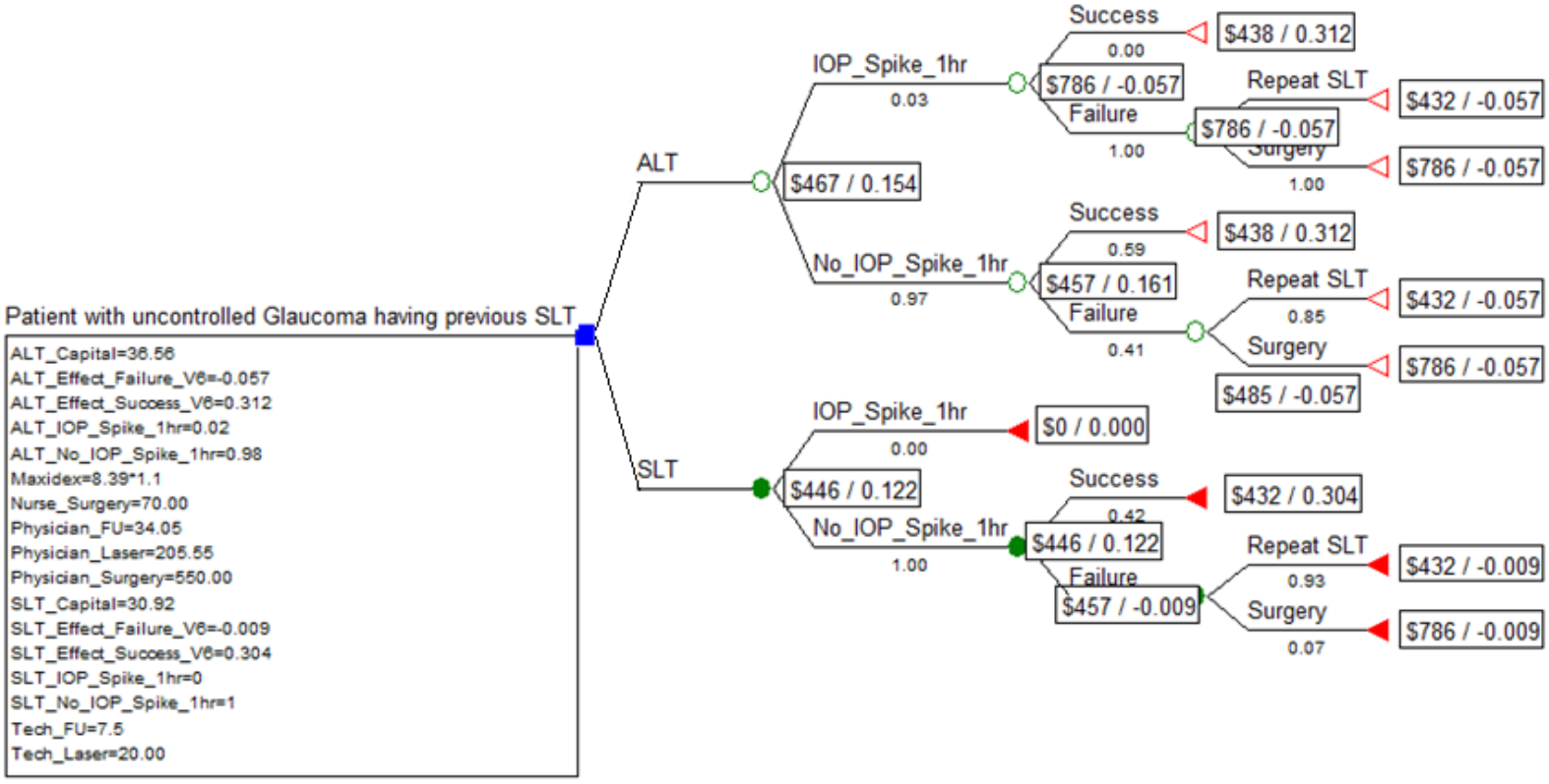

Figure 8: Expected Values of Cost/Effectiveness from Decision Model Tree: Ministry Perspective

4.12: Incremental Cost-Effectiveness Ratio (ICER)

4.12.1 Societal perspective

Effectiveness of both treatment arms was calculated based on reduction of IOP by each intervention from the societal perspective (all age included). Effectiveness was calculated as an average of mean IOP reduction at 6-month post-laser follow-up from mean baseline IOP. No strategies were clearly dominated by any other. Cost-Effectiveness (C/E) ratio for SLT was 3645.03 and that for ALT was 3072.65. To switch from SLT to ALT, It would cost $ 356.49 for each extra unit IOP reduction. (Table 27).

Table 27: CEA of ALT vs SLT, base case: Societal perspective

Strategy	Cost	Incremental cost	Effectiveness at 6-month follow-up	Incremental effectiveness	C/E	Incremental C/E (ICER)
SLT	448.34		0.123		3645.03	
ALT	457.58	9.24	0.149	0.026	3072.65	356.49

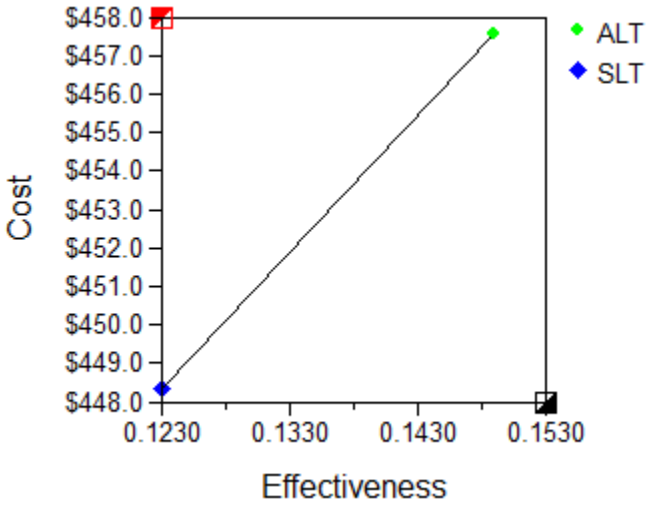

Figure 9: Cost-Effectiveness graph from the societal perspective

The cost-effectiveness graph from the societal perspective with cost on y-axis and effectiveness on x-axis showing none of the interventions were clearly dominated by any other, denoted by joining the ALT and SLT legend by a straight line.

4.12.2 Ministry Perspective

For ministry perspective, the same effectiveness as that of societal perspective for each corresponding group was used. Participants aged ≥ 65 years were considered. The results were similar as that of societal perspective with different values. To switch from SLT to ALT, It would cost $ 649.71 for each extra unit IOP reduction. (Table 28).

Table 28: CEA of ALT vs SLT, base case: Ministry perspective

Strategy	Cost	Incremental Cost	Effectiveness at 6-month follow-up	Incremental Effectiveness	C/E	Incremental C/E (ICER)
SLT	446.28		0.122		3644.32	
ALT	466.89	20.61	0.154	0.032	3028.25	649.71

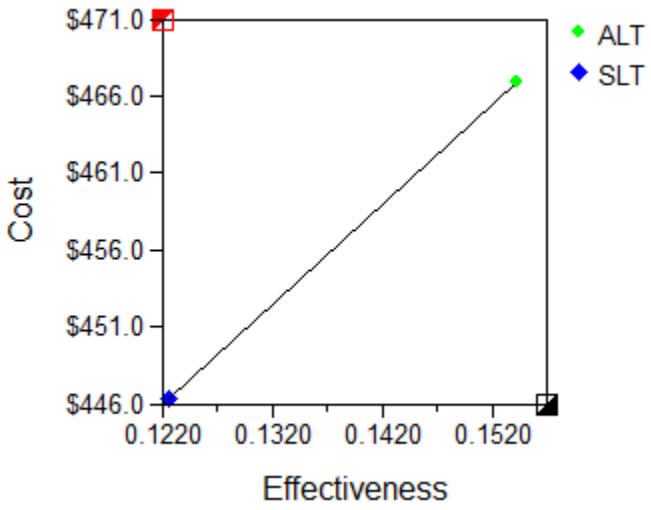

Figure 10: Cost-Effectiveness graph from ministry perspective

Cost-Effectiveness graph from ministry perspective with cost on y-axis and effectiveness on x-axis showing none of the interventions were clearly dominated by any other denoted by joining the ALT and SLT legend by a straight line.

4.13 Sensitivity Analysis

IOP lowering effectiveness and capital cost of ALT and SLT were considered as potential drivers of the decision model tree and the resultant ICERs. A one-way sensitivity analysis with 25% above and below value of base case variables with 4 equal intervals in between were used for both societal and ministry perspective.

4.13.1 One-Way Sensitivity analysis of Effectiveness: Societal perspective

A 25% lowering of ALT Success Effectiveness and 25% increase of SLT Success Effectiveness results in dominance of SLT over ALT. (Table 29).

Table 29: Sensitivity analysis of effectiveness value: Societal perspective

Group Variable	ICER		Dominance of Strategy
	25% lower from Base Case	25% higher from Base Case	
ALT Success	ALT is dominated by SLT	135.38	ALT is dominated by SLT when base case value is lowered by 25%
ALT Failure	449.34	295.44	None
SLT Success	162.11	ALT is dominated by SLT	ALT is dominated by SLT when base case value is increased by 25%
SLT Failure	348.69	356.49	None

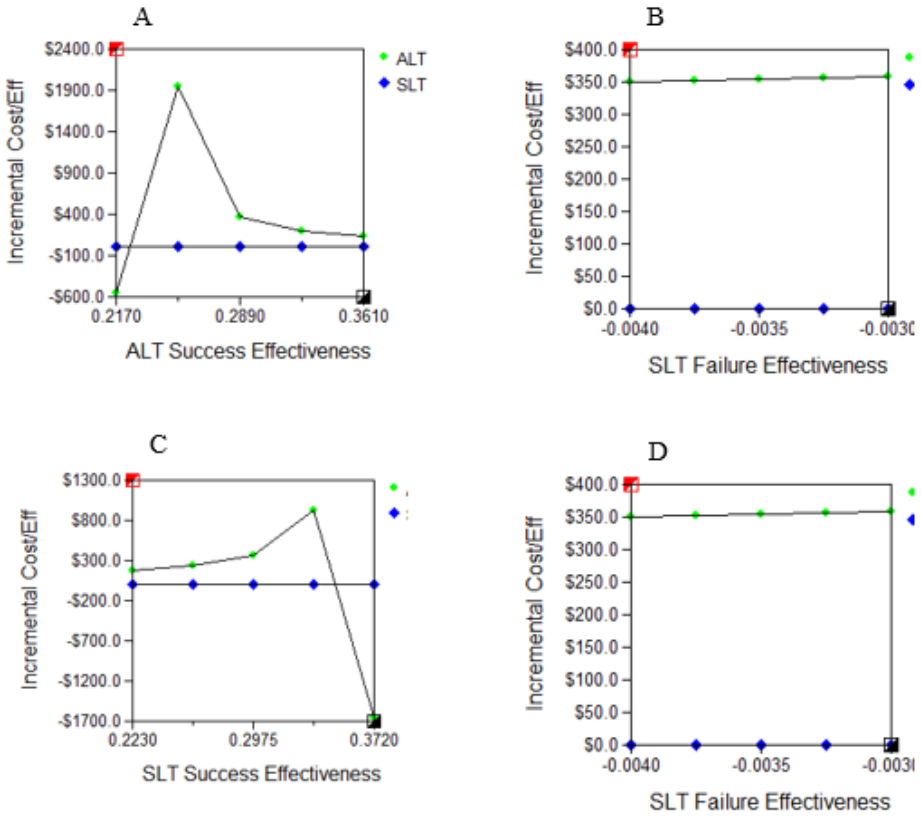

Figure 11: One-Way Sensitivity analysis of Effectiveness: Societal perspective

The horizontal axis of the graphs represent the effectiveness value, with base case value in the middle. The vertical axis is the incremental cost-effectiveness ratio (ICER).

4.13.2 One-Way Sensitivity analysis of Capital Cost: Societal perspective

One way sensitivity analysis of capital cost of ALT and SLT revealed that, none of the strategies were clearly dominated by any other.

Table 30: Sensitivity analysis of capital cost value from societal perspective

Group Variable	ICER		Dominance of Strategy
	25% lower from Base Case	25% higher from Base Case	
ALT Capital	149.15	563.83	None
SLT Capital	536.83	176.15	None

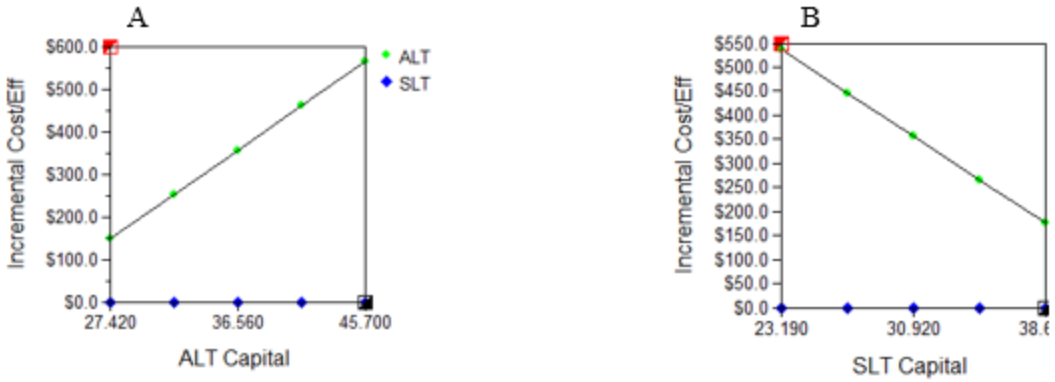

Figure 12: One-Way Sensitivity analysis of Capital Cost: Societal perspective

The horizontal axis of the graphs represent the capital cost value, with base case value in the middle. The vertical axis is the incremental cost-effectiveness ratio (ICER).

4.13.3 One-Way Sensitivity analysis of Effectiveness: Ministry Perspective

A 25% lowering of ALT Success Effectiveness and 25% increase of SLT Success Effectiveness results in dominance of SLT over ALT.

Table 31: Sensitivity analysis of effectiveness value: Ministry perspective

	ICER		
Group Variable	25% lower from Base Case	25% higher from Base Case	Dominance of Strategy
ALT Success	ALT is dominated by SLT	269.89	ALT is dominated by SLT when base case value is lowered by 25%
ALT Failure	800.91	546.54	None
SLT Success	323.83	ALT is dominated by SLT	ALT is dominated by SLT when base case value is increased by 25%
SLT Failure	615.92	674.37	None

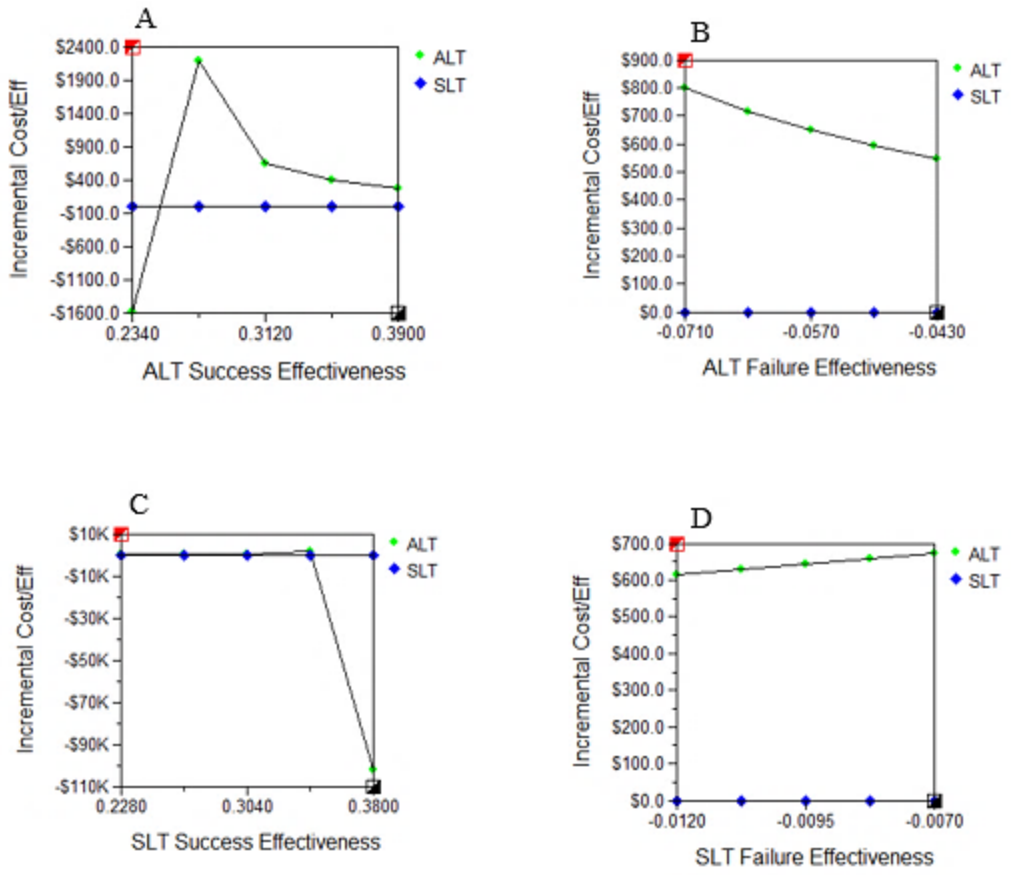

Figure 13: One-Way Sensitivity analysis of Effectiveness: Ministry perspective

The horizontal axis of the graphs represent the effectiveness value, with base case value in the middle. The vertical axis is the incremental cost-effectiveness ratio (ICER).

4.13.4 One-Way Sensitivity analysis of Capital Cost: Ministry Perspective

One way sensitivity analysis of capital cost of ALT and SLT revealed that, none of the strategies were clearly dominated by any other. (Table 32; See Appendix A for details).

Table 32: Sensitivity analysis of capital cost value: Ministry perspective

Group Variable	ICER		Dominance of Strategy
	25% lower from Base Case	25% higher from Base Case	
ALT Capital	484.8	814.62	None
SLT Capital	801.14	498.28	None

Figure 14: One-Way Sensitivity analysis of Capital Cost: Ministry Perspective

The horizontal axis of the graphs represent the capital cost value, with base case value in the middle. The vertical axis is the incremental cost-effectiveness ratio (ICER).

Chapter 5: Discussion

5.1 Results

In this thesis, the primary objective was to compute and compare the cost-effectiveness of two laser treatment modalities for uncontrolled open angle glaucoma (OAG) patients (including ocular hypertension, pigmentary dispersion syndrome and pseudoexfoliation syndrome) with at least one full previous SLT who were enrolled in an ongoing, active, equivalence parallel armed randomized multi-centered clinical trial entitled 'A randomized clinical trial of selective laser trabeculoplasty (SLT) in open angle glaucoma who had been previously treated with complete SLT'. Data from those patients who completed a 6-month post-laser follow-up (a total of 91 cases) were included in the analysis. Both societal and ministry perspective had been considered for the analysis. For societal perspective, all patients were considered. For ministry perspective, patients aged $\geq$ 65 years had been considered only. All analyses were done by comparing the intervention arms (ALT versus SLT). Based on the treatment outcome at 6-month post-intervention follow-up (either success or failure of treatment), two decision model trees, one for each perspective (societal and ministry), were developed. Ratio of IOP spike in mmHg at 1-hour post-laser was included in both the decision model trees. Weinreb et al. (1983) reported progression of visual field (VF) loss in advanced glaucoma patient experiencing post-laser IOP spike. IOP in the early post-procedural period might be a good predictor of treatment outcome (Downes et al. 1994). Reductions of mean IOP in mmHg from baseline to 6-month post-intervention follow-up for both treatment outcomes for each intervention arm were calculated and used in the cost-effectiveness analysis as the effectiveness of corresponding outcome of intervention arm (i.e, ALT Success Effectiveness, ALT Failure Effectiveness, SLT Success Effectiveness, SLT Failure Effectiveness). For this thesis, the treatment success was defined as a reduction of IOP of 3mmHg or 20% reduction or both from baseline at 6-month post-intervention follow-up. The MOP of the running clinical trial and previous studies on IOP reduction of OAG

used either or both of the conditions as a treatment success (Akhtar 2014; Martow et al. 2011; Mao et al. 2008; Hodge et al. 2005). For cost-effectiveness analysis (CEA), expected value of cost and effectiveness were determined from the decision model tree from both societal and ministry perspective, and incremental cost effectiveness ratios (ICERs) were determined. The expected value of individualized care in cost-effectiveness analysis and decision making is a useful tool to identify opportunity to improvement of efficiency in health care (van Gestel et al. 2012). A one-way sensitivity analysis for effectiveness value and capital cost for both intervention arms and perspectives were performed using a range of 25% above and below the base case value with 4 equal intervals in between. Due to the short horizon of follow-up, discounting was not considered for CEA. The impact of IOP reduction on quality of life (improved or not) would not have been apparent for this follow-up period and therefore was not an analysis option. So, willingness to pay by the patients for ALT and SLT treatment strategies was not considered for this scenario.

5.1.1 Clinical Trial Cohort

Baseline demographic characteristics were comparable between ALT and SLT intervention arm. The mean age of clinical trial cohort for both ALT and SLT groups were above 65 years, reflecting the natural progressive deterioration and chronicity of OAG. Symptoms affecting visual field, including visual loss, generally start at age 65 years and up (Access Economics Pty Limited). Most of the patients were Caucasians. Mean baseline IOP for both intervention arms were quite close (2.2% higher in SLT arm). While SLT group showed a steady and higher reduction of IOP for the first three month compared to ALT group, the scenario reversed back in favor of ALT at 6-month post-laser follow-up. At that time, 58.7% eyes of ALT arm achieved successful outcome and for SLT arm, it was 42.2%.

5.1.2 Use of IOP lowering medications at baseline:

Among 91 participants, a total of 60 participants were on 1 or more IOP lowering medications. The mean number of medications for ALT group was 1.22 (95% CI: 0.90 to 1.53) and for SLT it was 1.36 (95% CI: 0.97 to 1.74). This very close approximation of two means (of number of medications) represent a proxy for homogeneous distribution of severity of disease across the randomized group. This also rationalized the exclusion of medication costs used at baseline for the cost-effectiveness analysis.

5.1.3 Costing Aspects

For calculation of cost, we considered the charges of health care delivery personnel, procedural costs, post-operative medication costs and per-patient capital costs of interventions as direct costs, as these were the core costing for performing laser treatments for OAG. The costs of hospital infrastructures, overheads and buildings were not considered as they were difficult to assess and assigning them to the specific procedure like laser therapy for OAG in a hospital setting might cause much variability and sensitivity to methods and results (Tan et al. 2009; Finkler et al. 2007; Barnett, 2009). We also did not consider indirect cost such as wage loss due to the intervention procedure of patients and their accompanying personnel, as both ALT and SLT were outpatient procedure that neither required long time absence from normal daily tasks nor in-patient care. We assumed that, this indirect cost would have an unsubstantial impact on cost outcome. Travel cost was also not considered with the assumption of similar expense in both intervention arms as an effect of proper randomization and thus would have a minimal impact, if at all, in the cost outcome. The per patient capital cost of ALT and SLT intervention groups were $36.56 and $30.92, respectively.

5.1.4 Effectiveness Aspects and IOP reduction at 6-month follow-up

Laser treatment modalities for OAG were intended to reduce the pre-treatment IOP to a target level. So the reduction of post-laser IOP from baseline to 6-month

follow-up visit had been considered as an effectiveness of ALT and SLT intervention arms for this thesis. Effectiveness had been determined for both societal and ministry perspective. From societal perspective, the effectiveness of IOP reduction from baseline for SLT success group was slightly higher than corresponding ALT group (0.297 mmHg versus 0.289 mmHg). They remained similar for failure group also (SLT: -0.003 mmHg, ALT: -0.051 mmHg). For the ministry perspective, effectiveness of success and failure of ALT were higher than their SLT counterpart (ALT Success: 0.312 mmHg, SLT Success: 0.304 mmHg; ALT Failure: -0.057 mmHg and SLT Failure: -0.009). From societal perspective, expected value of effectiveness of ALT intervention was 0.149 mmHg and for SLT intervention, it was 0.123 mmHg. From the ministry perspective, expected effectiveness for ALT and SLT group were 0.154 mmHg and 0.122 mmHg, respectively. The effectiveness of both intervention arms remained close to each other.

The difference of mean IOP reduction at 6-month post-laser follow-up for both intervention arms from both societal and ministry perspectives were not significant statistically.

5.1.5 Cost-Effectiveness Analysis (CEA) and Incremental Cost Effectiveness Ratio (ICER): Societal perspective

The expected cost and effectiveness of ALT and SLT from the constructed decision model tree were used to determine which laser modality was cost-effective at 6-month post-laser follow-up from societal perspective. None of the interventions were clearly dominated by any other. Expected cost of ALT was a little higher than SLT ($458 versus $448, respectively) and so as the effectiveness (0.149 mmHg versus 0.123 mmHg). ALT strategy was slightly costly and slightly more effective compared to SLT. To switch from SLT to ALT, it would cost $356.49 for each extra unit IOP reduction.

5.1.6 Cost-Effectiveness Analysis (CEA) and Incremental Cost Effectiveness Ratio (ICER): Ministry Perspective

The Ministry perspective also revealed similar results as that of societal perspective with different values. Expected cost of ALT was higher than SLT ($467 versus $446, respectively) and so as the effectiveness (0.154 mmHg versus 0.122 mmHg). Expected cost and effectiveness of SLT from societal and ministry perspective were almost close to each other; whereas they were a little higher for ALT from ministry perspective. Cost-Effectiveness(C/E) ratio of SLT was 3644.32 and that for ALT was 3028.25. To switch from SLT to ALT, it would cost $ 649.71 for each extra unit IOP reduction.

5.1.7 Sensitivity Analysis: Societal perspective

For effectiveness variables, a 25% lowering of ALT Success Effectiveness and 25% increase of SLT Success Effectiveness results in dominance of SLT over ALT. No other variables show any clear dominance to each other.

Varying capital costs also revealed similar results as that of base case analysis. None of the interventions were clearly dominated by any other.

5.1.8 Sensitivity Analysis: Ministry Perspective

One-way sensitivity analysis from the ministry perspective, , also produced similar results as that of societal perspective. A 25% lowering of ALT Success Effectiveness and 25% increase of SLT Success Effectiveness results in dominance of SLT over ALT. Other variables did not show any clear dominance upon each other.

Sensitivity analysis of capital costs also revealed similar results as that of base case for ministry perspective with no clear dominance of the interventions by any other.

5.1.9 Willingness to pay for 1mmHg reduction of IOP: ICERs from other IOP lowering agents in similar scenario:

Lachaine et al. (2008) conducted a cost-effectiveness analysis of prostaglandin analogues for ophthalmic use. They did a systematic literature searches and conducted this CEA study from ministry perspective by using a decision analytic model considering PGAs with other comparative IOP lowering agents as first line of treatment and for both eyes assuming a 100% patient compliance. Costs were calculated from Ontario sources. Effectiveness was defined as reduction of IOP from at six month from baseline. For a six month duration of treatment, they calculated the ICER. When comparing Timolol with Latanoprost, Latanoprost was costly and more effective than Timolol and the ICER was 81.80 dollars. When comparing Timolol with Travoprost, Travoprost was costly & more effective than Timolol & ICER was 110.61 dollars. These ICERs for reduction of 1 additional mm Hg of IOP are much less than our calculated ICERs. In other words, Willingness to pay for 1mmHg reduction of IOP is much less than our calculated ICER. (Table 33).

Table 33: Cost-effectiveness analysis of prostaglandin analogues for ophthalmic use

Strategy	Cost (C)	Incremental Cost	IOP reduction at 6-month (E)	Incremental IOP reduction	C/E	Incremental C/E (ICER)
Timolol	112.52		6.31		17.84	
Latanoprost	200.37	87.85	7.38	1.07	27.15	81.80

VS

Timolol	112.38		6.73		16.69	
Travoprost	191.64	79.26	7.45	0.72	25.73	110.61

5.2 Strengths of the Study

The major strength of this study is its active equivalence parallel armed randomized, single blinded, multi-centered clinical trial to assess the effectiveness of ALT and SLT in terms of IOP reduction from baseline. The study protocol

included a generalizable study population, permissive eligibility criteria, an easily administered treatment protocol and outcomes that are almost the same compared to regular care of such patients across Canada. One of the major criticisms of clinical trial based cost-effectiveness analysis is the application of rigorous protocol that might not be compatible with regular health care delivery for similar patients, especially may compliance could have been compromised in regular patient care and the costing might not reflect the real scenario (Drummond et al. 2015). This study design diminished these criticisms due to the very short single treatment protocol, where compliance is 100% guaranteed and use of regular patient care set-up for trial patients, the cost of which is a true mirror image of direct patient care costing in a regular hospital out-patient or ophthalmological health care delivery center.

5.3 Limitations of the study

The study has several limitations. The sample size used for this thesis is less than the calculated sample size (91 instead of 144 eyes) of the trial, so the power of the study was reduced. The 6-month follow-up outcomes may vary when one year or more follow-up period would be considered. In that case, cost-effectiveness analysis of the intervention arms may yield different results. Although it was assumed that, indirect cost of treatment would not have a substantial impact on cost calculation, it would bolster any cost-effectiveness analysis, especially for societal perspective, if authentic data of indirect treatment costs could be collected from the patients.

5.4 Conclusion

Our study result revealed that, for a 6-month post-intervention follow-up for uncontrolled glaucoma patients who have had at least one previous full SLT, neither ALT nor SLT strategies were clearly dominated by any other. ALT is slightly more effective and slightly costly over SLT strategy. To switch from SLT

to ALT, it would cost $ 356.49 for each extra unit IOP reduction from societal perspective and from ministry perspective, the same would cost $ 649.71. This ICERs were much higher in comparison to ICERS of other IOP lowering strategies in similar situations. Sensitivity analysis with effectiveness variables showed dominance of SLT over ALT for some instance. SLT has the theoretical plausibility of repeatability and it is also easier to perform than ALT. All these factors should be considered when opting between ALT and SLT strategies for treatment of open angle glaucoma in patients having previous full SLT treatment.

5.5 Implication of Study Results and Future Direction

Our study provides information regarding the cost-effectiveness of SLT versus ALT in uncontrolled OAG patients previously treated with full SLT. As none of the alternatives were a dominant strategy at 6-month post-laser follow-up, and the cost and effectiveness of both strategies do not differ greatly, either options could be opted by the treating ophthalmologist considering the CEA. ALT is slightly more effective and also slightly costly. SLT has theoretical advantage of repeatability and its application is easy than that of ALT. A long term follow-up study with additional authentic information on indirect treatment costs from the patients in the future may provide more convincing cost-effective analysis information. It will help both the health policy makers and health care providers to choose between SLT and ALT treatment strategies with more confidence for the betterment of open angle glaucoma patients.

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Appendix

Appendix A: One-way Sensitivity Analysis Table

Appendix A1: ALT Effect Success Sensitivity: Societal Perspective

ALT Effect Success	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
0.217	SLT	448		0.123		3645.03	
	ALT	458		0.107		4293.13	(Dominated)
0.253	SLT	448		0.123		3645.03	
	ALT	458	9	0.128	0.005	3581.77	1944.49
0.289	SLT	448		0.123		3645.03	
	ALT	458	9	0.149	0.026	3072.65	356.49
0.325	SLT	448		0.123		3645.03	
	ALT	458	9	0.17	0.047	2690.25	196.23
0.361	SLT	448		0.123		3645.03	
	ALT	458	9	0.191	0.068	2392.49	135.38

Appendix A2: ALT Effect Failure Sensitivity: Societal Perspective

ALT Effect Failure	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
-0.064	SLT	448		0.123		3645.03	
	ALT	458	9	0.144	0.021	3187.28	449.34
-0.0575	SLT	448		0.123		3645.03	
	ALT	458	9	0.146	0.023	3128.92	397.57
-0.051	SLT	448		0.123		3645.03	
	ALT	458	9	0.149	0.026	3072.65	356.49
-0.0445	SLT	448		0.123		3645.03	
	ALT	458	9	0.152	0.029	3018.37	323.11
-0.038	SLT	448		0.123		3645.03	
	ALT	458	9	0.154	0.031	2965.98	295.44

Appendix A3: SLT Effect Success Sensitivity: Societal Perspective

SLT Effect Success	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
0.223	SLT	$448		0.092		4,877.49	
	ALT	$458	$9	0.149	0.057	3,072.65	162.11
0.26025	SLT	$448		0.108		4,168.07	
	ALT	$458	$9	0.149	0.041	3,072.65	223.44
0.2975	SLT	$448		0.123		3,638.82	
	ALT	$458	$9	0.149	0.026	3,072.65	359.40
0.33475	SLT	$448		0.139		3,228.83	
	ALT	$458	$9	0.149	0.01	3,072.65	918.06
0.372	SLT	$448		0.155		2,901.87	
	ALT	$458		0.149		3,072.65	(Dominated)

Appendix A4: SLT Effect Failure Sensitivity: Societal Perspective

SLT Effect Failure	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
-0.004	SLT	448		0.122		3662.3	
	ALT	458	9	0.149	0.026	3072.65	348.69
-0.004	SLT	448		0.123		3657.97	
	ALT	458	9	0.149	0.026	3072.65	350.61
-0.004	SLT	448		0.123		3653.64	
	ALT	458	9	0.149	0.026	3072.65	352.55
-0.003	SLT	448		0.123		3649.33	
	ALT	458	9	0.149	0.026	3072.65	354.51
-0.003	SLT	448		0.123		3645.03	
	ALT	458	9	0.149	0.026	3072.65	356.49

Appendix A5: ALT Capital Sensitivity: Societal Perspective

ALT Capital	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
27.42	SLT	448		0.123		3645.03	
	ALT	452	4	0.149	0.026	3036.56	149.15
31.99	SLT	448		0.123		3645.03	
	ALT	455	7	0.149	0.026	3054.6	252.82
36.56	SLT	448		0.123		3645.03	
	ALT	458	9	0.149	0.026	3072.65	356.49
41.13	SLT	448		0.123		3645.03	
	ALT	460	12	0.149	0.026	3090.69	460.16
45.7	SLT	448		0.123		3645.03	
	ALT	463	15	0.149	0.026	3108.74	563.83

Appendix A6: SLT Capital Sensitivity: Societal Perspective

SLT Capital	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
23.19	SLT	441		0.123		3585.1	
	ALT	455	14	0.149	0.026	3054.54	536.83
27.055	SLT	445		0.123		3615.06	
	ALT	456	12	0.149	0.026	3063.59	446.66
30.92	SLT	448		0.123		3645.03	
	ALT	458	9	0.149	0.026	3072.65	356.49
34.785	SLT	452		0.123		3674.99	
	ALT	459	7	0.149	0.026	3081.7	266.32
38.65	SLT	456		0.123		3704.96	
	ALT	460	5	0.149	0.026	3090.76	176.15

Appendix A7: ALT Effect Success Sensitivity: Ministry Perspective

ALT Effect Success	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
0.234	SLT	446		0.122		3644.32	
	ALT	467		0.11		4262.32	(Dominated)
0.273	SLT	446		0.122		3644.32	
	ALT	467	21	0.132	0.009	3540.84	2192.57
0.312	SLT	446		0.122		3644.32	
	ALT	467	21	0.154	0.032	3028.25	649.71
0.351	SLT	446		0.122		3644.32	
	ALT	467	21	0.176	0.054	2645.3	381.36
0.39	SLT	446		0.122		3644.32	
	ALT	467	21	0.199	0.076	2348.34	269.89

Appendix A8: ALT Effect Failure Sensitivity: Ministry Perspective

ALT Effect Failure	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
-0.071	SLT	446		0.122		3644.32	
	ALT	467	21	0.148	0.026	3150.61	800.91
-0.064	SLT	446		0.122		3644.32	
	ALT	467	21	0.151	0.029	3088.22	717.43
-0.057	SLT	446		0.122		3644.32	
	ALT	467	21	0.154	0.032	3028.25	649.71
-0.05	SLT	446		0.122		3644.32	
	ALT	467	21	0.157	0.035	2970.57	593.68
-0.043	SLT	446		0.122		3644.32	
	ALT	467	21	0.16	0.038	2915.04	546.54

Appendix A9: SLT Effect Success Sensitivity: Ministry Perspective

SLT Effect Success	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
0.228	SLT	446		0.091		4929.13	
	ALT	467	21	0.154	0.064	3028.25	323.83
0.266	SLT	446		0.107		4190.46	
	ALT	467	21	0.154	0.048	3028.25	432.23
0.304	SLT	446		0.122		3644.32	
	ALT	467	21	0.154	0.032	3028.25	649.71
0.342	SLT	446		0.138		3224.13	
	ALT	467	21	0.154	0.016	3028.25	1307.72
0.38	SLT	446		0.154		2890.81	
	ALT	467		0.154		3028.25	(Dominated)

Appendix A10: SLT Effect Failure Sensitivity: Ministry Perspective

SLT Effect Failure	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
-0.012	SLT	446		0.121		3696.85	
	ALT	467	21	0.154	0.033	3028.25	615.92
-0.01075	SLT	446		0.121		3674.78	
	ALT	467	21	0.154	0.033	3028.25	629.57
-0.0095	SLT	446		0.122		3652.97	
	ALT	467	21	0.154	0.032	3028.25	643.83
-0.00825	SLT	446		0.123		3631.42	
	ALT	467	21	0.154	0.031	3028.25	658.75
-0.007	SLT	446		0.124		3610.12	
	ALT	467	21	0.154	0.031	3028.25	674.37

Appendix A11: ALT Capital Sensitivity: Ministry Perspective

ALT Capital	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
27.42	SLT	446		0.122		3644.32	
	ALT	462	15	0.154	0.032	2994.32	484.8
31.99	SLT	446		0.122		3644.32	
	ALT	464	18	0.154	0.032	3011.29	567.26
36.56	SLT	446		0.122		3644.32	
	ALT	467	21	0.154	0.032	3028.25	649.71
41.13	SLT	446		0.122		3644.32	
	ALT	470	23	0.154	0.032	3045.21	732.17
45.7	SLT	446		0.122		3644.32	
	ALT	472	26	0.154	0.032	3062.18	814.62

Appendix A12: SLT Capital Sensitivity: Ministry Perspective

SLT Capital	Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
23.19	SLT	439		0.122		3583.76	
	ALT	464	25	0.154	0.032	3011.3	801.14
27.055	SLT	443		0.122		3614.04	
	ALT	466	23	0.154	0.032	3019.78	725.43
30.92	SLT	446		0.122		3644.32	
	ALT	467	21	0.154	0.032	3028.25	649.71
34.785	SLT	450		0.122		3674.6	
	ALT	468	18	0.154	0.032	3036.72	574
38.65	SLT	454		0.122		3704.88	
	ALT	470	16	0.154	0.032	3045.2	498.28

Appendix B: Different Forms Used in the RCT

Form 0 -Participant Contact Form For the Main Study

Study ID#_____; Initials:_____ DOB:_____ F ( ); M ( )

Full Name of the Participant:_____

Hospital chart #_____

What's the best time to call you?

From_____To _____; From_____To _____;
From_____To _____

Tel # to reach you? Home phone ( ) or cell phone
( )

Email (if you preferred)? _____

<u>If you have someone else to answer the phone or arrange your appointment:</u>

Relationship: _____

Name:_____

What's the best time to call him/her?

From_____To _____; From_____To _____;
From_____To _____

Tel # to reach him/her? Home phone ( ) or cell phone
( )

Email (if he/she preferred)? _____

Form 1-Randomization Form

Study ID #	Study site #	Study Eye	Patient initials	Today's date (m/d/y)	Visit	Staff initials
					Randomization	

Informed Consent

1. Has the participant had the study explained to him/her, signed the **Consent Form and had a copy given to him/her**? Yes No

2. Does the participant meet all inclusion and exclusion criteria? Yes No

Study Eye (check one) [ ] OD [ ] OS

3. Does the patient **agree to be randomized**? Yes No

4. Web-based Randomization

5. Randomization Number_____

6. Treatment group: Arm 1 ( ) Arm 2 ( )

Form 2-Inclusion and Exclusion Check List

Study ID #	Study Site #	Study Eye	Patient initials	Today's date (m/d/y)	Visit
					Screening

Inclusion Criteria (yes):

1. From one of the practices participating in this study ( ).
2. Older or equal to 18 years of age ( ).
3. Open angle glaucoma including pigmentary dispersion syndrome and pseudoexfoliation syndrome ( )
    a) Open angle glaucoma ( )
    b) Pigmentary dispersion syndrome ( )
    c) Pseudoexfoliation syndrome ( )
    d) Ocular hypertension ( )
4. Previous 360 degree SLT (One time of 360 degree SLT or two 180 SLT on the same eye) ( )
5. Intraocular pressure greater than 16 mm Hg on at least two consecutive occasions separated by one month ( )
6. Two sighted eyes. Sighted is defined as best corrected visual acuity of 20/200 or better in the absence of an advanced VF defect which is defined below (Exclusion Criteria (b)). Two eyes of the same patient may not be included in the study.
7. Willing to participate and sign the consent Form ( ).

Exclusion Criteria (No):

1. Any evidence of secondary open angle glaucoma (other than pigmentary and pseudoexfoliation) or narrow angle glaucoma (where the anterior trabecular meshwork is not visible 360 degrees). These patients would make the study population too heterogeneous ( ).
2. Previous non laser glaucoma surgery in the eye being considered for treatment as this changes the angle architecture too unpredictably to be included ( ).
3. Intraocular surgery anticipated in the 12 months after treatment ( )
4. Any corneal disease obscuring adequate visualization of the 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. Any previous ALT ( )

***IF NO WAS ANSWERED TO ANY INCLUSION CRITERIA, OR YES TO ANY EXCLUSION CRITERIA DO NOT ENROLL**

Investigator's Signature Date

Form 3-Baseline Clinical Examination

(1 of 3 pages)

Study ID #	Study Site #	Study Eye	Patient initials	Today's date (m/d/y)	Visit
					Screening

1. **Type of Glaucoma: _____**
2. **previous IOP (eg, laser booking date): Measuring date ( )**
   1) OD ____ OS ____ 2) OD ____ OS ____ 3) OD ____ OS ____
   Average IOP on booking date (2 or 3 measures): OD_____OS_____

Demographics

Date of birth: _____/_____/_____ (dd/mm/yyyy) **Gender:**[ ] M [ ] F **Eye Colour:** _____

Race:
[ ] Caucasian
[ ] African
[ ] Asian
[ ] Middle East
[ ] South America
[ ] Aboriginal
[ ] or Self Defined _____

Primary Open Angle Glaucoma Risk Factors:
(check all that apply)
[ ] Family History
[ ] Age (over 60 years)
[ ] Myopia
[ ] Elevated IOP (over 21mHg)
[ ] Ethic background (increased risk if not Caucasian)
[ ] Concomitant Medical Conditions (hypertension, diabetes, hypothyroidism)
[ ] Other(s):
_____

Study Eye: (check one) [ ] OD [ ] OS

SLT History:

TYPE OF LASER: -SLT	**DATE OF Laser**	**EYE(S) -OD -OS -both**	**Degrees: -180 -360 -other**	**LOCATION: -inferior -superior -nasal -temporal -other**	**Power: SLT: _. _mj**	**Application (shots): _ _ _**	**Total Energy = (**power x applications) **SLT: _ _ mj**

Ocular Medical and Surgical History (excluding previous ALT or SLT)

DIAGNOSIS/SURGERY	**EYE(S)**	**ONSET <5YEARS 5-10 YEARS >10YEARS**	**ONGOING OR RESOLVED**

Form3 (Baseline, 2/3)

Non-Ocular Medical and Surgical History:

DIAGNOSIS/SURGERY	**ONSET (<5 YEARS; 5-10 YEARS; >10 YEARS)**	**ONGOING OR RESOLVED**

Intraocular Pressure (IOP)

METHOD OF MEASUREMENT	TIME	IOP (mmHg)
□ **Goldman Applanation Tonometry** IOP: take two measurements & average them if the diff. is < 2 mm Hg. -If the difference ≥3 mm Hg, take 3 measurements and take the median as the value.	**____:____hrs (24 hour clock)**	**1. OD ____ OS ____** **2. OD ____ OS ____** **3. OD ____ OS ____** **Average IOP** **OD ____ OS ____**

Target IOP for this Patient?_____

Signature of Mire Reader **Date**

Signature of Dial reader **Date**

Central Corneal Thickness (CCT):

METHOD OF MEASUREMENT	TIME	CCT (µM)
□ **Ultrasound Pachymetry**	**___:___ hrs (24 hour clock)**	**OD _____ µm** **OS _____ µm**

Signature of Person Performing CCT **Date**

Form3 (Baseline, 3/3)

Best-Corrected Visual Acuity (BCVA):

METHOD OF MEASUREMENT	TIME	VISUAL ACUITY
□ **Snellen**	**___:___ hrs (24 hour clock)**	**OD _____** **OS _____**

* For consistency please use the same chart in the same room, using the same lighting throughout the trial.

Signature of Person Performing BCVA **Date**

SCORING	RIGHT EYE (OD)	LEFT EYE (OS)
Modified Shaffer **Closed** **Schwalbe's Line** **Trabecular Meshwork** **Scleral Spur** **Ciliary Body Band**	**Gonioscopy (with gonio lens)** **Grade 0** □ **Grade 1** □ **Grade 2** □ **Grade 3** □ **Grade 4** □	**Gonioscopy (with gonio lens)** **Grade 0** □ **Grade 1** □ **Grade 2** □ **Grade 3** □ **Grade 4** □
None **Light** **Medium** **Dark Brown** **Almost Black**	**Trabecular Meshwork (Angle) Pigmentation** **Grade 0** □ **Grade 1** □ **Grade 2** □ **Grade 3** □ **Grade 4** □	**Trabecular Meshwork (Angle) Pigmentation** **Grade 0** □ **Grade 1** □ **Grade 2** □ **Grade 3** □ **Grade 4** □
PAS is absent or present	**Peripheral Anterior Synechiae** **Absent** □ **Present** □	**Peripheral Anterior Synechiae** **Absent** □ **Present** □
	Cup to Disc Ratio **0.__**	**Cup to Disc Ratio** **0.__**
Cells Scoring: **0=0 cells; +0.5=1-5 cells (trace); +1=6-15 cells; +2=16-25 cells; +3=26-50 cells; +4=>50cells** **Flare Scoring:** **0=None; +1=Faint; +2=Moderate; +3=Marked; +4= Intense**	**Anterior Chamber Inflammation** **Cells _____** **Flare _____**	**Anterior Chamber Inflammation** **Cells _____** **Flare _____**

Signature of Person Performing Ophthalmic Examination **Date**

Form 4-Laser Treatment Log Record

(page 1 of 2)

Study ID #	Study Site #	Study Eye	Patient initials	Today's date (m/d/y)	Visit	Study arm 1 or 2
					Laser treatment	

Study Eye: (check one) [ ] OD [ ] OS

Prior to Laser Check IOP, BCVA and AC for inflammation

<u>Intraocular Pressure (IOP):</u> or Not Done □ (Screening and Treatment Combined)

METHOD OF MEASUREMENT	TIME	IOP (MMHG)	Baseline IOP rule
□ **Goldman Applanation Tonometry** To measure IOP: -Take two measurements and average them if the difference is within 2 mm Hg. -If the difference is greater than 3 mm Hg, take 3 measurements and take the median as the value.	**____:____hrs (24 hour clock)**	**1. OD ____ OS ____** **2. OD ____ OS ____** **3. OD ____ OS ____** **Average IOP OD ____ OS ____**	Average of IOP on booking date (Avg OD____ OS_____) and laser date (if different date from the baseline measurement date) (Avg OD____ OS_____) Baseline IOP: OD____ OS_____ * the computer will do the calculation of Baseline IOP, you may verify it, if you have any doubt, please let Francie know .

Signature of Mire Reader **Date**

Signature of Dial reader

<u>Best-Corrected Visual Acuity (BCVA):</u> or Not Done □ (Screening and Treatment Combined)

METHOD OF MEASUREMENT	TIME	VISUAL ACUITY
□ Snellen	___:___ hrs (24 hour clock)	OD _____ OS _____

***If three letters or more are read correctly on that line, capture that line on the source document (ie; if the patient reads all but 2 letters correctly on the 20/20 line, you will still record 20/20 as the visual acuity)**
***As per inclusion (e): Two sighted eyes. Sighted is defined as best corrected visual acuity of 20/200 or better**
***If the patient cannot read 20/400 or better, check for CF, HM, LP**
*** For consistency please use the same chart in the same room, using the same lighting throughout the trial, if possible**

Signature of Person Performing BCVA **Date**

Form 4-Laser Treatment Log Record (page 2 of 2)

Study ID #	Study Site #	Study Eye	Patient initials	Today's date (m/d/y)	Visit	Study arm 1 or 2
					Laser treatment	

<u>CELLS SCORING:</u> 0=0 CELLS; +0.5=1-5 CELLS (TRACE); +1=6-15 CELLS; +2=16-25 CELLS; +3=26-50 CELLS; +4=>50CELLS <u>FLARE SCORING:</u> 0=NONE; +1=FAINT; +2=MODERATE; +3=MARKED; +4= INTENSE	<u>ANTERIOR CHAMBER INFLAMMATION</u> (OD) CELLS _____ FLARE _____	<u>ANTERIOR CHAMBER INFLAMMATION</u> (OS) CELLS _____ FLARE _____

Signature of Person Performing AC Examination **Date**

Laser treatment:

Time: _ _hour_ _min	**ALT**		**SLT**	
	Protocol (p)	Actual	**Protocol**	Actual
Location	□Inferior 180 (p) □superior 180 □nasal 180 □temporal 180		□Inferior 180 (p) □superior 180 □nasal 180 □temporal 180	
Applications	50		50	
Spot size	50 uM		400 uM	
Duration	0.1 sec		3 nsec	
Power range	400-800 mW		0.5 -1.4 mJ	
Total energy (Application x power)	_ _application x ___mW /1000	_ _._ _ _W	__applications x _._mJ	_ _ ._ mJ
Total Energy Level from the Machine?				
Brimonidine-post laser	1 drop		1 drop	

Signature of Person Performing Laser **Date**

Form 5 -Follow-Up Examinations (for 1 h, 1wk, 1 /3/6 mon)

(page 1 of 2)

Study ID #	Study Site #	Study Eye	Patient initials	Today's date (m/d/y)	Visit (1H/1W/1M/3M/6M)	Study arm 1 or 2

Any changes to concomitant medications? Yes□ (document on concomitant medication form) No□
Any Adverse Events to report? Yes □ (document on Adverse Event Log) No□

Intraocular Pressure (IOP):

METHOD OF MEASUREMENT	TIME	IOP (MMHG)
□ **Goldman Applanation Tonometry** To measure IOP: -Take two measurements and average them if the difference is within 2 mm Hg. -If the difference is greater than 3 mm Hg, take 3 measurements and take the median as the value.	**____:____hrs (24 hour clock)**	**1. OD ____ OS ____** **2. OD ____ OS ____** **3. OD ____ OS ____** **Average IOP OD ____ OS ____**

***≥5mmHg increase in IOP is considered an Adverse Event, please document on Adverse Event Log.**
Medication given for elevated IOP? Yes□ (document on concomitant medication form) No□

Signature of Mire Reader **Date**

Signature of Dial reader

If additional IOP measurements taken, please document below.

If additional medication given for elevated IOP, please document on concomitant medication form.

Time: ___:___ hrs OD ___mmHg
OS ___mmHg

Time: ___:___ hrs OD ___mmHg
OS ___mmHg

Time: ___:___ hrs OD ___mmHg
OS ___mmHg

Form 5 -Follow-Up Examinations (for 1 h, 1wk, 1 /3/6 mon)
(page 2 of2)

Study ID #	Study Site #	Study Eye	Patient initials	Today's date (m/d/y)	Visit (1H/1W/1M/3M/6M)	Study arm 1 or 2

Best-Corrected Visual Acuity (BCVA):

METHOD OF MEASUREMENT	TIME	VISUAL ACUITY
□ Snellen	___:___ hrs (24 hour clock)	OD _____ OS _____

***If three letters or more are read correctly on that line, capture that line on the source document (ie; if the patient reads all but 2 letters correctly on the 20/20 line, you will still record 20/20 as the visual acuity)**
***As per inclusion (e): Two sighted eyes. Sighted is defined as best corrected visual acuity of 20/200 or better**
***If the patient cannot read 20/400 or better, check for CF, HM, LP**
*** For consistency please use the same chart in the same room, using the same lighting throughout the trial, if possible**

Signature of Person Performing BCVA **Date**

CELLS SCORING: **0=0 CELLS; +0.5=1-5 CELLS (TRACE); +1=6-15 CELLS; +2=16-25 CELLS; +3=26-50 CELLS; +4=>50CELLS** **FLARE SCORING:** **0=NONE; +1=FAINT; +2=MODERATE; +3=MARKED; +4= INTENSE**	**ANTERIOR CHAMBER INFLAMMATION (OD)** **CELLS _____** **FLARE _____**	**ANTERIOR CHAMBER INFLAMMATION (OS)** **CELLS _____** **FLARE _____**

Signature of Person Performing Examination **Date**

Other findings by Investigator:_____

_____

_____ **Course/Complications:** (check all that apply)

[ ] Anterior Chamber Reaction 3+ or greater
[ ] Pain or Discomfort
[ ] Blurred Vision
[ ] IOP Spike (increase of 5mmHg or more) indicate increase __mmHg
[ ] Persistent IOP Elevation
[ ] Peripheral Anterior Synechiae
[ ] Corneal cloudiness
[ ] Scarring
[ ] Others: _____
[ ] None

Appendix C: Recalculation of Power of the Study for Reduced Sample Size

As we have an active control group (ALT) and a comparator group (SLT), the total sample size (for both active control and comparator group) would be:

$$2(N) = 2\{2v^2 (Z_\alpha+Z_ß)^2 /d^2\}$$

When $2(N) = 91$

$v^2 = 5^2$

$Z_\alpha = 1.96$

$d^2 = 3^2$

Then, $Z_ß = 0.9$

When $Z_ß = 0.9$, the power of the study = 81%

Curriculum vitae

Name: Muhammad Rakibuz-Zaman

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2014-2016, MSc (Epidemiology)

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Publication:
(Selected)

- Hamade N, Hodge WG, Rakibuz-Zaman M, Malvankar-Mehta MS. The Effects of Low-Vision Rehabilitation on Reading Speed and Depression in Age Related Macular Degeneration: A Meta-Analysis. PLoS ONE.2016;11(7) :1-15.
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Conference Presentation:

- Muhammad Rakibuz-Zaman, MBBS, Jeffrey Tin-Yu Chow, William Hodge, MD, PhD, FRCSC, Francie F. Si, MD, MSc, Cindy Hutnik, BSc, MD, PhD, FRCSC, Marcelo Nicolela, MD, FRCSC, Andrew Crichton, MD, FRCSC, Catherine Birt, MD, FRCSC, Karim F. Damji, MD, FRCSC, E. Sogbesan, MD, Dariusz Gozdzik, Lesya Shuba, MD, PhD, FRCSC, Michael Dorey, MD, FRCSC, Bryce Ford, MD, FRCSC. Repeat SLT vs ALT, interim analysis of demographics and safety. Ivey Eye Institute Ophthalmology Research Day, London, ON, Nov. 2015. Podium Presentation.

Poster Presentation:

- Clinico-Histopathological Characteristics of Skin Lesions among Arsenicosis Patients in Bangladesh. [Forgery International Workshop (From 21-23 November, 2011 in India)]