Clinical and Patient-Reported Outcomes of Primary Selective Laser Trabeculoplasty in Open Angle Glaucoma & Ocular Hypertension

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Section 1: Overview

1.1 Declaration

I, Anurag Garg, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

1.2 Abstract

Aims

To investigate the clinical efficacy of primary selective laser trabeculoplasty (SLT) as initial therapy in newly-diagnosed treatment-naïve open-angle-glaucoma (OAG)/ ocular hypertension (OHT) patients. To also investigate patient-reported outcome measures related to health-related quality of life (HRQL) between primary SLT and topical medication.

Methods

Pre-specified and post-hoc analyses performed using data derived from the Laser in Glaucoma and Ocular Hypertension ('LiGHT') Trial, a multi-centre randomised-controlled trial.

Results

718 patients (1235 eyes) were randomised: 356 patients (613 eyes) were allocated to SLT (Laser-1st pathway) and 362 patients (622 eyes) to medical treatment (Medicine-1st pathway).

Early absolute IOP-lowering following primary SLT was no different between OHT and OAG eyes (adjusted mean difference = -0.05mmHg; 95% confidence interval (CI) -0.6 to 0.5mmHg; p=0.85). No difference was noted in early absolute IOP-lowering between topical medication and primary SLT (adjusted mean difference = -0.1mmHg; 95% CI, -0.6 to 0.4mmHg; p=0.67). At 36-months, 536 eyes (87.7% of 611 eyes) of 314 patients (88.5% of 355 patients) were available for analysis in Laser-1st pathway. 74.6% of eyes (400 eyes) treated with primary SLT achieved

drop-free “disease-control” at 36-months; 58.2% (312 eyes) following single SLT. 6 eyes of 6 patients experienced immediate post-laser IOP spike with 1 eye requiring treatment.

115 eyes of 90 patients received repeat SLT during the first 18 months of the trial. Repeat treatment maintained drop-free IOP control in 67% of these eyes for a subsequent 18 months, with no clinically-relevant adverse events.

At 36-months, there was no significant difference in all HRQL measures between the treatment arms, including EQ-5D-5L (adjusted mean difference = 0.01; 95% CI, –0.01 to 0.03; p=0.23).

Conclusions

This work supports primary SLT to be a safe and clinically effective alternative to topical treatment that could be offered as a first-line IOP lowering treatment to patients with OAG or OHT.

1.3 Impact Statement

Glaucoma is a progressive, multifactorial optic neuropathy and is the leading cause of irreversible blindness in the world. Glaucoma is often associated with elevated intraocular pressure (IOP) and is characterised by degeneration of retinal ganglion cells (RGCs), leading to irreversible visual loss. The aim of glaucoma treatment is to slow or stop disease progression and preserve patients' vision & quality of life for the duration of their lifetime. IOP is the only modifiable risk factor proven to alter the disease course in glaucoma.

Over the past two decades, selective laser trabeculoplasty (SLT) has become an established treatment to lower intraocular pressure for open-angle-glaucoma (OAG) and ocular hypertension (OHT). SLT uses a 532nm Q switched, frequency-doubled Nd:YAG laser that delivers a short pulse duration (3 nanoseconds) to reduce IOP by increasing aqueous outflow through the trabecular meshwork (TM).

The procedure is short and outpatient-based, with quick recovery and good safety profile. SLT has the potential advantage of avoiding issues associated with topical IOP lowering medications such as local and systemic side effects and variable patient adherence. Studies investigating SLT as a primary treatment have found a similar IOP lowering efficacy and success rate to topical medication using various success criteria. However, few studies have evaluated primary SLT in true treatment-naïve patients and there is limited knowledge of the clinical efficacy, safety and tolerability of primary SLT in such patients.

The work in this thesis demonstrates that primary SLT is an effective and safe treatment for newly diagnosed OHT and OAG patients. It can provide predominantly drop-free IOP control over a minimum of 36 months, with less intense treatment, fewer adverse events and reduced need for ocular surgery. It also appears to be repeatable in eyes demonstrating initial IOP lowering response.

Moreover, no significant difference was found in PROMs analysis between SLT and topical medication at 36 months, which suggests that in this particular cohort of patients with largely early disease, the HRQL burden of both treatments appears to be equivalent.

These findings, combined with the cost-effectiveness of SLT which was also demonstrated as part of the LiGHT study, strongly suggests that primary SLT could be offered as a first-line treatment to treatment naïve OAG/OHT patients instead of topical medication. This would represent a change in current clinical practice and has implications for the delivery of glaucoma care in both developed and developing countries alike.

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1.6 List of Publications & Abstracts

The following publications and abstracts have arisen in connection with this work:

Peer reviewed publications

Garg A, Gazzard G. Treatment choices in newly diagnosed primary open-angle glaucoma and ocular hypertension patients. Eye (Lond). 2020 Jan;34(1):60-71

Garg A, Vickerstaff V, Nathwani N, Garway-Heath D, Konstantakopoulou E, Ambler G, et al. Efficacy of Repeat Selective Laser Trabeculoplasty in Medication-Naïve Open-Angle Glaucoma and Ocular Hypertension during the LiGHT Trial. Ophthalmology 2020 Feb DOI: 10.1016/j.ophtha.2019.10.023

Garg A, Vickerstaff V, Nathwani N, Garway-Heath D, Konstantakopoulou E, Ambler G, et al. Primary Selective Laser Trabeculoplasty for Open Angle Glaucoma and Ocular Hypertension: Clinical Outcomes, Predictors of Success and Safety from the Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial. Ophthalmology 2019 Sep;126(9):1238-1248.

Gazzard G, Konstantakopoulou E, Garway-Heath D, **Garg A**, Vickerstaff V, Hunter R, et al. Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial. Lancet. 2019 Apr 13;393(10180):1505-1516

Garg A, Gazzard G. Selective laser trabeculoplasty: past, present, and future. Eye (Lond). 2018 May;32(5):863-876.

Abstracts

Garg A, Vickerstaff V, Nathwani N, Konstantakopoulou E, Gazzard G Primary SLT treatment for Normal Tension Glaucoma; a subset analysis from the LiGHT trial. ARVO Annual Meeting 2020

Garg A, Vickerstaff V, Nathwani N, Garway-Heath D, Konstantakopoulou E, Ambler G, et al. Efficacy of Repeat Selective Laser Trabeculoplasty in Medication-Naïve Open-Angle Glaucoma and Ocular Hypertension during the LiGHT Trial. UKEGS Annual Meeting 2019

Garg A, Vickerstaff V, Nathwani N, Konstantakopoulou E, Dowse E, Gazzard G. Primary Selective Laser Trabeculoplasty for Primary Open Angle Glaucoma & Ocular Hypertension: Early Clinical Outcomes from a Prospective, Multi-centre Randomised Controlled UK Trial
ARVO Annual Meeting 2018

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Section 2: Introduction

2.1 Glaucoma

Glaucoma is a progressive, multifactorial optic neuropathy (1, 2). It is the second leading cause of blindness worldwide following cataract, and is the leading cause of irreversible blindness in the world (3). Glaucoma is often associated with elevated intraocular pressure (IOP) and is characterised by degeneration of retinal ganglion cells (RGCs) leading to irreversible visual loss.

2.1.1 Definition and Classification

Glaucoma can be broadly classified based on the appearance of the irido-corneal angle (4). Open-angle, closed-angle, and developmental glaucoma all exist, and these can be further sub classified into primary and secondary types.

Open angle glaucoma (OAG) can be primary or secondary. Primary open-angle glaucoma (POAG) typically manifests as an adult-onset disease. It can also occur without elevated IOP, often referred to as normal-tension glaucoma (NTG). Secondary open-angle glaucomas include those associated with conditions such as pseudoexfoliation (PXF) or pigment dispersion syndrome (PDS).

Closed-angle glaucoma can be primary (e.g. pupillary block) or secondary (e.g. inflammatory or neovascular causes). Developmental forms of glaucoma include primary congenital glaucoma and glaucoma associated with syndromes (e.g. Aniridia or Axenfeld–Rieger syndrome).

Individuals can also have elevated IOP without detectable glaucomatous damage. These individuals are at an increased risk for developing POAG and are referred to as suffering from Ocular Hypertension (OHT) (5).

2.1.2 Epidemiology

Glaucoma affects more than 70 million people worldwide (6). It is predicted that by 2020, almost 80 million people worldwide will have glaucoma, of which ~75% will be POAG. Population level surveys suggest that only 10-50% of patients with glaucoma are aware of their disease (7, 8). Whilst POAG is the most common form of glaucoma, the different subtypes of glaucoma do vary amongst races and countries. In the United States for example, the black population has a higher POAG prevalence than the white population. The prevalence of POAG in East Asian populations is higher than primary angle closure glaucoma (PACG), but in certain regions such as Mongolia and Burma, PACG is more prevalent than POAG (9).

2.1.3 Anatomy & Physiology

Aqueous humour dynamics

The maintenance of intraocular pressure in the eye is a balance between secretion of aqueous humour and its drainage (see Figure 1). Aqueous humour is secreted posterior to the iris by the ciliary body and then flows anteriorly into the anterior chamber. Aqueous humour provides nutrients to the iris, lens, and cornea. Drainage is through 2 pathways – into the venous circulation via the trabecular meshwork (TM) and independently through the uveoscleral pathway (10).

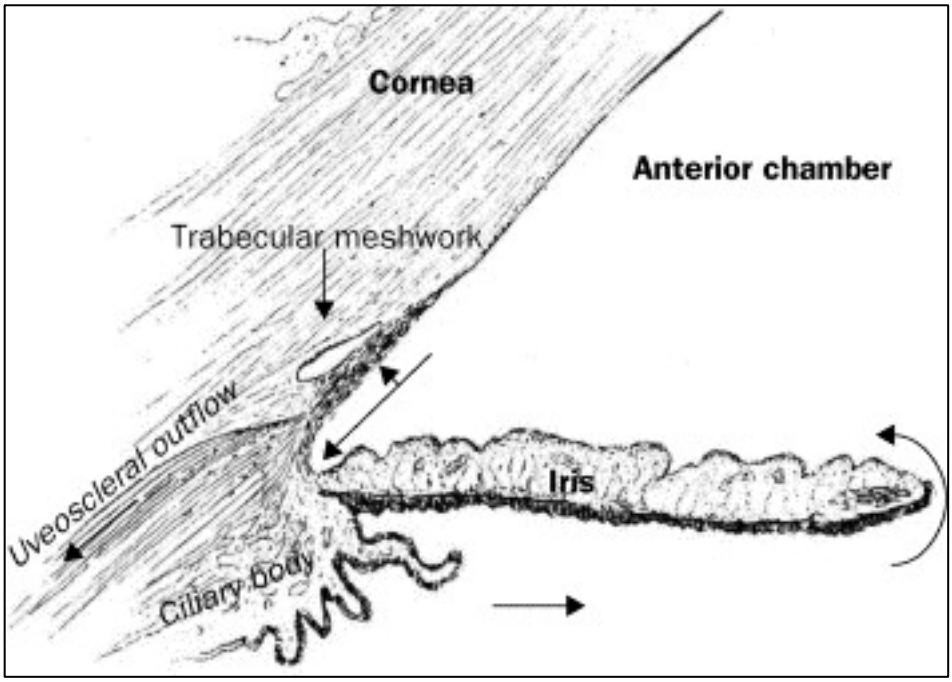


Figure 1 : Physiology of aqueous humour – IOP is determined by a balance between secretion & drainage of aqueous humour. Arrows show direction of flow; aqueous humour is secreted by ciliary body into the posterior chamber, passes posterior to the iris and through the pupil into the anterior chamber, exiting through the TM or uveoscleral outflow pathways. Taken from Weinreb & Khaw (11).

The Optic Nerve & Inner Retina

RGCs are central nervous system neurons that have their cell bodies in the inner retina of the eye and axons in the optic nerve. Axons of RGCs comprise the retinal nerve fibre layer, the innermost layer of the retina. The human optic nerve

contains about one million nerve fibres(10). These axons converge on the optic disc. The optic disc is about 1.5 mm in diameter and vertically oval. Its size varies, and is largest in highly myopic individuals. The convergence of the axons forms a central depression in the disc, known as the optic cup. The fibres exit the eye as the optic nerve after traversing the lamina cribrosa. RGC axons (as part of the optic nerve) convey visual information from the eye to the brain, synapsing to the lateral geniculate nucleus (LGN) in the thalamus of the midbrain. Degeneration of these RGCs in glaucoma results in 'cupping', a characteristic appearance of the optic disc due to neural loss which is manifest as visual loss (see Figure 2).

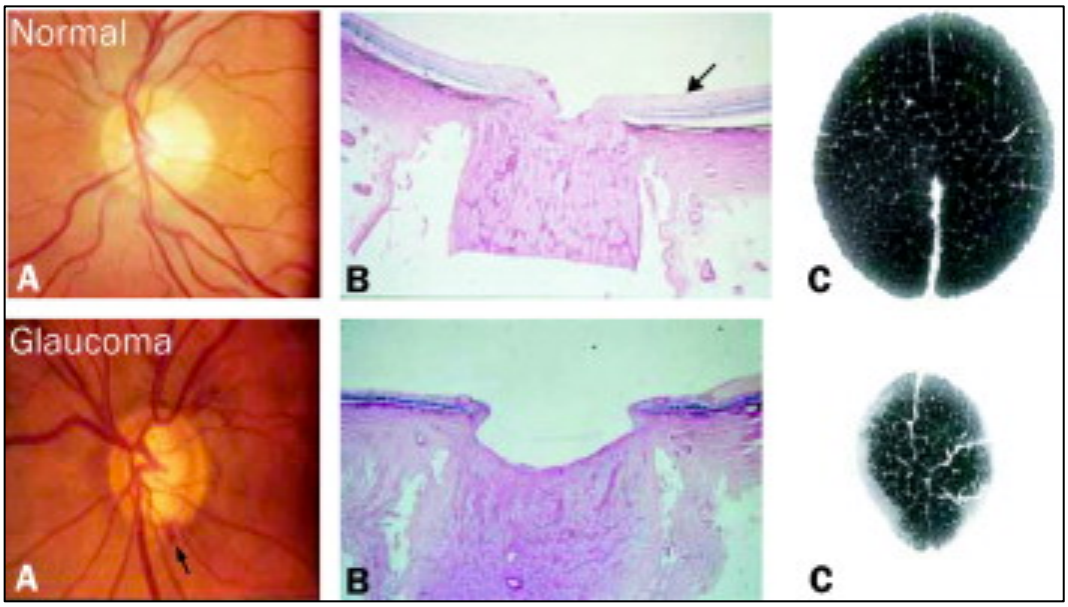


Figure 2: (A) Optic nerve in healthy and glaucomatous eyes–the normal optic disc has a small central cup. The central cup of the glaucomatous disc is enlarged and deepened, and the surrounding neuro-retinal rim is thinned. Optic disc haemorrhage (arrow) is sometimes observed in an eye with glaucoma. (B) Longitudinal cross-section of normal and glaucomatous optic nerve. The retinal nerve fibre layer (arrow) is the innermost layer of the retina, and is thin in the glaucomatous optic nerve. (C) Transverse section of normal and glaucomatous optic nerve. The normal optic nerve has about 1 million optic nerve fibres. As glaucoma progresses, the number of nerve fibres is reduced, and concomitant reduction in diameter of the optic nerve is seen. Taken from Weinreb & Khaw (11).

2.1.4 Pathophysiology of Glaucoma

The exact pathogenesis of glaucoma is not fully understood, but acquired and genetic factors are known to be contributory.

The level of IOP has been shown to heavily influence RGC death (3). In open angle glaucoma, there is increased resistance to aqueous outflow through the TM, leading to impaired aqueous drainage and elevated IOP. It is thought that elevated IOP can cause mechanical stress on the posterior structures of the eye, notably the optic nerve at the lamina cribrosa (11). The lamina cribrosa is a weak point in the wall of the pressurised eye and raised IOP can result in its' compression with consequent mechanical axonal damage and disruption of axonal transport in the optic nerve (12, 13).

Trophic factors, including brain-derived neurotrophic factor, are retrogradely transported from the axonal terminals of RGCs in the LGN to their cell bodies in the inner retina, and are essential for the survival of these cells. Interruption to the delivery of these essential trophic factors is fatal for their survival. This has been demonstrated both in experimental models of glaucoma (12) and post mortem human eyes (11). RGC death can precipitate changes to other important cells within the retina including astrocytes and retinal microglial cells (14, 15) as well as changes in the LGN and visual cortex (16, 17).

Raised IOP can also have other harmful effects. In mouse models of glaucoma, raised IOP has been shown to induce mitochondrial fission, causing subsequent disruption within RGCs and astrocytes (18) which are left unable to meet energy

demands imposed on them by the induced metabolic stress, resulting in their death (3).

The pathophysiology of glaucoma cannot be solely attributed to elevated IOP however. This is evidenced by NTG patients who demonstrate glaucomatous optic neuropathy despite normal IOP and conversely, OHT patients who have elevated IOP without detectable glaucoma damage.

Ren et al found NTG patients can have abnormally low cerebrospinal fluid (CSF) pressure in the optic nerve subarachnoid space, resulting in a large pressure gradient across the lamina cribrosa (19). Furthermore, the pressure gradient across the lamina was similar between a NTG patient with normal IOP and low CSF pressure vs. a glaucoma patient with high IOP and normal CSF pressure. In their study, glaucomatous visual field defects were positively correlated with the trans-lamina cribrosa pressure difference. Proof of concept was demonstrated when OHT patients with raised IOPs were shown to have a relatively raised CSF pressure. The elevated retro-lamina cribrosa pressure compensated for an increased IOP leading to a net normal trans-laminar pressure difference such that glaucomatous optic nerve damage did not develop (20). Thus, increased trans-lamina cribrosa pressure difference (and not elevated IOP) may actually be a significant factor in glaucoma pathophysiology. Other factors such as impaired microcirculation, altered immunity and oxidative stress may also contribute to glaucoma pathogenesis (3).

Genetic studies of POAG suggest that it is a genetically complex trait. Genetic linkage studies of large affected families have identified mutations in several

causative genes such as Myocilin (MYOC) and Optineurin (OPTN) that are capable of causing POAG with minimal influence from other genes or the environment. Mutations in the Myocilin (MYOC) gene occur in juvenile or early adult forms of POAG, characterised by marked elevation of IOP. The prevalence of MYOC mutations in POAG patients is between 3-5% with carriers of the mutation manifesting an autosomal dominant trait. The glaucoma phenotype develops in 90% of cases (4). The exact mechanism of how the mutation causes glaucoma remains unclear, but it is thought abnormal myocilin accumulates in the intracellular space of TM cells. This may trigger loss of function in these cells, limiting the aqueous outflow pathway and resulting in elevated IOP. Aqueous outflow studies have demonstrated impaired outflow in patients with MYOC mutations, thus supporting this theory (21). Mutations in the Optineurin (OPTN) gene on chromosome 10p14 have also been shown to be associated with POAG (22). OPTN is thought to have a neuroprotective role in reducing the susceptibility of RGCs to apoptotic stimuli and thus a mutation in this protein is thought to lead to premature RGC death.

Studies have shown that despite identification of at least ~20 'causative' genes, these account for <10% of POAG cases in the general population. It is therefore likely that the hereditary aspect of many of the remaining cases of POAG is due to the combined effects of several genes (polygenic) and that gene-environment interactions are important.

Quantitative endophenotype traits related to POAG pathogenesis such as IOP, vertical cup-to-disc ratio, and central corneal thickness are also highly heritable and likely to be influenced at least in part by genes. Recent advances in genomic

technologies and genome-wide association studies (GWAS) have greatly accelerated the discovery and understanding of genes and genomic regions associated with POAG and influencing the quantitative endophenotype traits related to POAG pathogenesis. They have found the CAV1/CAV2 locus on chromosome 7q34 to be associated with POAG in European derived populations (23). These genes encode proteins (Caveolins) which are involved in cell signalling and endocytosis. The CDKN2BAS locus on chromosome 9p21 has also been shown to be related to glaucoma risk (24) but the mechanism by which this gene cohort contributes to POAG susceptibility is not clear. A more recent GWAS study presented a meta-analysis of 139,555 European participants, identifying 112 genomic loci associated with IOP, 68 of which were novel (25). These loci suggest a strong role for angiopoietin-receptor tyrosine kinase signalling, lipid metabolism, mitochondrial function and developmental processes underlying risk for elevated IOP.

Despite these developments, less than 10% of glaucoma patients are currently accounted for by these genetic associations. This may in part be due to the genes identified having a modest effect size in explaining overall glaucoma risk. What is more likely however, is that there are still further genetic associations related to glaucoma aetiology which are still undiscovered. Further identification of genetic loci will not only increase our understanding of the pathways involved in IOP and glaucoma, but also raises the possibility of using genetic markers in the future to improve disease screening or even predict of the natural history of disease in people at risk of glaucoma.

2.1.5 Risk Factors for Glaucoma

There are several risk factors related to both development and progression of glaucoma, with the overall risk increasing with the number and strength of risk factors.

As previously discussed, elevated IOP is an important factor (26), as this can increase the 'absolute trans-laminar pressure gradient' and therefore the risk of optic nerve damage. Lowering the IOP reduces this gradient and thus alleviates pressure on the optic nerve.

In a meta-analysis of population-based studies, the odds ratio for POAG was 1·73 (95% CI 1·63–1·82) for each decade increase in age beyond 40 years(9) confirming that increasing age is a risk factor for POAG. Though the exact mechanism behind this association is not known, increasingly it is thought that increasing neuronal vulnerability may be linked to age. In mouse models of glaucoma, mitochondrial abnormalities have been shown to be a precursor to neuronal dysfunction occurring prior to detectable degeneration(27). Retinal levels of nicotinamide adenine dinucleotide (NAD), an important molecule in energy and redox metabolism, decrease with age and render ageing neurons vulnerable to disease related insults. Oral administration of the NAD^+ precursor nicotinamide (vitamin B_3) was protective both prophylactically and as an intervention(28). These findings potentially support therapeutic use of vitamin B_3 in glaucoma and potentially other age-related neurodegenerations, but further studies in human subjects are required.

Across all ethnic origins, individuals of Black African ancestry have been shown to have the highest prevalence of POAG (5·40%, 95% CI 3·17–8·27%) (9). The onset of optic nerve damage also tends to occur at an earlier age, the damage can be more severe at the time of detection, and surgical outcomes can be less successful due to increased inflammation and scarring relative to Caucasian patients (29).

Positive family history is also a strong risk factor for development of glaucoma. First-degree relatives of individuals with primary open-angle glaucoma have up to an eight-fold increased risk of developing the disease compared with the general population (30, 31)

High myopia with a myopic refractive error of roughly more than –8 dioptres is another strong risk factor for glaucoma. The Singapore Malay Eye Study showed an association between moderate or high myopia (greater than –4 dioptres) and a higher prevalence of POAG (32). It has been suggested that the important factor for myopia-associated increase in glaucoma susceptibility is the myopia associated enlargement of the optic disc (33). This is thought to cause secondary stretching and thinning of the lamina cribrosa (in association with an elongation and thinning of the peripapillary tissues) leading to biomechanical changes in the optic nerve head and an increase in glaucoma susceptibility.

Other factors that have been shown to have an association with development of POAG include thin central corneas (central corneal thickness <556 μm) and a vertical or horizontal cup-to-disc ratio of greater than 0·4 (as determined from stereoscopic disc photographs) (34).

Certain systemic conditions have been shown to have an association with development or progression of glaucoma, though the evidence for this is weaker (10). These include systemic hypertension, cardiovascular disease, migraine, and peripheral vasospasm. Socioeconomic status can affect early detection of glaucoma and initiation of and adherence to treatment, therefore this factor is also associated with prognosis of the disease (35).

2.1.6 Clinical Features & Diagnosis

The main clinical feature of POAG is progressive, gradual, painless visual loss. The visual field defects that develop do not occur until a large proportion of RGCs have been lost (36) and thus patients seldom 'self-detect' their condition until an advanced stage has been reached. Raised IOP, which is typically associated with POAG, is often asymptomatic and detected incidentally by opticians, though markedly elevated IOPs can cause symptoms such as headaches and visual disturbance. The mainstay of detection of glaucoma is examination of the optic disc and retinal nerve fibre layer.

<u>Assessment of the optic disc</u>

Optic disc examination is valuable for early glaucoma diagnosis as optic nerve appearances often change before detectable visual field loss. Indeed, studies have shown that as many as half of RGCs can be lost before the visual field test shows evidence of glaucoma (36, 37). Visual loss is thus usually not perceived until the disease is quite advanced.

The optic disc should be examined with a magnified stereoscopic view. This examination is best done at the slit lamp biomicroscope with an indirect lens or a contact lens. Optic disc changes consist of diffuse or focal narrowing or notching of the disc rim, especially at the inferior or superior poles (see Figure 3). Examination of the retinal nerve fibre layer adjacent to the optic disc can also provide useful information. In the healthy eye, there is high reflectivity from the relatively thick retinal nerve fibre layer in the superior and inferior bundles. In glaucoma,

reflectivity in these regions is reduced and there are even focal areas where reflections are absent.

As well as subjective clinical assessments, several objective and quantitative methods for assessment of the optic disc and the retinal nerve fibre layer now exist including scanning laser polarimetry, confocal scanning ophthalmoscopy and disc optical coherence tomography (OCT).

Of these, OCT imaging has increasingly been adopted as the main tool used for optic nerve head (ONH) and retina analysis over the past decade. It is a non-invasive optical technique that allows for in vivo cross-sectional imaging of the ONH and retina (38). Newer versions of OCT technology, such as spectral domain OCT (SD-OCT), are more sophisticated and have advantages in glaucoma assessment over earlier time domain OCT (TD-OCT). These include increased axial resolution and faster scanning speed, leading to lower susceptibility to eye movement artefacts (39). Moreover, advances in segmentation algorithms have enabled the quantitative assessment of individual retinal layers, including in the macular region. Since a significant proportion of the RGC population resides in the macula, measuring the macular ganglion cell complex (GCC), which includes the RNFL, ganglion cell layer (GCL), and inner plexiform layer (IPL) has increasingly been used to assess RGC loss clinically and compare with an internal normative database. To date, studies have demonstrated the high diagnostic power of evaluating the macular GCC and shown that it is comparable to that of RNFL analysis (40). More recently, swept-source OCT (SS-OCT), with its advantages in

speed and wavelength (for deeper penetration) relative to SD-OCT, has been introduced and employed in the glaucoma field for imaging of deep ocular structures such as the lamina cribrosa, as well as for wide-field visualisation of the posterior pole including the optic nerve head and macula with one, single-scan protocol (41).

Assessment of the visual field

In glaucoma, changes arise more commonly in the peripheral visual field prior to any changes being noted in central visual acuity and visual field. Characteristic visual field abnormalities include a 'nasal step' scotoma (respecting the horizontal raphe), inferior or superior arcuate scotoma, paracentral scotoma, or generalised depression (10) (see Figure 3). Standard automated perimetry utilises a white stimulus on a white background is routinely used in clinical practice to quantify the patient's visual field. Although useful for both diagnosing glaucoma and for determining whether glaucoma is progressing, standard perimetry has been shown to be insensitive to loss of RGCs especially early in the course of the disease (36, 37). Selective perimetry modalities such as short wavelength automated perimetry and frequency doubling perimetry isolate specific RGC populations and have been shown to be more sensitive to detecting glaucoma earlier than standard visual field testing (42, 43).

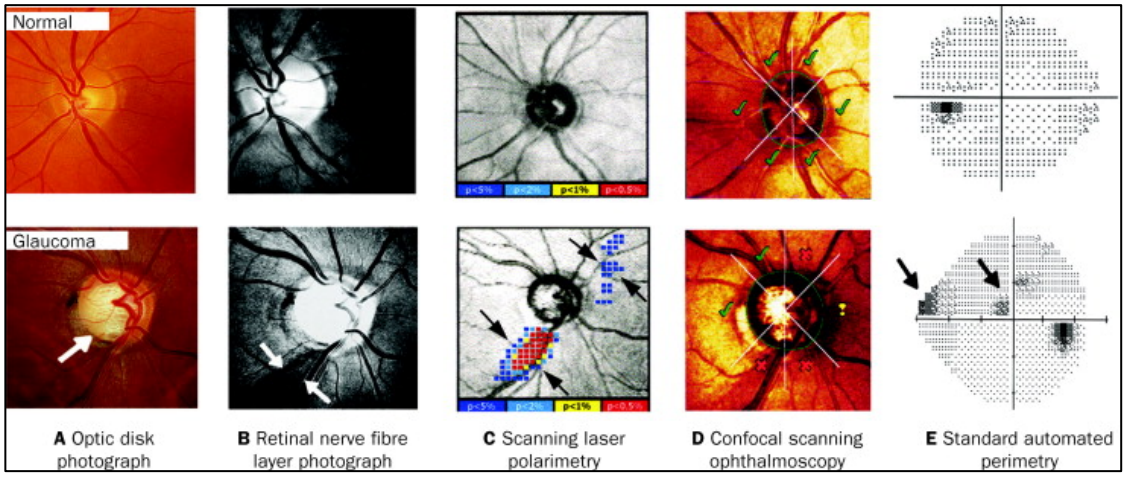


Figure 3: (A)Optic nerve in healthy and glaucomatous eyes–the normal optic disc has a small central cup. The central cup of the glaucomatous disc is enlarged and deepened, and the surrounding neuro-retinal rim is thinned. Optic disc haemorrhage (arrow) is sometimes observed in an eye with glaucoma. (B). Retinal nerve fibre layer photography: uniform reflections in healthy eye; poor reflections in inferotemporal region (arrows) in glaucomatous eye. (C) Scanning laser polarimetry: retinal nerve fibre layer thickness is reduced inferotemporally and superonasally. (D) Confocal scanning laser ophthalmoscopy: neuroretinal rim area is within normal limits (ticks) in healthy eye, but reduced in inferior and superonasal regions (crosses) in glaucomatous eye. (E) Standard automated perimetry: normal blind spot and superior scotomas (arrows) in glaucoma. Taken from Weinreb & Khaw (11).

2.1.7 Treatment of Glaucoma

Aims of Treatment

The aim of glaucoma treatment is to slow or stop disease progression and preserve patients' vision & quality of life for the duration of their lifetime.

IOP is the only modifiable risk factor proven to alter the disease course in glaucoma (44). Several clinical trials have demonstrated the benefit of IOP lowering in preventing the development of POAG and slowing disease progression.

The Ocular Hypertension Treatment Study (45) randomised patients with OHT to treatment versus no treatment. At the end of 5 years follow-up, 4.4% of patients in the medication group vs 9.5% in the untreated group developed signs of glaucoma. The Early Manifest Glaucoma Trial (46) randomised early POAG patients to treatment (laser trabeculoplasty + topical beta blocker) versus no treatment. After a median follow-up of 6 years, progression was less frequent in the treatment group (45%) compared to in the control group (62%).

More recently, the United Kingdom Glaucoma Treatment Study (UKGTS) demonstrated that POAG patients treated with IOP lowering medication were less likely to demonstrate visual field progression at 24 months compared to those treated with placebo (hazard ratio 0.44; 95% confidence interval, 0.28-0.69; p=0.0003), confirming that IOP lowering was associated with alteration of the disease course and reduced visual field progression (44). Furthermore, these studies demonstrated that the *degree* of IOP lowering could influence disease

progression. The EMGT study estimated that each 1 mmHg reduction in IOP reduced the risk of disease progression by approximately 10% (46).

IOP lowering has also been shown to be effective in delaying disease progression in glaucoma patients without elevated IOP, a condition known as Normal Tension Glaucoma (NTG). In the Collaborative Normal Tension Glaucoma Study (CNTG), 140 patients with NTG received IOP-lowering medical or surgical treatment in one eye. At the study endpoint, there was a slower rate of incident visual field loss in cases that achieved IOP lowering of 30% or more from baseline IOP compared to untreated fellow eyes(47).

Current management strategies recommend IOP lowering toward a target IOP, where the rate of disease progression is slowed sufficiently to avoid functional impairment from the disease (48). Target IOP for an individual eye is established from pre-treatment IOP levels, the severity of visual field loss, risk factors for progression, life expectancy and potential for adverse effects from treatment (3). In general, the initial target IOP aims for a 20-50% reduction from baseline IOP. This must be continuously re-evaluated however during follow-up and adjusted depending on treatment effect & disease progression. IOP lowering can be achieved by medication, laser or surgery (either alone or in combination).

Medication

Topical IOP lowering medications are currently the mainstay of POAG treatment and widely used, with approximately 1.2 million prescriptions being issued per

month in the UK (49). Whilst topical medications are effective, there are several potential pitfalls associated with their use.

A significant proportion of patients require more than one type of drop, with a third of patients in the UK using more than one medication. In addition, as glaucoma is a chronic and progressive disease, instillation of medication becomes a lifelong commitment, with patient compliance therefore becoming essential for successful management. Studies show however that patient compliance with topical medication can be variable (50, 51). Reported non-compliance rates range from 24% to 80% depending on definition (50-53) and up to half of those started on glaucoma treatment had discontinued eye-drops by six months in one study (54). There are several reasons for potential poor compliance. Drops are expensive, with side effects that limit acceptability and impair health related quality of life (HRQL) (55). Long-term topical medications are often associated with pain on instillation & can cause multiple ocular and systemic side effects. Their use requires regular monitoring and frequent adjustment with approximately 22% of changes to drop regimes being due to adverse reactions (56).

In addition, glaucoma patients are frequently elderly and may have other co-morbidities which may reduce their ability to take medication such as diminished cognition, poor hearing, and arthritis of their hands. Long-term drop use has also been shown to be a strong risk factor for later surgical failure, due to conjunctival fibroblast activation by medications or preservatives (57, 58).

Several classes of medication are used to lower IOP in glaucoma. The prostaglandin analogues reduce IOP by increasing the outflow of aqueous humour, primarily through the uveoscleral pathway (59). They have also been shown to activate matrix metalloproteinases (MMPs), which then remodel extracellular matrix within the TM and reduce outflow resistance, allowing the aqueous humour to flow out via this route (60).

In general, prostaglandins have become the first line of treatment because of their IOP lowering efficacy, once daily application & minimal systemic side-effects. Ocular side-effects include gradual irreversible darkening of the iris in a small percentage of patients. This effect is due to an increase in melanosomes (61). Other side-effects include increased growth and hyperpigmentation of eyelashes, conjunctival hyperaemia, loss of periorbital fat & periocular skin pigmentation (3).

The $\alpha 2$ adrenergic agonists reduce secretion of aqueous humour initially and then primarily increase aqueous outflow (62). Topical $\alpha 2$ adrenergic agonists are associated with allergic conjunctivitis, can cause sedation, and have the potential for systemic sympathomimetic activity.

Carbonic anhydrase inhibitors reduce aqueous secretion. Topical forms of this medication (e.g., dorzolamide, brinzolamide) have few systemic side effects compared with oral acetazolamide but are less effective at IOP lowering compared to the oral form and they should not be used in individuals with allergies to sulphonamides.

Beta blockers are also still widely used & also reduce aqueous secretion. They can have cardiovascular and respiratory side-effects, especially in the elderly (63).

Cholinergic agonists (e.g., pilocarpine) increase aqueous outflow but have substantial ocular side-effects, in particular blurring of vision due to the small pupil and induced myopia, which restrict their use.

Medications in Development

Newer medical treatments are in development. Most of these are IOP lowering treatments with new mechanisms of action, better efficacy, tolerability and convenience.

Trabodenoson is a highly selective adenosine-1 receptor agonist. It upregulates MMP-2 expression in the TM, resulting in remodelling of the extracellular matrix, thus lowering outflow resistance and enhancing aqueous humour outflow (64). In a phase 2 RCT, topical trabodenoson was compared against placebo and achieved a mean change of 4.1mmHg from baseline whilst being well tolerated (65). However, in a phase 3 trial vs placebo, there was no significant difference in IOP lowering between groups.

Netarsudil is a Rho-kinase (ROCK) inhibitor and norepinephrine transporter inhibitor (66). It has been shown to cause IOP lowering through several mechanisms. Primarily, it causes relaxation within the TM and contraction of the ciliary muscle, leading to an increase in aqueous humour outflow through the TM (67). It also decreases aqueous production and decreases episcleral venous

pressure(68, 69). Different studies have assessed its efficacy alone (70) and in combination with existing medications such as latanoprost (71). Despite a short follow up duration, they have demonstrated non-inferiority to currently available treatments but side effects such as conjunctival hyperaemia in a high proportion of patients was noted.

Latanoprostene Bunod (LBN) is a modified prostaglandin analogue which has a dual mechanism of action. Upon topical administration into the eye, it is hydrolysed by endogenous esterases into latanoprost acid, the active component of latanoprost, and butanediol mononitrate, which breaks down into nitric oxide (NO) and inactive 1,4-butanediol (72).

Latanoprost acid increases aqueous outflow through the uveoscleral pathway (59), whilst NO causes relaxation within the TM and increases aqueous outflow through the TM and Schlemm's canal (73). Several phase 3 studies have evaluated LBN (74-76) and found it to be more effective at IOP lowering than topical beta blocker at 3 months whilst maintaining a similar safety profile to other prostaglandin analogues.

<u>Laser</u>

Laser trabeculoplasty (LT) is a laser treatment modality which reduces IOP and is increasingly being used worldwide. The use of laser trabeculoplasty to reduce IOP is discussed more extensively in the next Chapter 2.2.

Surgery

Incisional glaucoma surgery is usually performed if IOP lowering is insufficient following topical medication or laser. In patients with poor compliance or those intolerant to medication, incisional surgery can also be performed as the first step in the treatment of glaucoma.

Several different IOP lowering surgeries exist – penetrating (e.g. trabeculectomy, tube surgery) vs. non-penetrating surgery (eg. deep sclerectomy, viscocanalostomy, canaloplasty). Their use in clinical practice is a combination of surgeon preference (having considered the IOP lowering evidence and safety profile of each procedure) & patient factors.

Trabeculectomy remains the most common initial operation for patients with advanced glaucoma in most countries (3). Trabeculectomy lowers IOP by creating a new drainage site for aqueous humour outflow underneath the conjunctiva (77). Glaucoma drainage device, or tube surgery, has traditionally been reserved to treat patients with refractory cases of glaucoma or at high risk of failure. The two most commonly used glaucoma drainage implants are the Ahmed valve (New World Medical, Rancho Cucamonga, CA) and the Baerveldt implant (Abbott Medical Optics, Santa Ana, CA).

The Tube vs Trabeculectomy (TVT) study selected patients who had previous trabeculectomy and/or cataract extraction with uncontrolled glaucoma on maximal medical therapy and randomised them to either Baerveldt 350mm^2 implant or repeat trabeculectomy with mitomycin C (MMC). At 5 years post operatively, the cumulative probability of failure was 29.8% in the tube group vs

46.8% in the trabeculectomy group (hazard ratio = 2.15, 95% CI, 1.30 to 3.56; p=0.02). Furthermore, the rate of reoperation was significantly greater in the trabeculectomy group (29%) vs tube group (9%) (p=0.025) (78). The Primary Tube vs Trabeculectomy (PTVT) study is evaluating the effectiveness of tube surgery vs trabeculectomy with MMC in medically uncontrolled glaucoma patients who have not undergone previous incisional ocular surgery (79). 36 month clinical outcomes demonstrated that there was no significant difference in the rate of surgical failure between tube group (33%) and trabeculectomy group (28%) at 3 years (p = 0.17; hazard ratio, 1.39; 95% confidence interval, 0.9-2.2). Trabeculectomy achieved significantly lower IOP with use of fewer medications compared with tube surgery at 3 years; mean ± standard deviation IOP was 14.0±4.2 mmHg in the tube group and 12.1±4.8 mmHg in the trabeculectomy group at 3 years (p = 0.008), and the number of glaucoma medications was 2.1±1.4 in the tube group and 1.2±1.5 in the trabeculectomy group (P < 0.001). Serious complications producing vision loss or requiring reoperation occurred with similar frequency in both treatment arms(80).

Other studies have evaluated the efficacy and safety between the 2 most common glaucoma drainage devices. The Ahmed Baerveldt Comparison ('ABC') Study was a prospective randomised study in which patients with previous intraocular surgery or refractory glaucoma and IOP> 18mmHg were randomised to either implantation of the Ahmed FP7 valve or the Baerveldt 101-350 device. At 5 years follow up, there were similar rates of surgical success between the two devices (cumulative probability of failure: Ahmed group 44.7% vs. Baerveldt group 39.4%; p=0.65). Baerveldt implantation produced a greater IOP reduction and a lower rate of glaucoma reoperation, but was also associated with twice as many failures due

to safety issues such as persistent hypotony, loss of light perception or explantation (81).

The principle of non-penetrating glaucoma surgery is to create filtration through a naturally occurring membrane, the trabeculo-Descemet's membrane (TDM), which provides resistance to outflow. There is no penetration into the anterior chamber as a sclerostomy is not created. Two main techniques are described – deep sclerectomy and visco-canalostomy. Studies have demonstrated the IOP lowering is generally greater with trabeculectomy, however the main benefit of non-penetrating glaucoma surgery is the lower complication profile compared to trabeculectomy(82-84). The main disadvantage of non-penetrating glaucoma surgery techniques is that they are associated with a long and demanding learning curve with fewer surgeons performing them as a result.

Newer procedures and devices are emerging to lower IOP with a greater safety profile compared to incisional glaucoma surgery and these are collectively termed 'Minimally Invasive Glaucoma Surgery' (MIGS). MIGS procedures are commonly performed alongside cataract surgery. MIGS devices aim to lower IOP by increasing aqueous outflow through existing anatomical outflow pathways including through the TM into Schlemm's canal (85, 86), through the uveoscleral pathway (87) as well as through alternate pathways which are created iatrogenically such as subconjunctivally (88). The main advantage of MIGS is that most devices are non-penetrating and/or bleb-independent procedures, thus avoiding the major complications of fistulating surgery related to blebs and hypotony. The degree of IOP lowering however, is generally accepted to be less than that achieved by trabeculectomy or tube surgery. RCTs comparing IOP

lowering between combined surgery (cataract surgery + MIGS) vs cataract surgery alone have demonstrated that in a combined procedure, cataract surgery achieves the majority of IOP lowering with an additional modest (but statistically significant) lowering of IOP achieved by the MIGS device (86, 87, 89). A reduction in the number of topical IOP lowering medications required by patients post-operatively is also a potential benefit. Whether the additional IOP lowering is clinically beneficial in terms of preventing long term disease progression, whilst also taking into account the extra cost of the device, is still to be determined. Moreover, limited long term follow up data exists for the majority of MIGS devices and there are few RCTs establishing their use as evaluated by the Cochrane Eye and Vision Group database (90-94). A recent long term follow up safety study of a MIGS device (CyPass Micro-Stent; Transcend Medical, Inc., Menlo Park, CA) has demonstrated unacceptable endothelial cell count loss over 5 years, leading to its' withdrawal. Whilst the exact role of MIGS is yet to be established, it may be that MIGS procedures will exist alongside rather than replacing more invasive IOP lowering surgical options. They may be used in early or moderate POAG patients where lesser degrees of IOP lowering are acceptable and as a means of postponing more invasive surgical interventions (95).

Neuroprotection

Neuroprotection is the term used for therapies that are independent of IOP lowering and aim to protect retinal ganglion cells (RGCs) from axonal injury and slow functional loss. Studies using animal models of glaucoma have demonstrated success of various different neuroprotective treatments to preserve RGCs and their function (96), however this success has not translated into human clinical trials thus far. Several reasons have been purported for translational failure (97). Whilst

some solutions to address these have been suggested (96), translation of laboratory results to clinical trials in glaucoma remains limited and as yet, there are still no reliably proven neuroprotective treatments related to glaucoma that are available to humans currently.

2.2 Laser Trabeculoplasty

In this chapter, we perform an up to date evaluation of Laser Trabeculoplasty (LT), in particular Selective Laser Trabeculoplasty (SLT). We trace the origins of SLT from previous derivatives of LT and review the current role of SLT in clinical practice. We outline future directions of SLT research and present emerging technologies that are further developing this important treatment modality.

2.2.1 Origins of Lasers to Reduce IOP: Early Laser Trabeculoplasty

The use of laser to lower IOP in glaucoma patients began in the 1970s with early attempts meeting with limited success. Goniopuncture using the Q-switched ruby laser produced a temporary reduction of IOP, whilst high energy argon (major wavelengths at 488 and 514nm) laser photocoagulation of the trabecular meshwork caused acute post-laser IOP spikes (98, 99).

In 1979, Wise and Witter used argon laser at lower energy levels to those used previously and reported successful short-term reduction of IOP by approximately 10 mmHg in 40 phakic eyes. Despite 65% of these eyes eventually requiring additional medication, this study showed that argon laser trabeculoplasty (ALT) did have the potential to lower IOP in glaucoma patients (100).

2.2.2 ALT: Mechanism of Action

IOP reduction seen in ALT was mediated by an increase in aqueous outflow, confirmed by both tonographic and aqueous dynamic studies (101, 102). The exact mechanism underlying this increase in outflow however, remained unclear. Wise and Witter proposed the mechanism to be mechanical. They postulated laser induced thermal burns to the TM caused tissue and collagen contraction. This would reduce the diameter of the inner trabecular ring, reversing collapse of the meshwork and thus maintain aqueous outflow(100). Histological studies that had analysed animal and human eyes having undergone ALT reported different findings. Using electron microscopy, these studies demonstrated significant damage characterised by focal coagulative disruption to the TM with connective tissue and cellular debris deposited within the intra- trabecular spaces (103-106).

Moreover, it was noted that ultrastructural changes to the TM were evident quicker than onset of the ALT IOP lowering response, suggesting that the mechanism of action was not likely to be solely due to mechanical and structural means (107)

An additional 'biological' theory was suggested for the mechanism of ALT whereby the thermal energy from ALT modified local cellular signalling pathways to precipitate a cascade of cellular changes enabling increased aqueous outflow. These changes included altered cytokine secretion, MMP induction, increased cell division, repopulation of burn sites and macrophage recruitment (108)

2.2.3 ALT: Efficacy

The average initial fall in IOP with POAG post ALT was about 30% from baseline. A greater response was noted with higher pretreatment IOP and thus eyes with NTG demonstrated a smaller effect (109). ALT was found to be successful in IOP lowering when used as either primary treatment (110) or as an adjunct to POAG patients on maximal medical treatment (101) with IOP reductions reported between 6.4-9.7mmHg (26-33%) from pre-treatment baseline. It was also found to reduce the diurnal IOP fluctuation within treated individuals (111, 112).

There were limitations however. Firstly, the effect of ALT was noted to diminish over time. Schwartz et al performed 360-degree ALT on 72 patients with uncontrolled OAG on maximal medical treatment and reported their success rate of 77% at 2 years had fallen to 46% at 5 years (113). In a different study by Spaeth and Baez, in 109 eyes with uncontrolled OAG on maximal medical treatment that received ALT, 32% needed filtration surgery at 1 year, 65% at 5 years and 95% at 10 years (114). Failure was noted to be highest in the first year and subsequently occurred at a rate of 10% per year (115).

Repeatability of ALT treatment on failed eyes was also significantly less successful than initial treatment. Richter et al performed 180 degrees of ALT retreatment to 40 eyes that had previously undergone 360-degree ALT and found only 32% of eyes demonstrated at least 3mmHg reduction in pre-treatment IOP (116).

Analysis of predictors of ALT success or failure yielded varied and sometimes conflicting results. Increasing age was found to be a relatively consistent positive

predictor of treatment success (113, 115), with younger patients demonstrating increased risk of failure (117). Earlier smaller studies had suggested that race could be a baseline predictor, with black patients being shown to have a lower success rate (32%) at 5 years compared to white patients (65%) (113). However, subsequent analysis from the Advanced Glaucoma Intervention Study (AGIS), with a large patient cohort of 779 eyes and longer follow up (8-13 years) than previous studies did not find race to be a risk factor for ALT failure (117).

Evaluation of ALT efficacy in different subtypes of glaucoma such as pigmentary and exfoliative demonstrated similar efficacy to POAG, though largest IOP reductions and earlier failures were noted in exfoliative glaucoma. Other forms of secondary open angle glaucoma had limited response to ALT with uveitic and developmental glaucomas often showing little or no useful fall in IOP (118).

2.2.4 ALT: Adverse Events

The main adverse events related to ALT were transient acute IOP spikes post-laser, development of peripheral anterior synechiae (PAS), corneal endothelial changes and acute anterior uveitis (109).

With acute IOP spikes, in one study of 271 eyes, a rise of more than 5mmHg post laser occurred in 34% of patients and a rise of more than 10mmHg occurred in 12% of patients whom had undergone 180 degrees of ALT. (119)

The frequency and severity of IOP elevations were positively associated with use of higher energy levels, 360-degree treatment, posterior placement of bums, angle pigmentation, and a low preoperative facility of outflow. Most post-treatment IOP peaks were reported to occur within the first 2 hours and were thought to occur from swelling of the trabecular meshwork or obstruction of the trabecular spaces by debris (120).

Development of PAS was another important complication that was noted more frequently with posteriorly placed burns and with higher power levels (121, 122).

The possibility of ALT also having an adverse effect on subsequent drainage surgery was a further concern. One study found the incidence of encapsulated blebs to be up to three times higher in eyes previously treated with ALT (15.4%) compared to eyes that had not received anterior segment laser (4.7%) (123). A larger retrospective analysis conducted from the AGIS study found an increased frequency of bleb encapsulation within the first 12 months of trabeculectomy

surgery in eyes treated with prior ALT (18.5% of eyes) compared to untreated eyes (14.5% of eyes), though this was not statistically significant (unadjusted relative risk, 1.27; 95% CI = 0.81, 2.00; p =0 .23) (124).

2.2.5 Role of ALT

The benefit of ALT compared to medical treatment was that it was an outpatient procedure that was relatively quick, well tolerated and safe. It avoided the inconvenience and side effects of regular medical treatment and potentially delayed the risks of intraocular glaucoma filtration surgery. However, its loss of effect with time and possible association with higher bleb encapsulation in subsequent glaucoma drainage surgery meant that for a time, the optimum role for ALT was considered to be as an adjunct treatment to control intraocular pressure in patients on maximal tolerated medical treatment and a means of delaying filtration surgery.

Some studies did evaluate ALT's role as a primary treatment. The Glaucoma Laser Trial Research Group found better IOP control with ALT alone compared to a single medication at 6 months, 1 year and 2 years but inferior control at 5 years or if 2 medications were used (110, 125). Compared to surgical treatments, it was found that trabeculectomy achieved significantly lower IOPs with a reduced need for subsequent medication(126, 127).

2.2.6 Emergence of SLT

In 1983, Anderson and Parrish (128) found that radiation energy could be applied and selectively absorbed by a selective pigmented cell population within a tissue composed of multiple cell types, to cause damage. This process was known as Selective Photothermolysis (SP). The inherent properties of the tissue provided target selectivity and reduced collateral damage.

Selective photothermolysis had two principle requirements – firstly, the desired target had to have an intracellular chromophore with greater energy absorption at the laser wavelength than its surrounding tissue. Secondly, the laser duration could not exceed the time required for thermal diffusion into the tissue – also known as the thermal relaxation time (108).

ALT fulfilled the first requirement of SP, as melanin contained within the pigmented trabecular meshwork acted as the chromophore responsible for absorbing laser energy. However, the laser duration of ALT (~0.1sec) was much longer than the thermal relaxation time of melanin (1microsecond). This allowed heat, initially generated within pigmented cells to dissipate and damage surrounding TM tissue. Histological studies confirmed this by demonstrating non selective tissue disruption and photocoagulation of the TM (103).

Over the next decade, a new treatment called Selective Laser Trabeculoplasty (SLT) would supersede ALT to become the principal laser treatment modality.

First introduced by Latina & Park in 1995, SLT used a 532nm Q switched, frequency doubled Nd:YAG laser that was able to deliver a much shorter laser pulse duration (3nanoseconds). It satisfied the dual criteria required for selective photothermolysis, thus preventing heat dissipation outside of pigmented TM cells and causing less collateral damage as a result (129). During the development of the SLT laser, a larger spot size (400 microns) was chosen compared to smaller spot sizes used with other laser treatments (e.g. 10 microns used with Nd:YAG, 50 microns used with argon laser in ALT) as the energy irradiance per unit area (for any amount of energy delivered) would be less, thus avoiding extremely high energy irradiances and the potential for collateral damage(130).

Since SLT received FDA approval in 2001, it has increasingly been adopted into clinical practice. Arora et al reported 75 647 trabeculoplasty procedures performed per annum in the USA in 2001 had increased to 142 682 procedures in 2012 (131).

The immediate benefits of SLT are clear. Similar to ALT, the procedure is quick, outpatient based with minimal recovery time and a good safety profile. However, the role of SLT in the treatment paradigm of glaucoma is still not well defined. In this section, we review the existing literature, to give current perspectives on important aspects related to SLT that are relevant to its role in clinical practice.

2.2.7 SLT: Mechanism of Action

Similar to ALT, SLT has been demonstrated by tonographic and aqueous dynamic studies to increase aqueous outflow through the trabecular meshwork (132-134). A recent study has shown in vivo expansion of Schlemm's canal following SLT, possibly as a consequence of this increased aqueous outflow (135).

Kramer & Noecker carried out histopathological comparisons of human eyes that had undergone ALT vs. SLT (136). They showed lesser damage to the trabecular meshwork in SLT eyes with no evidence of coagulative damage or disruption of the corneoscleral or uveal trabecular beam structure. They reported that the only ultrastructural evidence of laser-tissue interaction was cracks being seen within intracytoplasmic pigment granules and disruption of trabecular endothelial cells. Cvenkal et al also compared morphological changes after low power ALT and SLT (136). They demonstrated that both lasers cause splitting and fragmentation of the trabecular beams of the trabecular meshwork, but the extent of the damage was smaller and the preservation of long-spacing collagen better after SLT than after ALT. More recent histological studies have demonstrated that higher power SLT can cause more extensive damage to the TM than lower power SLT (137).

We can conclude that SLT does not cause the same level of structural damage as induced by ALT, but, any TM damage that is incurred by SLT could be energy dose dependent.

With increasing evidence demonstrating limited structural damage to the TM post SLT, it has become clear that the mechanical and structural theories which

underpin the mechanism of action in ALT are thought not to be fully applicable to SLT. This is supported further by studies that have demonstrated SLT to induce biological changes that modulate increased aqueous outflow through the TM, including changes in gene expression, cytokine secretion, matrix metalloproteinase induction and trabecular meshwork remodelling.

Using microarray analysis, SLT has been shown to modulate expression of several genes in trabecular meshwork including those related to cell motility, extracellular matrix production, membrane repair, reactive oxygen species production (138). In vitro studies have demonstrated an increase in pro-inflammatory cytokine expression including interleukin 1 alpha, interleukin 1 beta, tumour necrosis factor alpha and interleukin 8 post SLT (139).

These cytokines increase stromelysin-1 expression (MMP-3), an important matrix metalloproteinase implicated in trabecular meshwork extracellular matrix remodelling to permit increased aqueous outflow through the juxtacanalicular meshwork (140).

Increased monocyte recruitment to the TM has also been noted post SLT, thought to be as a result of increased chemokine production (141). Monocytes have been found to increase aqueous outflow in vivo and increase permeability in Schlemm's canal in vitro, possibly as a consequence of further cytokine secretion or by directly phagocytosing debris within the TM.

Further animal studies have shown an increase in endothelin-1, which is thought to contribute to the acute IOP rise and subsequent fall seen post SLT(142). A rise in

lipid peroxide levels and decrease in antioxidant enzymes such as glutathione S transferase and superoxide dismutase post SLT may be due to the increased inflammatory response precipitated by SLT (143).

Interestingly, in vitro studies have demonstrated that SLT and prostaglandin analogues may share a common pathway of action by inducing intercellular junction disassembly in Schlemm's canal cells and TM cells. Alvarado et al performed an in vitro study where cultured human Schlemm's canal cells and TM cells were exposed to either direct laser irradiation or different topical medications including prostaglandin analogues(144). It was found that both laser irradiation and prostaglandins induced increased permeability within these cells, supporting a theory for a common mechanism to mediate their IOP lowering effects.

2.2.8 SLT: Clinical Technique

SLT is commonly performed using topical anaesthetic and a gonioscopic laser lens such as a Latina SLT lens (Ocular Instruments, Bellevue, WA, USA) with a coupling medium(145). Within SLT treatment parameters, spot size (400 microns) is fixed but number of shots, energy level, total energy delivered and laser pulse duration are variable. The fixed spot size of 400 microns is relativel

In their first pilot study using SLT, Latina et al used 50 non-overlapping shots placed over 180^0 of the TM, as they believed these settings would selectively target pigmented TM cells without causing coagulative damage to the TM structure or non-pigmented cells based on their previous in vitro experiments (129, 146). The energy level was initially set at 0.8mJ and decreased by 0.1mJ increments until no visible effects or bubble formation was observed. In current practice, typical treatment parameters are 50 to 100 shots applied over 180^0 (to 360^0) with laser energy adjusted to 0.6-1.4mJ and an expected endpoint of no visible tissue reaction or small microbubbles (145).

Studies have evaluated whether treating different degrees of the trabecular meshwork with SLT influences lowering of IOP. The evidence is mixed; some studies support the association of greater IOP lowering efficacy with greater degree of SLT treatment, whilst others show no difference in IOP lowering efficacy and degree of SLT treatment. Chen et al compared IOP lowering efficacy in OAG patients randomised to receive either 90^0 SLT vs. 180^0 SLT and found no significant differences in IOPs at 1, 4 and 7 months between the 2 groups ($p=0.21$)(147), with similar findings for 90^0 SLT vs. 360^0 SLT (148). Goyal et al

conducted a RCT comparing 180^0 SLT vs. 360^0 SLT in patients with untreated POAG or OHT and found mean IOP reduction at 1 month was 6.9mmHg and 8.2mmHg in the two groups respectively, with no significant difference noted between the two groups (p= 0.35)(133). Nagar et al, compared IOP lowering efficacy of 90^0, 180^0 and 360^0 SLT and found no difference between 180^0 and 360^0 SLT treatments at 12 months follow up (149). Both groups were more effective at IOP lowering than the 90^0 SLT group.

Separate studies have found that overlapping application of SLT spots resulted in lesser IOP reduction compared to a non-overlapping treatment protocol (150) whilst there was no difference in IOP reduction when using 120 spots vs 160 spots (151).

The energy settings used in SLT have also been subject to investigation. Tang et al compared 39 patients receiving 100 shots of 360^0 SLT using low energy settings (0.3-0.5mJ) vs. 35 patients who received 100 shots of 360^0 SLT using standard energy settings (0.6-1.0mJ) (152). They found there was no difference in IOP lowering between both groups at all time points up to and including 1 year. In addition, there was a reduced incidence of adverse events associated in the lower energy setting group. This is in contrast to two other studies that have found a positive association between higher total energy use per SLT treatment and IOP lowering response. Lee et al found higher SLT energy use (in the range of 214.6 to 234.9mj) was associated with a greater IOP lowering response, however this study was limited by a small sample size and short duration of follow up (1 month)(153). A separate study by Habib et al, reported a positive correlation between total energy used and amount of IOP reduction achieved up to 3 years follow-up

however regression analysis to investigate this association further was not performed (154).

A more recent study has evaluated SLT efficacy using a shorter laser pulse duration of 1ns compared to conventional 3-5ns. They found no difference in IOP lowering and frequency of adverse events between the two arms in treatment naïve POAG, OHT and NTG patients with follow up to 6 months (155).

It has been common practice to prescribe topical IOP lowering medication either pre-operatively or immediately post laser trabeculoplasty to prevent IOP spikes (156). A recent meta-analysis of 22 trials involving 2112 patients by Zhang et al has investigated efficacy of perioperative medications for preventing increased IOP post laser(157). They found that patients receiving medication had a lower risk of IOP increase of 10 mmHg or greater within first 2 hours compared with those receiving no medication or placebo (risk ratio (RR) 0.05, 95% confidence interval (CI) 0.01 to 0.20) and up to 24 hours (RR 0.22, 95% CI 0.11 to 0.42). They found there was no advantage of medication being administered before or after laser trabeculoplasty in terms of preventing IOP spikes and that there was no difference in effectiveness between different alpha2-agonists (brimonidine versus apraclonidine). The only adverse effect noted in the use of topical alpha-2 agonists was conjunctival blanching which quickly resolved.

Usage of topical anti-inflammatory drops post laser trabeculoplasty is also a practice which has been evaluated. Medications such as topical non-steroidal anti-inflammatory (NSAID) drops (158-162) and steroid drops are commonly prescribed post trabeculoplasty procedures (149, 163, 164). The rationale for their

use initially came from the use of ALT and the post procedure side effects seen including transient acute anterior uveitis. Prescribing anti-inflammatory drops would diminish immediate inflammatory reactions seen within the eye. However, as an important mechanism of action for SLT was purported to be via a biological pathway including production of pro-inflammatory cytokines, topical anti-inflammatories administered post procedure could be counter-productive.

The evidence for the use of topical anti-inflammatory drops is also mixed. De Keyser et al performed a prospective RCT of 132 eyes evaluating the use of anti-inflammatory drops (either Indomethacin 0.1% or Dexamethasone 0.1% TDS for 1 week) vs. control (no treatment) (165). They found no statistically significant difference in anterior chamber reaction between the treated groups and their controls, nor between the 2 treatment groups at all time points (1 hour, 1 week, 1 month, 3 months, 6 months). There was also no statistically significant difference in conjunctival redness, reported pain or IOP lowering efficacy of SLT between the treatment groups and their controls, nor between the 2 treatment groups. These findings support previous studies which have concluded that the use of anti-inflammatory agents after SLT has not been shown to cause a significant reduction in inflammation or altered IOP lowering efficacy (166, 167).

A different RCT has recently reported significantly greater IOP lowering efficacy at 12 weeks in eyes treated with either topical NSAID or steroid compared to placebo (168) though there are limitations to the study design. As well as a short length of follow up (12 weeks) compared to other studies, different SLT treatment protocols (180 degree, 270 degree or 360 degree treatment) were permitted at the treating clinician's discretion during the trial. Despite 1:1:1 randomisation of steroid,

NSAID and placebo to the study eyes, the results showed uneven distribution of eyes with the different treatment protocols among the 3 groups; a greater proportion of eyes in the placebo group received 180 degree treatments vs a greater proportion of eyes in the steroid and NSAID groups receiving 360 degree treatments. Since studies have shown that 360-degree SLT treatments are associated with greater IOP lowering than 180-degree treatments (149), this could have meant that the greater IOP lowering result demonstrated in this study was partially influenced by the greater degree of treatment rather than exclusively due to the post-laser topical steroid or NSAID treatment.

2.2.9 SLT: Clinical Efficacy in OAG/OHT patients

The first efficacy data for SLT was reported by Latina et al (146) who applied 50 non-overlapping shots over 180 degrees of TM and demonstrated a mean IOP reduction of 6mmHg in uncontrolled POAG eyes previously treated with ALT and 5.8mmHg in eyes without prior ALT treatment. Overall, 70% of eyes exhibited an IOP reduction of greater than or equal to 3mmHg.

Further interventional studies (164, 169-174) have since reported mean IOP reductions in the range of 3-8mmHg from pre-treatment baselines, equivalent to approximately 15-32% reduction from pre-treatment IOP. Average reduction in IOP following SLT is reported as 21.8-29.4% at 6 months, 16.9-30% at 12 months, 7.7-27.8% at 2 years, 24.5-25.1% at 3 years, 23.1%-29.3% at 4 years, 22.6-32.1% at 5 years, and 22.8% at 6 years (145, 175).

The IOP lowering effect of SLT diminishes with time. Based on a success criteria of reduction in IOP>20% from baseline IOP, success rates vary from 66.7-75% eyes at 6 months, 58-94% at 12 months, 40-85% at 2 years, 38-74% at 3 years, 38-68% at 4 years, 11.1-31% at 5 years. The mean survival time (time for 50% of eyes to fail) is approximately 2 years (145).

2.2.10 SLT vs ALT in OAG/OHT patients

To date, there have been at least 10 studies that have compared SLT vs. ALT, with 9 studies comparing 180 degree treatment between the two arms and one trial comparing 360-degree treatment (176). In terms of IOP reduction from baseline, all studies have reported no difference between the treatment arms. One study of a younger cohort of glaucoma patients (<60 years old) reported better outcomes of SLT at 1 year but this effect regressed at 2 years follow up.

A meta-analysis by Wong et al (177) evaluated 4 randomised controlled trials comparing efficacy of SLT and ALT(158, 159, 162, 163). Inclusion criteria required at least 6 months follow up duration. Exclusion criteria excluded any studies where SLT was performed as a prophylactic treatment, as an adjunct to other laser or operation, or where invasive procedures were performed at the same time. These studies were conducted between 2011 and 2013 and included one multicentre and 3 single centre trials.

Author/year	Liu 2002	Bovell 2011	Kent 2013	Rosenfeld 2012
Setting	Single Centre	Single Centre	Multicentre	Single Centre
Location	Canada	Canada	Canada	Israel
Ethnicity	Asian, black, white	n/a	n/a	n/a
Age (years, mean (SD)	48.7 (9.4)	69.7 (10.52)	72.9 (9.86)	71.95
Type of glaucoma	POAG, juvenile OAG, PXF, NTG, PDS, mixed mechanism	OAG, PXF, PDS, others	PXF	POAG, PXF, PDS, OHT
Concomitant treatment	Medication	Failed MTMT or previous ALT (>6 months previously)	Failed MTMT	Failed MTMT
SLT parameters	0.7-8mH, 45 to 55 applications over 180 degrees	0.47-1.5mJ, 50 applications over 180-360 degrees	Total power 31.9 +/- 29.4mJ, 50+/- 3.86 applications over 180 degrees	0.8-1.2mJ, 50-70 non-overlapping applications over 180 degrees
Number of eyes	20	89	45	22
Duration of study (year)	2	5	6 months	1
Baseline IOP (mmHg) Mean (SD)	19.1 (4.5)	23.8 (4.9)	23.1 (4.22)	25.36 (1.83)
IOP reduction (%)	7.7	31.1	29.4	16.90
Treatment success in SLT arm	>20% or ≥3mmHg reduction, without need for further surgery: 40% Not requiring 2nd LT/trabeculectomy: 75%	20% IOP lowering with no additional medical, laser, or surgical interventions: 25%	≥20% reduction: 73%	≥15% reduction: 75%
Drainage surgery in SLT arm	N/A	30.3% (including diode cyclophotocoagulation)	N/A	9.09%
Treatment in control arm	ALT	ALT	ALT	ALT

Spot size was 400 microns and duration was 3 nanoseconds for SLT in all studies.

Table 1: Summary of RCTs comparing SLT vs. ALT (adapted from Wong et al (177)

The studies included patients with primary open angle glaucoma (POAG), pseudoexfoliation (PXF), pigment dispersion syndrome (PDS), uveitic glaucoma and normal tension glaucoma. In 3 out of the 4 studies(159, 162, 163), patients included had uncontrolled IOP despite maximally tolerated medical treatment and previous ALT(163). In one study (158), patients with IOP not adequately lowered with medication alone were included.

The power settings used for ALT were between 300-1300mW, duration 0.1 second and spot size of 50 microns with 45-55 applications over 180 degrees. For SLT in the 4 RCTs, 180 degrees of trabecular meshwork was treated, using 400 microns spot size, duration 3 nanoseconds, power 0.2-1.7mJ with 45-70 applications.

In the comparison between SLT and ALT, there was a pooled total of 150 eyes in the SLT group and 140 eyes in the ALT group. Definition of success varied between the studies. 3 out of 4 studies aimed for >20% IOP lowering without need for further surgery (158, 159, 163) whereas one study was less stringent – opting for 15% IOP reduction (162).

The difference in pooled mean IOP reduction post SLT compared to ALT was not significant -0.5mmHg (95% CI: -1.5mmHg, 0.4mmHg). From 2 studies (158, 163) the effect of SLT vs. ALT in reducing the number of medications was calculated and was also not significantly different. Achievement of treatment success for SLT vs. ALT – Odds Ratio 1.2 (95% CI: 0.7 to 1.8) was similar between both groups ($p>0.05$). Overall, Wong et al (177) concluded that SLT demonstrated comparable efficacy with ALT in patients with maximally tolerated medication.

These findings are in agreement with 2 previous meta-analyses that have evaluated SLT vs. ALT (125, 178). A third meta-analysis by Wang et al, analysing 6 studies, has reported SLT to have a superior IOP lowering efficacy to ALT. It has been suggested that this difference in results could have arisen as the third meta-analysis included quasi-randomised controlled trials as part of their analysis (179).

2.2.11 SLT vs. Topical Medication in OAG/OHT patients

Several trials have compared SLT against topical medication in treating OAG and OHT patients (176). Within the SLT group of these studies, there is often variability in the degree of the trabecular meshwork treated. Most common parameters used by studies include either 90^0, 180^0 or 360^0 SLT treatment of trabecular meshwork.

Nagar et al performed an RCT comparing 90^0, 180^0, 360^0 SLT vs. 0.005% latanoprost to control IOP in OAG and OHT patients at 2 UK centres (149). They found success rates to be significantly higher in the latanoprost group compared to 90^0 and 180^0 SLT treatment groups. Furthermore, no significant difference was noted between latanoprost and 360^0 SLT treatment group.

In a subsequent RCT by the same group, 20 patients receiving 360^0 SLT were compared against 20 patients taking 0.005% latanoprost (180), SLT was found to decrease IOP by 4.7mmHg on average (95% CI 3.6 to 5.7mmHg; $p<0.01$) with a similar reduction achieved from latanoprost. There was no difference in treatment success at last follow up (4-6 months) between groups ($p=0.4$) and both were found to reduce daily IOP fluctuation. The study was limited however by a small sample size and short duration of follow up, limiting the applicability of the findings.

To date, 2 meta-analyses comparing SLT with medication have been performed (177, 181). Both included 4 RCTs, but Li et al (181) also included one further prospective non-randomised trial(182).

	Lai 2004	Nagar 2005	McIlraith 2006	Nagar 2009	Katz 2012
Design	**Single centre, RCT**	**Multi centre RCT**	**Multi centre, Prospective non RCT**	**Single centre, RCT**	**Multi centre RCT**
Location	**China**	**UK**	**Canada**	**UK**	**USA**
Number of Eyes (SLT: medication)	**29:29**	**128:39**	**74:26**	**20:20**	**67:60**
Follow up (months)	**60**	**12**	**12**	**4-6**	**9-12**
Mean Age	**51.9**	**63**	**62**	**N/A**	**N/A**
Baseline IOP Mean (SD)	**26.8 (5.6) / 26.2 (4.2)**	**29.3/29**	**26/ 24.6**	**26.1 (4) / 22.8 (4.5)**	**25 (2.2)/24.5(2.2)**
Diagnosis	**POAG, OHT**	**POAG, OHT, PDS, PXF**	**POAG, OHT, PDS, PXF**	**POAG, OHT**	**POAG, PXF, OHT**
Definition of success	**IOP≤21 mmHg**	**IOP reduction≥20%**	**IOP≤22 mmHg**	**IOP reduction≥20%**	**Arrived target IOP**
SLT treatment	**360 degrees**	**360/180/90 degrees**	**180 degrees**	**360 degrees**	**360 degrees followed by 180 degrees**
Average energy	**1.0 +/- 0.1mJ**	**0.2-1.7mJ**	**0.8mJ**	**0.2-1.4mJ**	**0.2-1.2mJ**
Medication	**Topical beta blocker, pilocarpine, dorzolamide, latanoprost as monotherapy or combination**	**Latanoprost 0.005%**	**Latanoprost 0.005%**	**Latanoprost 0.005%**	**Topical prostaglandin analogue, Beta blocker, brimonidine, carbonic anhydrase inhibitor, in combination**

Table 2: Summary of prospective comparative controlled trials comparing SLT vs. topical medication (adapted from Li et al (181)

In the analysis by Li et al, there were 492 eyes of 366 patients with open angle glaucoma. The age range of patients was 25-82 years. Study sites included USA, China, Canada and the UK. The mean duration of follow up ranged from 4-60months. In 4 out of 5 studies, 360 degree SLT was performed with an average power setting between 0.2mj and 1.7mJ. The mean baseline IOP ranged from 25-29mmHg in SLT groups and from 22.8- 29mmHg in medication groups.

Definition of success varied between studies. 4 studies compared SLT with medication in terms of IOP reduction whilst a single study classified success as meeting target IOP. Within IOP reduction as a success criterion, differences were still noted between studies. One study chose IOP reduction to as IOP <21mmHg

after intervention(174) whilst the remaining 3 used at least 20% IOP reduction from baseline(149, 180, 182).

Evaluation of IOP reduction from baseline between the 2 treatments used 4 studies involving 325 eyes. SLT showed no significant difference in IOP reduction compared to medication (weighted mean difference (WMD) 0.6, 95% CI: -0.24, 1.43). Comparing the proportion of patients achieving target endpoint IOP at follow up end point, the difference in success rates between the SLT group and medication group was also not statistically significant (pooled OR 0.84, 95% CI: 0.42, 1.68). Similar analyses related to IOP reduction and treatment success performed by Wong et al also demonstrated no significant difference between SLT and medication.

Whilst these findings are important, some limitations could impact the results. Data was derived and pooled from trials of different durations with some missing data in all phases of follow up. With treatment success, since different definitions were used to define success, caution may need to be applied regarding generalisability of results.

In summary, meta-analysis data suggests that SLT is as effective as medication in control of IOP with similar success rates.

2.2.12 SLT vs. Surgical Treatments in OAG/OHT patients

There are no studies which evaluate SLT vs. glaucoma filtration surgery. Previously, ALT has been evaluated against trabeculectomy surgery and was found to be inferior with respect to IOP lowering and reducing number of concurrent medications (126). SLT has been shown to have similar clinical efficacy to ALT (177) and thus we can infer that comparisons between SLT and trabeculectomy surgery would be expected to yield similar results.

More recently, Fea et al compared the reduction of intraocular pressure and glaucoma medications in 25 eyes that received SLT vs. 31 eyes that received stand-alone placement of the Hydrus microstent, a microinvasive glaucoma surgery (MIGS) device (183). At 12 months, there was a significant decrease in IOP in both groups. The Hydrus group also demonstrated a significant decrease in number of medications from baseline. Comparison between groups revealed a 3-fold greater reduction in medication use in the Hydrus group compared with SLT (-1.4 ± 0.97 vs.-0.5 ± 1.05, P = 0.001). 47% of patients were medication free at 12 months in the Hydrus group vs. only 4% in the SLT group. The Hydrus group experienced a higher frequency of post-operative complications however - three patients experienced a temporary reduction of visual acuity post-operatively and two patients had post-operative IOP spikes that resolved within one week. No complications were noted in the SLT group. These results suggest that MIGs devices may have a similar IOP lowering efficacy to SLT and can reduce the number of medications that patients are taking. However, unlike SLT which can be performed in an outpatient clinic setting, MIGs insertion is a surgical procedure performed in theatre associated with an increased adverse events profile. Further

studies are needed to fully compare MIGs vs. SLT to evaluate clinical effectiveness and safety.

2.2.13 SLT as Primary Treatment in OAG/OHT patients

Most studies that have investigated primary SLT have done so by comparing its efficacy against topical medical treatment. As described in the previous section, these studies, which include both randomised and non-randomised prospective trials have found that clinically, primary SLT has a similar IOP lowering efficacy and success rate as topical medication.

However, several of these studies have included in the SLT arm, patients that were previously taking topical medications which were subsequently stopped for a variable duration (4 weeks to 3 months) prior to receiving SLT (149, 163, 182). As such, these patients were not truly treatment naïve prior to receiving SLT. Despite a washout period to mitigate against residual effects of prior topical treatment, some studies have shown SLT to be less effective when used following topical treatment. McIlraith et al reported clinical outcomes in 87 eyes previously on topical glaucoma medication which were discontinued 4 weeks prior to SLT(182). The amount of IOP reduction was significantly less in this group compared to the primary treatment (treatment naive) group (average IOP reduction in primary treatment group: 8.1mmHg vs. washout group: 6.4mmHg, $p<0.001$) The authors suggested that the length of washout time could have been inadequate meaning that true baseline IOP was hence not reached at the initiation of the study. An alternative explanation is that SLT is more effective as a primary treatment. Further robust research is required to investigate the efficacy of primary SLT in

treatment naïve patients such that we can establish the true efficacy of primary SLT.

2.2.14 SLT as Adjunct Treatment in OAG/OHT patients

Similar to ALT, SLT has also been investigated as an adjunct treatment for patients on concurrent medical therapy as a means of further IOP reduction(184, 185).

Weinand et al reported clinical outcomes of 52 POAG eyes who received adjunct SLT whilst on topical medical treatment (184). The average reduction in intraocular pressure (IOP) from baseline post SLT was 24.3% (6.0 mmHg) at 1 year, 27.8% (6.12 mmHg) at 2 years, 24.5% (5.53 mmHg) at 3 years, and 29.3% (6.33 mmHg) at 4 years.

Lee et al performed a RCT of 41 medically controlled POAG patients evaluating the effect of adjuvant SLT vs. medication alone (186). At 6 months follow up, the average IOP in the SLT group was 7.6% lower than the medication only group ($p=0.03$) and the SLT group required significantly fewer anti-glaucoma medications compared with the medication only group ($p=0.02$). Adjunct SLT in POAG patients with uncontrolled IOPs despite medical therapy has been shown to be effective (187-189), whilst other studies have demonstrated a reduction in the number of concurrent glaucoma medications needed to control IOP following treatment (189-191) .

In a retrospective analysis of 206 patients, Woo et al investigated the effects of concurrent topical medication on the efficacy of first time adjunct SLT (192). Patients were grouped into different groups (0-3) based on the number of medications they were taking prior to SLT and then followed up for 5 years. Average IOP reduction following SLT varied between 21.8- 29% across all groups

at 6 months and between 23.6 - 25.6% at 5 years with no statistically significant difference noted between groups. Mixed model analysis demonstrated no significant interactions between number of medications and post-treatment IOP response over time and was in agreement with previous studies that have demonstrated this. Patients taking 2 or 3 medications had a higher proportion of repeat SLT and / or trabeculectomy surgery compared to those on none or one medication. This is to be expected as patients on multiple medications are often closer to maximal tolerated medical therapy and more likely to be suffering from advanced glaucoma with uncontrolled IOPs. Importantly, whilst there were 206 patients initially in the study, only 55 patients remained at 5 years due to a combination of loss to follow up and patients requiring additional intervention. This makes the interpretation of the longer term outcomes difficult and reiterates that the effect of SLT effect is largely temporary.

2.2.15 SLT post other treatment interventions

SLT has been shown to be effective as an adjunct treatment in patients who have previously undergone ALT. Mean IOP reduction at 1 year in 30 OAG patients receiving primary SLT (23%) was no different to 27 OAG patients who received SLT after prior ALT (19.3%) (193).

Recently, Zhang et al investigated the efficacy of SLT in advanced POAG patients who had previously undergone trabeculectomy surgery but had uncontrolled IOPs despite this and required additional topical treatment (194). In this small study of 18 eyes, they found at last follow up (9 months) a reduction of mean IOP from 21.3mmHg to 16.2mmHg with 77.7% of patients achieving a reduction of >20% from pre-treatment IOP. The study was small however with a short duration of follow up (<12 months), limiting the scale of the conclusions that can be made. A small study by Sluch et al has also suggested the beneficial effect of SLT after canaloplasty surgery (195).

In conclusion, SLT is effective as an adjunct treatment in OAG patients on medical treatment. It is effective as a means of potentially delaying the need for filtration surgery in uncontrolled OAG patients but also may have a role in some patients who have undergone filtration surgery as a means of further IOP reduction.

2.2.16 SLT: IOP fluctuation reduction

Large diurnal IOP fluctuations are thought to be an independent risk factor for glaucoma progression (196). Nagar et al reported that both SLT and prostaglandin analogues are successful at reducing IOP fluctuation in POAG patients, but prostaglandins are more effective (3.6mmHg, 95% CI 3.2-3.9mmHg vs. 2.5mmHg (2.2-2.9mmHg, p =0.04) (180). The method for measuring IOP fluctuation in this study however was basic and prone to error; the 'diurnal' measurement was in fact based on the greatest IOP difference between 2 out of 4 IOP measurements taken between 0800am and 1800pm.

Kiddee et al confirmed that SLT and prostaglandins reduce IOP fluctuations in both POAG and NTG patients, whilst they also demonstrated that prostaglandins are more effective at reducing IOP fluctuation throughout a 24-hour period, whereas SLT's effect is more pronounced during the night time (197). Prasad et al demonstrated that extent of SLT treatment may also influence IOP fluctuation (198). In their retrospective study, 22 patients received 360^0 SLT vs. 19 patients received 180^0 SLT and were followed up for 2 years. The percentage of eyes with inter-visit IOP fluctuation (SD) <or=2 mm Hg was significantly greater in 360-degree SLT treatment group (86%) than in the 180-degree SLT treatment group (52%) (p=0.03) but the study was limited by a small sample size and retrospective design.

Two studies have utilised a more sophisticated means of measuring 24 hour IOP fluctuation post SLT using a contact lens sensor (CLS) (SENSIMED Triggerfish, Sensimed, Switzerland). Lee et al investigated 18 patients with NTG who were

treated with 360^0 SLT(199). They found at 1 month post treatment that in those patients who achieved treatment success (greater than or equal to 20% IOP reduction), there was a 24.6% reduction in 24 hour IOP variability whereas in unsuccessful patients, the 24 hour IOP variability actually increased by 19.2%. This is in contrast to a study by Tojo et al (200) who also investigated 24 hour IOP fluctuations using CLS in 10 NTG patients. They found the range of IOP fluctuations was not significantly changed between before and after SLT treatment over 24 hours (p=0.77) or during the daytime diurnal period (P=0.92). However the range of IOP fluctuations during the nocturnal periods significantly decreased from 290±86 mVEq before SLT to 199±31 mVEq after SLT treatment (P=0.014). SLT treatment was shown to significantly lower IOP and decrease IOP fluctuations during the nocturnal periods in NTG patients and is in keeping with the findings of Kiddee et al (197). Despite these results, both these studies had small sample sizes and crucially, the reliability and validity of CLS devices in measuring IOP in humans is still not established.

The changes in corneal shape detected by the CLS are thought to correlate highly with IOP. This has been demonstrated in enucleated pig eyes (201) but it has been difficult to validate in humans. This is because it is not possible to corroborate CLS IOPs immediately with an accepted gold standard measure such as goldmann applanation tonometry (GAT), since the contact lens in situ does not permit this. Furthermore, in a study investigating reproducibility of IOP reading results in the human subjects one week apart, the pearson correlation coefficient between the two sessions was 0.59 demonstrating only 'fair to good reproducibility' (202). Further studies are needed to validate the CLS as a reliable measure of IOP and whether it is a useful tool for monitoring IOP fluctuation.

2.2.17 SLT: Repeatability

The IOP lowering effect of SLT diminishes with time. Since SLT has been shown to cause minimal structural damage to the TM, repeat treatment has been considered a feasible option in suitable patients who require further IOP reduction. To date, there have been 7 studies reporting outcomes of repeat 360^0 SLT.

Ayala et al performed a prospective RCT to evaluate the effect of repeat SLT in POAG/PXF glaucoma patients (203). All patients were treated initially with 180° SLT in the lower half of the TM. Patients for repeat SLT were then randomised to receive further SLT in the previously treated TM area or in the 180^0 upper untreated TM area. A total of 40 patients were included in both groups. At baseline, there were no significant differences between the groups with regards to time between first and repeat SLT ($p = 0.78$), baseline IOP before first SLT ($p = 0.78$), or IOP before repeat SLT ($p = 0.32$). The study found no significant differences in IOP between the retreatment groups at all follow up time points including latest follow up at 6 months ($p = 0.66$). This suggests that repeat SLT in the same area of TM does not have a significant effect on IOP compared to two SLT treatments in two different areas. This also supports the theory that SLT retreatment provides a similar IOP lowering effect to primary treatment.

Several retrospective studies have evaluated repeat SLT. The largest of these studies by Francis et al evaluated 137 eyes with POAG or secondary OAG (excluding uveitic glaucoma) that had undergone two 360^0 SLT treatments at least 6 months apart (204). Percentage IOP reduction between the 2 treatments at 12-15 months was not significantly different (14.5% vs. 10.9%, $p=0.11$). A sub-

analysis of 62 patients where baseline IOPs were matched demonstrated 20% success at 12 months following both initial and repeat SLT (success criteria: IOP between 5-21mmHg and IOP reduction greater than or equal to 20% from baseline at 12 months).

Hong et al reported that in 44 eyes with uncontrolled OAG on maximum tolerated medical therapy where primary 360^0 SLT had initially been successful (success criteria: greater than or equal to 20% peak IOP reduction), repeat 360^0 SLT achieved success in 43.2% of eyes at 5-8 months compared to 50% success at initial SLT (205). There was no statistically significant difference between primary SLT and repeat SLT success rates. These findings are supported in a similar study by Polat et al (206), who performed a retrospective review of 38 eyes with OAG uncontrolled on medical therapy that had undergone 2 successive 360^0 SLT treatments. They found a significant reduction in IOP from baseline after both treatments through to 24 months follow up. Kaplan Meier survival analysis showed median survival time of 9 months for initial SLT and 12 months for repeat SLT when using a definition of success as greater than or equal to 20% reduction in IOP from baseline.

In a separate study of newly diagnosed POAG patients, repeat SLT had a similar mean IOP reduction and treatment success rate (IOP reduction greater than or equal to 20%) compared to primary SLT in 42 eyes (207) . Moreover, the mean duration of success in repeat treatment (13.1 months) was longer than initial treatment (6.9 months) though this difference was not statistically significant.

Khouri et al performed repeat 360^0 SLT on average 26 months after initial SLT in 51 eyes of 34 patients with OAG(208). Patients were stratified into those that had a successful response to initial SLT (greater than or equal to 20% IOP reduction from baseline) and a modest response to initial SLT (<20% IOP reduction from baseline). 41 % of eyes met the success criteria after primary SLT and 43% at repeat SLT. In the 22 eyes with treatment success after repeat SLT, the proportion of eyes with initial successful response (11 eyes) and modest response (11 eyes) was the same. This suggests that repeat SLT can be successful irrespective prior SLT success. In a different study by Khouri et al (209), they demonstrated longer term clinical outcomes of repeat 360^0 SLT and reported that at 24 months, 29% of eyes achieved IOP reduction > 20% as compared to 36% of eyes following initial treatment – a difference which was not statistically significant.

Overall, from the evidence available in the literature, there appears to be a clinical benefit to repeat SLT, though the majority of studies are retrospective with small sample sizes. Repeat SLT may be able to achieve a similar final IOP to successfully treated eyes receiving single initial SLT by exerting an additive effect to the previous SLT. The absolute IOP reduction may be less because of a lower pre-treatment IOP prior to repeat SLT compared to the untreated baseline IOP prior to initial SLT. In addition, there may be selection bias with repeat SLT, where patients who respond well to initial SLT are offered retreatment. Larger prospective studies investigating repeat SLT are required to investigate this question further.

2.2.18 SLT in PACG

SLT has not been commonly performed in Primary Angle Closure Glaucoma (PACG) patients. The procedure requires visualisation of the trabecular meshwork within the angle, which can be limited in such patients. Nonetheless, some studies have evaluated the efficacy of SLT in PAC/PACG patients where some of the angle is open and therefore the TM is accessible for treatment.

Narayanaswamy et al performed a prospective RCT to evaluate the effect of SLT in 100 PAC/PACG patients that had previously undergone laser iridotomy (210). Post laser, the angle had been opened (at least 180° visible posterior trabecular meshwork on gonioscopy) but IOPs were still greater than 21mmHg. 96 eyes were randomized to SLT and 99 eyes to prostaglandin therapy and followed up for 6 months. At 6 months, IOP decreased by 4.0 mm Hg (95% CI, 3.2-4.8) in the SLT group ($P < .001$) and by 4.2 mm Hg (95% CI, 3.5-4.9) in the PGA group ($P < .001$). There were no differences between the SLT and PGA groups in the absolute mean reduction of IOP (4.0 vs 4.2 mm Hg, respectively; $p = 0.78$) or in the percentage of reduction in IOP (16.9% vs 18.5%, respectively; $p = 0.52$). The procedure appeared safe in PAC/PACG patients with only one patient suffering from a transient IOP spike and no other adverse events reported.

A retrospective case control study by Ali Aljasim et al compared SLT in 59 eyes with PAC/PACG post PI vs. 59 eyes with POAG (211). Treatment criteria for SLT in the PAC/PACG group required an open angle with at least 180 degrees of visible TM. In both groups, SLT was performed as either a primary treatment for uncontrolled IOP or as an adjunct treatment for patients with uncontrolled IOP on

maximal tolerated medical therapy or those intolerant to medical therapy. Average postoperative follow was between 10-11 months. SLT achieved an average IOP reduction of 38% from baseline in the PAC/PACG group vs. 32.7% in the POAG group. (p=0.08). In both groups, SLT permitted reduction of glaucoma medication (by 1.6 medications in PAC/PACG vs. 1.5 medications in POAG, p=0.40). There was no significant difference in frequency of post laser IOP spike between groups - 10% (n=6 eyes) in the PAC/PACG group and 5% (n=3 eyes) in the POAG group developed an IOP spike (*P*=0.49).

2.2.19 SLT in NTG

Lee et al performed a prospective study of Chinese NTG patients evaluating 360^0 SLT efficacy (212, 213). Recruited patients had previously been taking topical medication but underwent a 1-month washout period prior to receiving SLT. Medication was resumed at 1 month to achieve a target 30% IOP reduction from pre-SLT IOP. 41 eyes were used for 12-month analysis and 34 eyes in the 24-month analysis. At 12 months, average IOP reduction was 14.7% from baseline (pre medication or SLT) levels and at 24 months, IOP reduction was 11.5% IOP from pre-study levels ($p<0.05$). There was also a 26.7% and 41.1% reduction in mean medication use at 12 months and 24 months respectively. Absolute success (IOP reduction of >20% from baseline washout IOP without addition of additional medication) was 22 % at 12 months and 11.1% at 24 months.

Overall, SLT has been shown to be of benefit in NTG patients. However, since these patients have often lower pre-treatment baseline IOPs compared to POAG patients, the absolute IOP reduction is often less. Moreover, if using commonly used success criteria (IOP reduction > 20% from baseline) as for POAG patients, the success rates in NTG patients appears lower.

2.2.20 SLT in Pseudoexfoliation Glaucoma

SLT has been shown to be an effective treatment for uncontrolled IOPs in PXF patients (214) as well as having comparable IOP lowering effect to OAG patients (173, 215-217). However, several of these studies are limited by retrospective design, small sample sizes, non-randomised patient selection as well as different treatment SLT protocols. In their review, Kennedy et al reported a mean IOP reduction for PXF eyes in the range of 31.5% at 12 months, 16.6% at 16 months, 31.4% at 18 months with a cumulative probability of maintaining greater than or equal to 20% IOP reduction in 64% of patients at 18 months and 47% at 36 months (218). A recent prospective study reported a treatment success (success criteria: IOP reduction greater than or equal to 20% from baseline) in PXF group compared to POAG group at 6 months (94.1% vs. 75%, p = 0.08), however there was no significant difference at 12 months (p=0.9). PXF also does not appear to be a risk factor for post-laser complications including inflammation.

2.2.21 SLT in Pigmentary Glaucoma

In a prospective study, Koucheki et al assessed the efficacy of 360^0 SLT in an Iranian cohort of patients with pigmentary glaucoma (PG), POAG and PXFG (173). At last visit (~16 months) the mean IOP reduction was 16.3% overall: 16.7% in POAG, 16.6% with PEX, and 14.5% in the PG group. The percentage of IOP reduction was not statistically significant among the groups (*P*=0.696) and there was no significant difference in success rates (p=0.597). Of note however, increased post procedure pain, inflammation and IOP spikes were noted in the PG group vs. the POAG and PXF groups. There was also a higher rate of further interventions e.g. repeat SLT or trabeculectomy surgery in the PG group (26.1%) vs the other 2 groups (POAG 16.5%, PXF 13.6%, p<0.001). A similar association had been found previously in a case series where increased post laser IOP spikes were noted in patients with heavily pigmented TM (219). The authors suggested that increased TM pigmentation in PG could cause more energy absorption following SLT resulting in increased pain as well as a possible lesser efficacy of SLT in PG patients. They also suggested that lower energy settings be used in PG patients to prevent the complications described.

Ayala et al performed a retrospective analysis of 30 PG eyes that had received 180^0 SLT assessing time to failure after SLT treatment (220). The average time to failure after SLT was 27.4 months. The success rate after 12 months was 85%, after 24 months 67%, after 36 months 44%, and after 48 months 14%. Only 2 eyes out of 30 experienced a post-laser IOP spike however in this study only 180^0 of TM was treated and the authors used lower energy. They concluded that SLT in PG patients

is effective initially for roughly 2 years prior to the effect waning after this time point.

2.2.22 SLT in Secondary Glaucoma

Though limited studies exist, the use of SLT in secondary steroid induced glaucoma has been investigated. Rubin et al (221) reported the results of 7 eyes that underwent SLT after intravitreal triamcinolone injections for macular oedema (6 eyes) or post central retinal vein occlusion (1 eye). Patients had elevated IOP despite maximum tolerated medical therapy prior to SLT (Mean pre-operative IOP 38.4mmHg±7.3). Following SLT, IOP decreased to 25.9mmHg±8.8 at 1 month (P<0.007), 23.9mmHg±10.6 at 3 months (P<0.006), and 15.7mmHg±2.2 at 6 months (P<0.001). Four patients required repeat SLT and two patients failed after the 3-month visit.

Bozkurt et al investigated whether prophylactic SLT could reduce or prevent the IOP rise often seen following intravitreal steroid injection(222). In their prospective study, 15 eyes underwent 360^0 SLT approximately 8 days prior to intravitreal triamcinolone injection for diabetic macular oedema. IOPs in both groups were initially reduced however the IOP rise from 1-3 months was reduced in the SLT group. This effect was evident up to 6 months.

In a different study of 15 uveitic eyes that had already received intravitreal steroid to control inflammation, the efficacy of SLT to reduce IOP was evaluated (223). Mean IOP prior to SLT was 30.57mmHg and had reduced to 14.85mmHg (51.4% reduction) at 1 month, 13.42 mmHg (55.7% reduction) at 6 months, and

15.14mmHg (50.4% reduction) at 12 months. Seven eyes (46.7%) achieved success criteria (IOP < 22 mmHg and/or a 20% or more reduction in IOP from the pre-SLT IOP) at 1-month, 6-month, and 12-month follow-up visits. One treated eye developed a prolonged IOP spike but there were no other adverse events including no new episodes of inflammation.

Zhang et al evaluated the efficacy of SLT in 42 eyes with silicone oil induced secondary glaucoma (224). 360^0 SLT was performed and mean IOP decreased from 23.1 ± 1.9 mmHg pre-treatment to 18.4 ± 3.7 mmHg after treatment ($p < 0.05$). Mean number of anti-glaucoma medications used for IOP control also decreased from 2.17 ± 1.21 to 1.25 ± 0.89 ($p < 0.05$).

Overall, SLT appears to have some clinical efficacy in secondary glaucoma patients. Further large scale studies are required to fully investigate this further.

2.2.23 SLT: Predictors of Success

SLT is not successful in all treated eyes. Several studies have analysed baseline patient factors that may predict success, frequently by performing univariate and multivariate regression analyses to look for associations.

Predictors of success comparisons between studies is difficult since multiple variations exist within studies including size of study, patient demographics, glaucoma subtype treated, SLT treatment parameters, length of follow up and indeed the definition of 'success' itself. This creates difficulty in establishing 'definite' robust predictors of SLT success and is reflected in the literature on this topic, where multiple studies have contradictory results to one another.

The most consistently reported patient factor which predicts SLT success is elevated baseline IOP, which has been demonstrated in several studies (225-230). This is partly explained by the most commonly used definition of success (IOP reduction greater than or equal to 20% from baseline) tending to favour elevated baseline IOPs, as the magnitude of IOP reduction post glaucoma treatment is often greater with higher IOPs. This is also reflected in NTG studies where baseline IOPs are lower and both absolute IOP reductions and success rates are also lower compared to other glaucoma subtypes (212, 213). One recent study suggested that patients with pre-treatment baseline of <14mmHg may not benefit from SLT at all (231).

A potential limitation of such success criteria is that though they are a marker of IOP reduction, they may not necessarily reflect real world clinical practice. For

example, though patients may achieve >20% IOP reduction from baseline IOP following SLT, if pre-treatment baseline IOPs are elevated, then following treatment these may still be elevated and too high to prevent glaucoma progression. Only a few studies have used pragmatic individualised target IOPs and assessed the 'pursuit of control' for different treatments to obtain target IOPs (232). Supporting this, recently Miki et al found that higher pre-treatment baseline IOP may in fact be associated with increased treatment failure in SLT patients (233). Patients with higher pre-treatment IOPs were more likely to need repeat SLT treatment or glaucoma filtration surgery as the magnitude of IOP reduction to control disease progression was larger and not achievable by single SLT treatment alone. Multiple other patient factors including sex, race, age, glaucoma type, TM pigmentation, lens status and central corneal thickness have been investigated and found not to be predictive of SLT success by some studies (218, 231). Hirneiß et al have shown that corneal biomechanical markers such as corneal hysteresis (CH) and corneal resistance factor (CRF) may be useful in helping to model the IOP lowering effect of SLT (234)

Regarding the effect of pre-existing topical medication on SLT success, Woo et al found no significant difference in success rate based on number of concurrent topical medications that patients were taking (192). This is different to Lee et al who found that using multiple antiglaucoma medications especially topical carbonic anhydrase inhibitor was associated with SLT treatment success (230).

Bruen et al found that pretreatment with prostaglandin analogue was associated with a decreased IOP lowering response (228). This is feasible as both SLT and prostaglandins have been purported to share a common mechanism of action and

hence the benefit of SLT would be greatest in prostaglandin naïve eyes and lower in prostaglandin treated eyes.

2.2.24 SLT: Complications & Adverse Events

SLT is a relatively safe procedure which is well-tolerated with low complication rates (235). Most of the complications associated with SLT are transient and self-limiting.

Kennedy et al reported an IOP rise of greater than or equal to 5mmHg has been reported in upto 28% of eyes post SLT (218). An increased incidence of IOP spikes have been noted in patients with pigmentary glaucoma and heavily pigmented TMs (173).

Anterior chamber inflammation is common post SLT with up to 83% of eyes demonstrating some degree of inflammation post SLT (235). Some studies have regarded the redness, photophobia and pain that patients report following SLT to be as a consequence of this inflammation. Furthermore, considering the biological changes that SLT induces, some regard transient acute anterior uveitis as a predictable consequence of treatment. Inflammation is usually transient and self-limiting and is supported by studies that have concluded that the use of anti-inflammatory agents after SLT has not been shown to cause a significant reduction in inflammation or altered IOP lowering efficacy (166, 167).

Occasionally however, inflammation post SLT may be severe. 2 case reports of post SLT choroidal effusions have been published to date (236, 237). Inflammation may not be limited the treated eye - one case report of bilateral acute anterior uveitis post unilateral SLT has also been reported (238). Unlike ALT, the development of peripheral anterior synechiae (PAS) is not common post SLT. In their meta-

analysis, Wong et al described only 2.86% of cases developed PAS (177) and it has been described to occur after repeat SLT (239).

Retinal changes post SLT are rare but those that have been described include cystoid macular oedema (240-242) and development of subretinal fluid (243).

The development of transient corneal endothelial changes is a well described occurrence post SLT. These have been reported to occur acutely, within an hour of the treatment (244) and are self-limiting with no long term changes to visual acuity, central corneal thickness or endothelial cell count on long term follow up (245, 246). A few case reports of transient corneal oedema and haze have also been reported with and without residual corneal stromal scarring and hyperopic shift (247-249).

2.2.25 SLT: Cost Effectiveness

Treatment of OAG/OHT aims to prevent disease progression in patients but also imposes significant costs on healthcare systems. The total annual costs in Australia for 2005 were $1.9 billion, of which $355 million were health system costs (250).

Furthermore, both direct and indirect costs have been found to be higher for severe disease states (US$623 for mild POAG to US$2511 for severe POAG) suggesting that more effective IOP control early in the disease could reduce future costs (251). Direct treatment costs in the UK were estimated at $627 per patient per year in 1999 (252).

Studies that have attempted to estimate the relative costs of SLT have used either economic modelling or estimates of the treatment cost rather than direct cost assessment, and none have been performed in the NHS setting. In the USA, Cantor et al compared the treatment costs of uncontrolled glaucoma treated with either further medications, SLT followed by further medications or surgery (253).

Using Markov modelling, with US cost assumptions based on Medicare fee schedules, they found the 5-year cumulative costs per patient were $6571, $4838 and $6363 in the medication, SLT and surgery arms, respectively. An Australian study modelled the cost benefit of laser trabeculoplasty as primary treatment compared to conventional medical treatment followed by laser then surgery and found a saving of $2.50 for every $1 spent on laser treatment, compared to initial medical therapy (250, 254). Furthermore, cost savings were projected to continue increasing over time since with an increasingly ageing population, the prevalence,

burden and hence treatment needed for POAG was also going to increase(250).

Other studies support primary SLT as a more cost-effective treatment option to topical medication for OAG/OHT patients. Seider et al calculated the time threshold at which bilateral SLT would become less costly than bilateral use of each topical medication by dividing the total costs of SLT by the monthly costs of each medication (255). They found that SLT becomes 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. This is supported by Lee & Hutnik who compared projected 6-year costs of primary selective laser trabeculoplasty (SLT) versus primary medical therapy in the treatment of open-angle glaucoma in a Canadian healthcare model (256). They found that if primary SLT treatment had to repeated at between 2-3 years, the use of primary SLT over mono-, bi-, and tri-drug therapy produced a 6-year cumulative cost-saving between and $206.54 and $3366.65 dollars per patient, respectively.

Guedes et al recently confirmed this, demonstrating using modelling that primary laser demonstrated a better cost effectiveness profile than topical treatment in the management of both mild and moderate glaucoma disease states (257).

Berdahl et al performed an analysis to compare the 5 year costs of initiating OAG patients on 3 different treatment arms – initial medication, initial SLT or insertion of x2 MIGs (iStent) devices (258). During years 1-5, patients could remain on initial treatment or move to another option or filtration surgery. The projected average cumulative cost at 5 years was lower in the SLT arm ($4730) vs. medications arm

($6217) however, the iStents arm was projected to be cheapest ($4420) despite highest initial year zero costs.

Of the cost effectiveness studies that have been carried out, none have been performed in a UK NHS setting. Further analysis of the cost-effectiveness of SLT in a UK setting would be advantageous to evaluate whether SLT could be similarly efficacious and cost effectiveness in the NHS and help inform practice in this setting.

2.2.26 SLT: Quality of Life

The potential patient benefits of SLT are clear. It is a proven alternative to medication with comparable clinical efficacy but avoids medication related side-effects and compliance issues. Despite this, there is little evidence to evaluate whether these perceived benefits manifest as a notable difference in quality of life (QoL) for patients receiving SLT vs. topical medication. Greater emphasis on patient-centred care has led to increasing use of patient reported outcome measures (PROMs) in glaucoma research (259, 260).

Lee et al performed a prospective, randomized control study recruiting 41 consecutive primary open-angle glaucoma subjects with medically-controlled IOP ≤21 mmHg (186). The SLT group (n=22) received a single 360-degree SLT treatment whilst the medication-only group (n=19) continued with their usual treatment regimen. In both groups, medication was titrated to maintain a target IOP defined as a 25% reduction from baseline IOP without medication, or <18 mmHg, whichever was lower. Quality of life outcomes were measured at baseline and at 6 months using the Glaucoma Quality of Life-15 (GQL-15) and Comparison of Ophthalmic Medications for Tolerability (COMTOL) survey scores. They found no statistically significant difference in the 6-month GQL-15 or COMTOL score as compared to baseline or between the two treatment groups despite a greater IOP reduction and reduction in number of medications in the SLT group. This is different to De Keyser et al (261) who used a different validated assessment tool for quality of life – the 'Treatment Satisfaction Survey for Intraocular Pressure (TSS-IOP) and found significant improvement in parameters including side effects,

eye appearance, convenience of use, ease of administration at 12 months compared to topical treatment.

With the emergence of PROMs in research and the array of instruments to choose from, it will be increasingly important in future studies to define which 'aspect' of quality of life is to be assessed. This could be general health quality of life (eg. EQ-5D-5L) which is often required for cost-effectiveness analyses but their utility in glaucoma specific ophthalmology studies has been questioned (262). Vision specific (eg. National Eye Institute Visual Function Questionnaire-25 NEI-VFQ-25) and even glaucoma specific (eg. Glaucoma Utility Index, Glaucoma Symptom Score) instruments do exist which assess different aspects of quality of life eg. visual function or ocular symptoms. It may beneficial for future studies to use similar QoL instruments to permit comparison between studies or for a consensus to be reached regarding which instruments to use for assessing certain aspects of QoL This could help 'standardise' PROMs reporting, as current evidence demonstrates a large variation in the instruments used. It will also be important to choose an appropriate QoL instrument which is ideally validated for the aspect of quality of life being measured. This is to ensure that the tool is sensitive enough to detect a change in QoL (if one exists) between two groups of patients and also to permit comparison of results between studies in the future.

2.2.27 SLT: Future & New Developments

Newer laser trabeculoplasty procedures are currently under investigation. Some pilot studies have compared their efficacy against conventional SLT and found potential advantages, though further large-scale research is required to establish whether any of these newer treatment modalities could supersede SLT in the future.

Micropulse Diode Laser Trabeculoplasty (MDLT)

Diode Laser Trabeculoplasty (DLT) was first demonstrated to be effective in IOP lowering in the early 1990s (263). It was however noted to cause similar coagulative damage as ALT (264). Micropulse Diode Laser Trabeculoplasty (MDLT) was first described by Ingvoldstad et al in 2005 (265). This technique uses trabeculoplasty with subvisible (subthreshold) applications of repetitive short diode (532nm, 577nm or 810nm) laser pulses spaced by a long relaxation time with spot size of 300microns. The relaxation time between pulses in MDLT allows the temperature to return to baseline in pigmented TM cells prior to the next micropulse and hence does not cause coagulative damage to the trabecular meshwork (266) and there is no blanching or bubble formation over the TM during the treatment. Post treatment inflammation is minimal hence no anti-inflammatory medications are required. MDLT results are variable- some studies reporting limited IOP lowering success (267) whilst others report better results mean IOP reduction between 19.5-22% with a good safety profile (268, 269). In a comparison with SLT, the percentage of eyes achieving IOP reduction >20% from baseline was similar between MDLT and SLT (270). However, firm conclusions cannot yet be made about the efficacy of MDLT, since several of these studies had

small sample sizes, limited duration of follow up (none beyond 12 months) and some were limited by retrospective design (271).

Titanium Sapphire Laser Trabeculoplasty (TLT)

TLT uses near infrared energy (790nm) in short pulses (5-10microseconds) with a spot size of 200microns. The near infrared wavelength is believed to penetrate deeper (~200microns) to the inner and outer walls of Schlemm's canal as well as the collector channels and ciliary body. The laser is believed to be selectively absorbed by pigmented phagocytic cells, preserving the trabecular meshwork tissue(272). The total radiation energy of TLT is approximately 250 times that of SLT but is delivered over a longer time period, resulting in a longer thermal relaxation time, causing minimal collateral coagulative damage as a result (273).

In a small RCT comparing TLT vs. SLT in OAG/OHT patients, 18 patients received 360^0 TLT vs. 19 patients received 360^0 SLT. At 12 months, mean IOP reduction was 22% from baseline in TLT group and 20% in SLT group. At 2 years, mean IOP reduction was 35% in TLT group and 25% from baseline. No statistically significant differences in IOP or success rates were noted between groups. Treatments had a similar adverse events profile but despite this, some concerns remain about the long burn duration and deeper penetration of TLT compared to SLT (273).

Pattern Scanning Laser Trabeculoplasty (PSLT)

The PASCAL photocoagulator (OptiMedica Inc, Santa Clara, California) was introduced in 2006 for semi-automated photocoagulation of the retina (274).This technology uses pulse durations that are longer than SLT (10-20msec vs 3

nanoseconds) but a smaller 100 micron spot size and computer guided predetermined pattern of spots. In a recent RCT (275), the safety, tolerability and IOP lowering efficacy of PSLT was compared against SLT. 29 OAG patients underwent PSLT in one eye and SLT in the fellow eye. There was no significant difference in mean IOP reduction at last follow up (6 months) with similar safety profiles. Interestingly, better comfort was reported using visual analogue scores in the PSLT group compared to the SLT group, thought to be due to shorter procedure duration compared to SLT. Despite these promising results, the sample size of the study was small and follow up did not extend beyond 6 months. Further larger studies with longer duration of follow up are required to investigate PSLT further to establish whether it is likely to supersede more commonly used laser modalities such as SLT.

Trans-scleral SLT without Gonioscopy Lens

Trans-scleral or Direct SLT allows 360^0 treatment around the perilimbal sclera overlying the TM without a gonioscopy lens. This eliminates corneal and gonioscopy related side effects (276, 277). It utilizes similar laser settings to conventional SLT and has similar IOP lowering efficacy but shots are fired simultaneously in less than 1 second reducing procedure duration. Direct SLT could potentially enable treatment to lower IOP in angle closure/ angle closure glaucoma patients as visible access to the TM is not required using this technique. If successful, direct SLT could be widely implemented including in the developing world, since ophthalmic surgeons would not necessarily be required and allied healthcare professionals could be trained to deliver the laser to patients instead. Further larger scale studies are underway to evaluate Direct SLT– the GLAUrious

trial is a prospective multicentre RCT comparing SLT vs. direct SLT. A separate trial evaluating its' use is currently recruiting in Israel.

2.2.28 SLT Conclusions

SLT is as effective as ALT and topical medication in OAG/OHT patients. It can be used as a primary treatment or adjunct treatment and has effect in other glaucoma subtypes and secondary glaucoma. It has been shown to reduce IOP fluctuation but its effect does subside over time. Since it causes minimal damage to the TM, SLT can be repeated and IOP lowering is present even if initial response with primary SLT was limited. Adverse events are uncommon after SLT and most of these are transient and self-limiting. SLT has been shown to be a cost-effective option for primary treatment of glaucoma patients and some evidence exists to show is associated with a better quality of life. Newer technologies are emerging to further develop SLT but these require further investigation with larger scale studies.

2.3 Aims & Objectives of Research

The preceding chapters have provided an introduction to glaucoma; reviewing the condition, classification, pathophysiology & available treatments including SLT. As our previous literature review has shown, there is a lack of RCTs comparing primary SLT with topical treatment and a lack of primary SLT data on truly 'treatment naïve' OAG and OHT patients.

The Laser in Glaucoma & Ocular Hypertension Trial ('LiGHT' Trial) is a multi-centre randomised controlled trial in which the primary outcome was to determine whether there was a difference in HRQL (using the EQ5D questionnaire) at 3 years between primary SLT compared to primary medical treatment in treatment naïve OAG and OHT patients in a pragmatic study that mirrors the realities of clinical decision-making,

The aims and objectives for this research project were set having reviewed and considered the current literature on SLT. The main aim of this research was ultimately to investigate the clinical efficacy of primary SLT in treatment naïve OAG and OHT patients.

The work presented in this thesis attempts to address important clinical questions related to the use of SLT in OAG and OHT using clinical data derived from the LiGHT trial. These analyses have value to both clinicians and patients in providing further information regarding clinical outcomes of primary SLT. Our results and potential conclusions will be important and clinically applicable, guiding future work in this area.

Question 1: Is SLT clinically effective as a primary treatment to lower IOP and maintain IOP control in treatment naïve OAG/OHT patients?

The use of primary SLT as initial therapy in treatment naïve OAG/OHT patients is limited. To date, there have only been 4 RCTs comparing primary SLT vs. topical medication (see Section 2.2.11). A meta-analysis of these 4 RCTs evaluating IOP reduction from baseline between the 2 treatments showed no significant difference in IOP reduction compared to medication (weighted mean difference (WMD) 0.6, 95% CI: -0.24, 1.43)(181). Comparing the proportion of patients achieving target endpoint IOP at follow up end point, the difference in success rates between the SLT group and medication group was also not statistically significant (pooled OR 0.84, 95% CI: 0.42, 1.68).

Whilst these findings are important, certain limitations could impact the results. Data was derived and pooled from trials of different durations with some missing data in all phases of follow up. In some of these studies, patients were not truly treatment naïve as they had been on topical treatment that was stopped for a variable period prior to undergoing SLT. With treatment success, since different definitions were used to define success, caution may need to be applied regarding the generalisability of the results.

Aim 1: To investigate the clinical efficacy of primary SLT as initial therapy in treatment naïve OAG/OHT patients

The LiGHT Study is a pragmatic, multi-centre RCT in which treatment naïve OAG/OHT patients were randomly allocated to receive either initial SLT versus

initial medical treatment, and followed up for a period of 36 months. Patients were treated to a pre-defined Target IOP based on baseline severity (see Section 3: Methods). LiGHT utilised a novel computerised decision support software using evidence-based objective criteria to suggest treatment escalation.

To evaluate clinical efficacy of primary SLT, we aim to assess and compare the IOP lowering effect of SLT vs. topical medication, comparing IOP reduction & percentage IOP reduction. We aim to compare ability to meet Target IOP at 36 months, rates of disease progression between the 2 treatment arms and IOP fluctuation through the course of 36 months.

Since patients in both treatment arms were treated to predefined target IOP using the same treatment escalation criteria, we aim to investigate whether there was a difference in 'treatment intensity' over the course of 36 months. This will be evaluated by comparing the cumulative number of clinical visits between treatment arms, the number of treatment escalations required to maintain IOP control over 36 months in both arms and the intensity of surgical treatment by comparing rates of cataract & IOP lowering surgery.

Question 2: Are there predictors of success for primary SLT in treatment naïve OAG/OHT patients?

SLT is not successful in all treated eyes. Several studies have analysed baseline patient factors that may predict success, frequently by performing univariate and multivariate regression analyses to look for associations. Predictors of success comparisons between studies is often difficult since multiple variations exist

within studies including size of study, patient demographics, glaucoma subtype treated, SLT treatment parameters, length of follow up and indeed the definition of 'success' itself. This creates difficulty in establishing 'definite' robust predictors of SLT success and is reflected in the literature on this topic, where multiple studies have contradictory results to one another (see Section 2.2.22).

Aim 2: To investigate 'predictors of success' of primary SLT in treatment naïve OAG/OHT patients

We aim to perform a predictors of success analysis for primary SLT in this trial. Unlike previous studies, we have one of the largest cohorts of treatment naïve OAG/OHT patients receiving primary SLT. In addition, patients are treated to pre-defined Target IOPs based on baseline disease severity.

Question 3: What is the repeatability of SLT when used as a primary treatment in treatment naïve OAG/OHT patients?

The IOP lowering effect of SLT diminishes with time. Since SLT has been shown to cause minimal structural damage to the TM, repeat treatment has been considered a feasible option in suitable patients who require further IOP reduction. There have been only a few studies that have investigated the repeatability of SLT but these have been small studies, with retrospective collected data and no clear pre-defined retreatment criteria. In addition, most have been studies in patients already on maximum topical medical therapy where SLT was used as an adjunct to medical treatment (see Section 2.2.16).

Aim 3: To investigate repeatability of primary SLT in treatment naïve OAG/OHT patients

We aim to assess the repeatability of SLT when used as a primary treatment in truly treatment naïve OAG/OHT patients. In this trial, data has been prospectively collected with pre-defined escalation criteria for SLT retreatment. In addition, SLT treatment settings/parameters are also pre-defined giving consistency which is lacking in previous studies.

Question 4: Is SLT safe and well tolerated when used as a primary treatment to lower IOP in treatment naïve OAG/OHT patients?

SLT is known to be a relatively safe procedure which is well-tolerated with low complication rates (235). Most of the complications associated with SLT are transient and self-limiting.

Aim 4: To investigate the safety & tolerability of primary SLT as initial therapy in treatment naïve OAG/OHT patients

By further reporting the adverse events associated with SLT in the LiGHT study at 36 months, we will add to the safety evidence of SLT. This could help to inform whether SLT is a safe alternative to topical medication as a primary treatment. Furthermore, we aim to collate the adverse events profile of the primary medication arm at 36 months to make comparisons on whether there is a difference in the reported ocular and systemic side effects between the 2 treatment arms.

Question 5: Is there a difference in glaucoma specific HRQL patient reported outcome measures between primary SLT and primary medication treatment?

Greater emphasis on patient-centred care in glaucoma has led to the increasing utilisation of patient reported outcome measures (PROMs) in glaucoma research (260, 262, 278). PROMS are a series of standardised and validated questions that are self-reported by patients to assess their own perspective on the impact of the disease and treatment on their health status, quality of life and functioning (279). This information is important to clinicians as it provides feedback on the care provided and can also be used to assess patient judged effectiveness of different treatments.

In LiGHT, the primary outcome is measuring difference in HRQL measured using the EQ-5D questionnaire at 36 months between the two treatment arms. The EQ-5D is a standardised measure of health status, applicable to a wide range of health conditions and treatments. Its name means 'EuroQol- 5 Dimensions - 5 Levels'. It comprises five dimensions of health: mobility, ability to provide self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression.

In addition to the EQ-5D questionnaire being completed during LiGHT, glaucoma specific HRQL patient reported outcome measure (PROMs) will also be completed by both treatment arms. Since these are purported to be 'more' disease specific, we will be able to measure patient reported outcome measures which are glaucoma specific between the two treatment arms and investigate whether there are differences between the two treatment groups at 36 months.

Aim 5: To investigate changes in glaucoma specific HRQL patient reported outcome measures between Primary SLT & Primary medication groups

We aim to analyse the glaucoma specific HRQL patient reported outcome scores of the Glaucoma Utility Index (GUI), Glaucoma Symptom Scale (GSS) and Glaucoma Quality of Life-15 (GQL-15) questionnaires completed by patients in both treatment arms and investigate whether any differences exist at 36 months.

Section 3: Methodology

From March 2017 till March 2019, I worked as a Clinical Research Fellow under the supervision of Professor Gus Gazzard, Chief Investigator (CI) of the LiGHT trial. I worked as part of a research team (3 research optometrists and 1 trial manager) at the largest trial site and coordinating centre located at Moorfields Eye Hospital.

During my tenure, I ran research clinics to review LiGHT trial patients attending for clinical assessment as part of their ongoing follow up. I prepared patients for treatment interventions such as SLT and also performed post-treatment evaluation of patients that underwent laser or surgery (cataract surgery and/or glaucoma surgery – trabeculectomy or tube surgery).

In addition to patient data acquisition, I was also involved in trial data management. This comprised clinical data entry into the online database (Sealed Envelope) and data monitoring of patient quality of life and clinical data gathered at other trial sites. Regular visits were made to these sites, to check patient notes and ensure that the trial processes outlined in the LiGHT protocol were being adhered to.

At the end of the 36-month trial period, I was involved in data cleaning of the clinical patient data. Clinical data was downloaded from the online database onto a statistical software programme and checked for outliers, missing data and inconsistencies. These were reported back to the relevant sites and any data errors were corrected prior to analysis.

I was subsequently involved in analysis of the clinical outcomes for the main trial and the further analyses performed as part of this thesis. For the pre-specified clinical analyses of the LiGHT trial, the statistical analysis plan was implemented (280). For the further clinical analyses performed as part of this thesis, an additional statistical plan was drafted in advance of the analyses, which was approved by the Chief Investigator and statistical team prior to implementation (see Appendix).

For data analysis, an integrated dataset of clinical and quality of life data was assembled using statistical analysis software. This was then used to calculate the clinical endpoints outlined in the trial and the additional analyses performed as part of this thesis. During data cleaning and data analysis, I worked closely alongside the lead trial optometrist (Neil Nathwani) and key member of the LiGHT trial statistical team (Dr Victoria Vickerstaff), who led the statistical analysis of the trial primary outcome (EQ5D analysis).

In the next section, we present the methodology from LiGHT relevant to the outcomes investigated in this thesis. The full methodology protocol of LiGHT is available for further reference (281).

3.1 Study Design

The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial was designed to assess the difference in HRQL, cost- and clinical-efficacy between two initial treatments for OAG and OHT.

The study was a pragmatic, multicentre, randomised clinical trial, unmasked to treatment allocation with two treatment arms – initial SLT followed by routine medical treatment (Laser 1st) vs routine medical treatment only (Medicine 1st).

Patients were randomised (1:1 ratio) to receive either SLT (Laser-1st) or medical therapy (Medicine-1st) as first line treatment. The study adhered to the tenets of the Declaration of Helsinki. Ethical approval was granted by the City Road and Hampstead Research and Ethics Committee (former Moorfields and Whittington Research Ethics Committee then East Central London REC, reference number: 12/LO/0940) on June 20th 2012.

The LiGHT trial is registered at www.controlled-trials.com (registration number ISRCTN32038223) and the full protocol can be accessed at: http://www.moorfields.nhs.uk/sites/default/files/LiGHT%20Trial%20Protocol%203.0%20-%2020-5-2015_3.pdf.

3.2 Inclusion criteria

The LiGHT Trial aimed to recruit patients with newly diagnosed OAG or OHT in one or both eyes from 6 collaborating specialist glaucoma clinics at large ophthalmic centres in the UK. Patients were required to have newly diagnosed OAG or OHT in one or both eyes, needing treatment.

We used NICE recommended thresholds for starting treatment (282), with stringent definitions of disease (OAG or OHT) for study entry eligibility.

Primary Open Angle Glaucoma was defined as:

- Open drainage angle [no irido-trabecular contact on non-indentation gonioscopy in primary position, TM visible over 360 degrees], with no secondary causes (such as trauma)

and

1) Reproducible glaucomatous VF defects as tested by the SITA 'Standard' algorithm on the Humphrey Visual Field Analyser (HVF) (i.e. reproducible defect, in at least, of two or more contiguous points with $P < 0.01$ loss or greater, or three or more contiguous points with $P<0.05$ loss or greater, or abnormal Glaucoma Hemifield Test, GHT);

or

2) Glaucomatous optic neuropathy (GON) with localised absence of the neuro-retinal rim or, cup disc ratio of 0.7 or more, or asymmetry of cup disc ratio of 0.2 or more in similar sized eyes / optic discs.

and

- Deemed to require treatment in the opinion of the treating (fellowship-trained) glaucoma specialist.

Subjects with pseudo-exfoliation were eligible (as for the EMGT study) (46). Subjects with GON and IOP in the normal range were also eligible.

OHT was defined as:

- IOP above 21 mmHg (requiring treatment as per NICE guidelines) with no evidence of glaucomatous optic neuropathy on disc assessment and no evidence of glaucomatous visual field loss on visual field testing.

Additionally, the following were required:

1. A decision to treat made by a Consultant Glaucoma Specialist
2. Age over 18 years and able to provide informed consent
3. Able to complete QoL, disease-specific symptom and cost questionnaires in English (physical help with completion and assistance with reading was be permitted as long as an interpreter was not required)
4. An ability to perform a VF test in the study eye(s) with <15% false positives. This is because VF tests with >15% false positives would not be able to be used for Guided Progression Analysis (GPA) as deemed 'excessive false positives' and would automatically be excluded by GPA software (*taken from Humphry Field Analyser Manual)* .

3.3 Exclusion criteria

Patients were not considered for the study if there was:

1. Advanced glaucoma in the potentially eligible eye: VF loss mean deviation worse than -12dB in the better or -15dB in the worse eye
2. Secondary glaucoma (e.g. pigment dispersion syndrome, rubeosis, trauma etc) or any angle closure

3. Any contra-indication to SLT (e.g. unable to sit at the laser-mounted slit-lamp; past history of or active uveitis, neovascular glaucoma, inadequate visualisation of TM)

4. Inability to use topical medical therapy due to e.g. physical infirmity and a lack of carers able to administer daily eye-drops

5. Previous treatment for OAG or OHT

6. Congenital or early childhood glaucoma

7. Visually significant cataract in symptomatic patients who wanted to undergo cataract surgery

8. Any current, active treatment for another ophthalmic condition in the Hospital Eye Service (HES) (this applied to both eyes, even if one was not in the trial, as the fellow eye might affect the patient's visit frequency)

9. Any history of retinal ischaemia, macular oedema or diabetic retinopathy

10. Age-related macular degeneration (AMD) with neovascularisation in either eye or geographic atrophy and VA worse than 6/36 in a study eye

11. Visual acuity worse than 6/36 in a study eye. Non-progressive visual loss better than 6/36 due to any comorbidity was permitted provided that it did not affect response to treatment or later surgical choices and was not under active follow-up (e.g. an old, isolated retinal scar no longer under review or amblyopia)

12. Any previous intra-ocular surgery, except uncomplicated phacoemulsification at least one year before (this applied to both eyes, even if one was not in the trial, as it could affect the required treatment intensity for any glaucoma in the fellow eye)

13. Pregnancy at the time of recruitment or intention to become pregnant within the duration of the trial

14. Medical unsuitability for completion of the trial – e.g. suffering from a terminal illness or too unwell to be able to attend hospital clinic visits

15. Recent involvement in another interventional research study (within 3 months)

3.4 Recruitment

Patients attending the HES for the first treatment of OAG/OHT were assessed for eligibility before treatment and, if eligible, were informed of the study by the local Trial Coordinator (along with written information).

3.5 Randomisation and masking

Following completion of all baseline assessments, eligible patients were randomised to one of two treatment groups: SLT (Laser-1st) or topical medical therapy (Medicine-1st). Randomisation was conducted using a web-based randomisation service, achieving full allocation concealment.

Stratified randomisation with random block sizes was used to randomise in a 1:1 ratio at the level of the patient, with the stratification factors of diagnosis (OHT/OAG) and treatment centre. Due to the pragmatic design of this trial the patients and clinicians were unmasked to the treatment arm; all clinical measures (IOP, VF, HRT), however, were done by masked observers and treatment decisions

were masked by the use of a computerised evidence-based decision support algorithm.

3.6 Baseline Assessment

At the baseline assessment, participants underwent visual acuity testing, slit-lamp examination, automated VF testing (Humphrey Field Analyser Mark II and the Swedish Interactive threshold algorithm standard 24-2 programme), HRT optic disc imaging, IOP measurement, gonioscopy, CCT measurement, assessment of the optic discs, maculae and fundi.

The patients also filled in the following baseline questionnaires: EQ-5D 5 level (EQ-5D) (283) Glaucoma Utility Index (GUI) (284), Glaucoma Symptom Scale (GSS) (285), Glaucoma Quality of Life – 15 (GQL-15; a visual function, rather than quality of life, measure)(286) and a modified version of the 'Client Service Receipt Inventory' (CSRI) questionnaire (287).

3.7 Disease stratification and initiation of treatment

Patients' clinical evaluation and test outcomes were entered into the clinical decision algorithm and a disease category and stage were determined. The algorithm used severity criteria from the Canadian Target IOP Workshop (288) with central field loss severity criteria defined according to Mills et al. 2006(289) (see Table 3). Severity stratification determined the follow-up frequency.

Severity	Definition for Treatment Target IOP				
	Optic Nerve		**VF MD**		**Central (10º) Scotoma on VF**
OHT	Healthy		Any		No GON related VFL
Mild OAG	GON	**+**	> -6dB	**+**	None
Moderate OAG	GON	**+**	-6dB < & > -12dB	**or**	At least 1 central 5º point <15dB but none <0dB & only 1 hemifield with central point <15dB
Severe OAG	GON	**+**	< -12dB	**or**	Any central 5º point with sensitivity <0dB Both hemifields contain point(s) <15dB within 5º of fixation

Table 3: Severity criteria for setting Treatment Target IOP from the "Canadian Target IOP Workshop" (with central field criteria defined according to Mills et al). VF MD: Visual field mean deviation GON: Glaucoma optic neuropathy

3.8 Computerised decision algorithm

The follow-up and treatment escalation protocols were enabled by a custom-written clinical decision support software which permitted real-time decision making based on the analysis of multiple clinical measures including HRT optic disc analysis, visual field assessment and IOP measurements. Pre-defined objective indicators of either disc or field deterioration (change in mean neuro-retinal rim area, as provided by the HRT, or Glaucoma Progression Analysis (GPA) VF analysis) or IOP above target triggered earlier follow-up and/or increased treatment intensity.

3.9 Setting individual target IOP

Once the decision to treat was made, a target IOP was set. The target IOP was eye specific and was objectively defined and adjusted by the computerised decision algorithm to avoid bias from unmasked treating clinicians. The lowest permitted target was 8 mmHg for OAG and 18 mmHg for OHT. Although CCT has an effect on IOP measurement and risk of progression, the true magnitude of this interaction is unknown because of complex non-linear interactions between CCT, 'true' IOP and corneal material properties; CCT was, therefore, not used in the algorithm for setting Target IOP. Myopia and family history were also not included in this algorithm, as data on the effect size of these risk factors on progression rates are weak. The target IOP was either an absolute reduction to below a specified level or a percentage reduction from baseline, whichever was lower. The process of setting the IOP target is shown in Figure 4. Greater reductions are required for greater disease severity as defined by Canadian Glaucoma Study criteria (48)

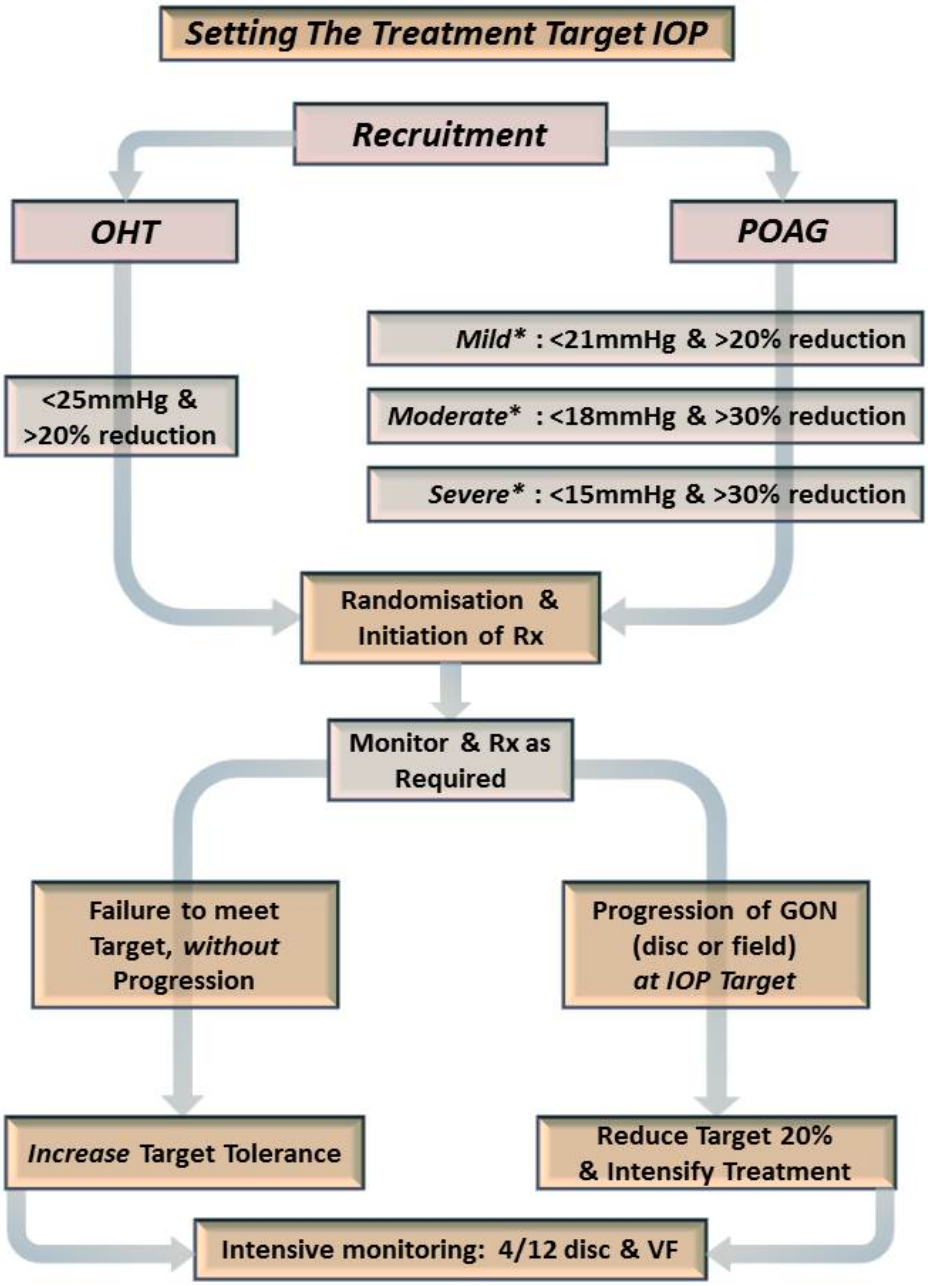


Figure 4: Process for target IOP setting. *Disease stratification according to Mills et al. 2006. IOP: Intra-ocular pressure, OHT: Ocular Hypertension, POAG: Primary Open Angle Glaucoma, GON: Glaucoma Optic Neuropathy, VF: Visual Field. Taken with permission from LiGHT Trial Protocol.

3.10 Failure to meet target IOP and target IOP re-evaluation

Diurnal fluctuation and measurement error can both lead to variation in measured IOP. To prevent an inappropriate escalation to more intensive treatment it was therefore important to repeat measurements that deviate only slightly from target IOP. Criteria for failure to meet, and to reassess, target IOP follow those of the Canadian Glaucoma Study taking into account that variation in IOP measurement may vary by as much as +/-4 mmHg (290).

a) If an eye was ≥2 mmHg but <4 mmHg above target IOP for 2 consecutive visits and showed possible or definite progression then the treatment was intensified and the target IOP remained unchanged

b) If an eye was ≥ 2mmHg and < 4mmHg above target IOP for 2 consecutive visits and showed no progression (with a minimum of 3 post baseline follow-up fields required to confirm progression, as per EMGT) then the target was adjusted upward. In this case the target IOP was revised to the mean of the previous 3 visits, where progression did not occur. If fewer than 3 follow-up VFs had been done, additional visits were required to confirm stability before the target IOP was relaxed

c) If an eye was ≥4 mmHg from target IOP at any visit then the eye was considered to have failed to reach target IOP and had advanced to the next level of treatment intensity (unless already on MMT), irrespective of any progression, unless the clinician identified poor concordance with treatment. The target IOP remained unchanged. In the presence of poor concordance and the absence of progression additional measures to improve concordance before escalation of treatment were permitted, as in usual clinical practice

d) If an eye on MMT was ≥2mmHg from target IOP and showed definite progression then glaucoma drainage surgery was offered to the patient

e) If an eye on MMT was ≥2 mmHg from target IOP and showed possible progression then the follow-up frequency was increased until progression was either confirmed or ruled out

f) If an eye was ≥2 mmHg from target IOP and on MMT and showed no progression (with at least 3 follow-up VFs) then the target IOP was adjusted (revised upwards to the mean of the previous 3 visits) with an increase in follow-up frequency. If fewer than 3 follow-up VFs had been done, additional visits were required to confirm stability

g) A patient with an eye with IOP above maximal IOP may have been offered surgery without progression at the discretion of the treating surgeon

h) If there was progression and IOP was at target IOP then the target IOP was reduced by 20%, according to the Canadian Glaucoma Study protocol (291) with a lower limit of 8 mmHg, and treatment intensified accordingly.

Failure to meet target can be due to poor compliance as well as a lack of drug efficacy. As in normal practice, compliance was discussed and patients counselled at each visit. Patients were given standard written information from the International Glaucoma Association (IGA), face to face instruction in drop administration and the offer of further nurse-led support.

Where poor compliance was thought to be the contributing factor, then education with written information and repeated face to face instruction in drop administration was given. If the decision was made to educate rather than

escalate a patient who was not at target IOP, then the reason for an algorithm over-ride was recorded ('non-compliance') and the patient recalled after 8 weeks for a repeat IOP check visit.

3.11 Treatment escalation

To minimise bias for escalating treatment, standardised criteria for any additional intervention were used according to a protocol following international guidelines by the EGS (292) American Academy of Ophthalmology Preferred Practice Pattern(293) and the South-East Asia Glaucoma Interest Group (294).

Treatment was escalated under the following circumstances:

1. 'Strong Evidence' of progression irrespective of IOP
2. IOP above target IOP by more than 4 mmHg at a single visit (irrespective of evidence for progression)
3. IOP above target IOP by ≥ 2mmHg and less than 4 mmHg for 2 consecutive visits and 'Less Strong Evidence' for progression (see below 'Defining progression'). If the IOP was above target IOP by less 4 mmHg with no evidence for progression, then the target IOP was re-evaluated

The process for escalating treatment is shown in Figure 5 and Figure 6.

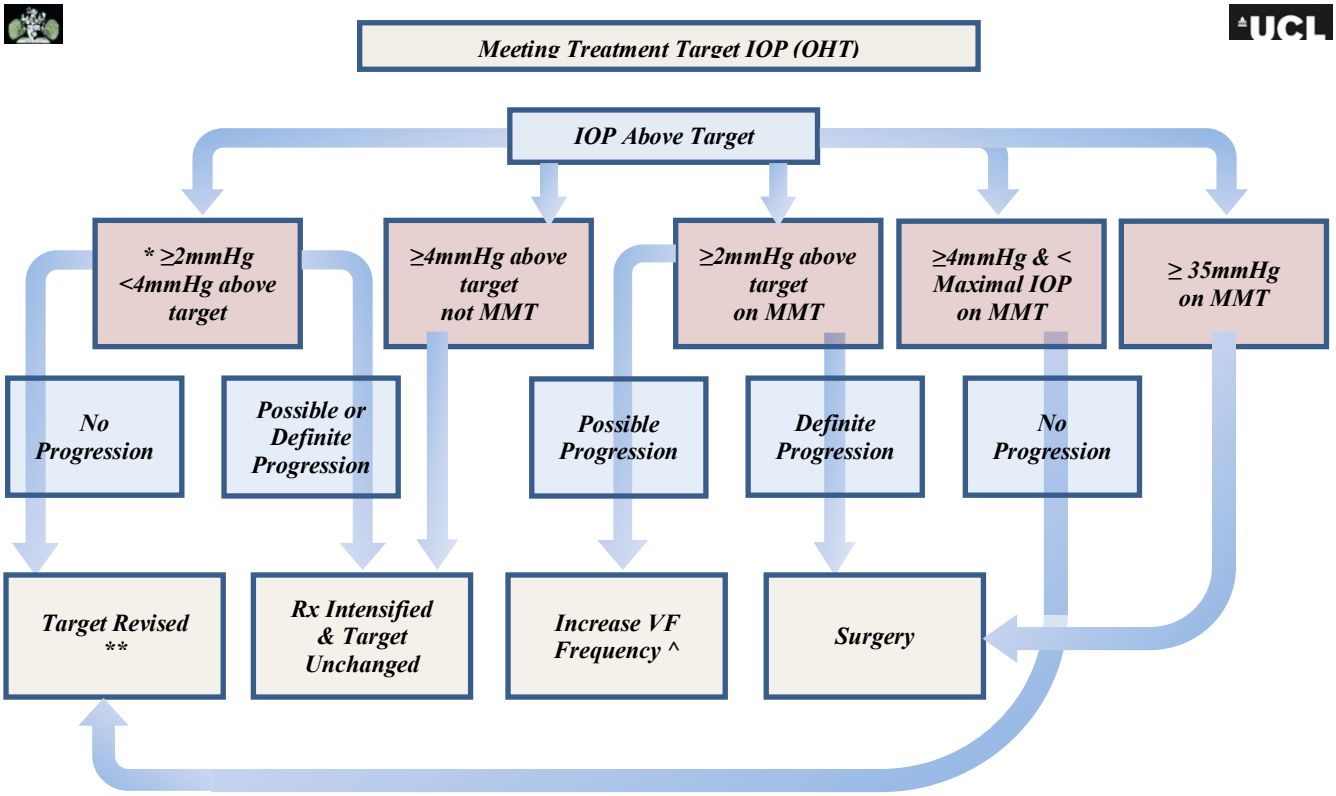


Figure 5: Process for escalating treatment in OHT. *On 2 consecutive visits. ** As per protocol. ^ Until progression confirmed/refuted. VF progression required 3 follow-up VF assessments. Maximal IOP: IOP above which surgery was offered even without progression or 35 mmHg for OHT, see text. IOP: Intra-ocular Pressure, MMT: Maximum Medical Therapy, VF: Visual Field. Taken with permission from LiGHT Trial Protocol.

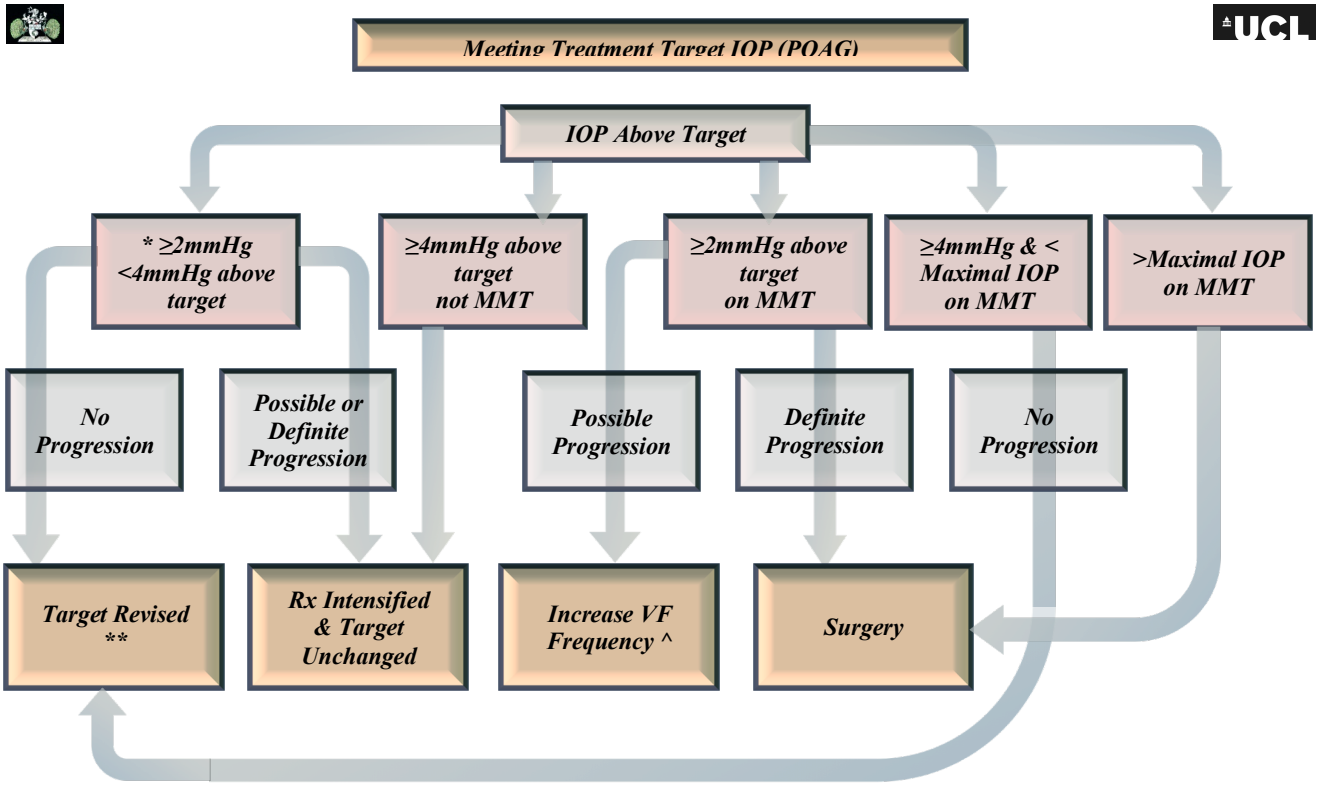


Figure 6: Process for escalating treatment in OAG. *On 2 consecutive visits. ** As per protocol. ^ Until progression confirmed/refuted. VF progression required 3 follow-up VF assessments. Maximal IOP: IOP above which surgery was offered even without progression or 35 mmHg for OHT, see text. IOP: Intra-ocular Pressure, MMT: Maximum Medical Therapy, VF: Visual Field. Taken with permission from LiGHT Trial Protocol.

More stringent criteria were applied before undergoing surgery than laser or medical treatment. This reflected the greater risk to vision from surgical complications. Strong evidence of progression +/- failure to meet target IOP was usually required in all but the most severe disease.

However, extreme elevations of IOP could have required surgery without progression, with lower thresholds in more damaged eyes. Any patient who was at, or above maximal IOP had their case reviewed (in person or remotely) by the PI for this decision to be made. In accordance with patient-centred care, the decision to operate was always a collaboration between clinician and patient. When an IOP lowering surgical intervention was indicated, cataract surgery was

permitted (in the presence of cataract, i.e. not clear lens extraction) when this was the consultant's usual practice.

3.12 Defining progression

Glaucoma progression

Glaucoma progression was detected using a combination of VF and HRT data. Progression of glaucoma was defined as:

- 'Strong evidence': GPA 'Likely progression' and/or HRT rim area >1% per year ($p < 0.001$)
- 'Less strong evidence' = GPA 'Possible progression' and/or HRT rim area >1% per year ($p < 0.01$)

Visual field progression

Worsening of VF loss was defined as 'Likely' or 'Possible', in the absence of any identifiable retinal or neurological cause. The 'minimum dataset' to determine VF progression was 2 reliable baseline VF measurements followed by 3 follow-up VF. Visual field series were independently assessed for progression using the automated algorithm software at each visit.

- 'Likely VF Progression' was 3 points or more on the HVF GPA software at <0.05 probability for change on 3 consecutive occasions.

- 'Possible VF Progression' was 3 points or more on HVF GPA software at p <0.05 probability for change on 2 consecutive occasions.

Standard GPA criteria weights central and peripheral field locations equally, whereas in clinical practice, there is usually a lower threshold for central field loss. Thus, if any of the 4 para-central points showed a triangle then the algorithm would recommend treatment escalation, when 2 GPA triangles (rather than 3) indicated deterioration on 2 or more consecutive occasions (rather than 3), with the second triangle being any point that is contiguous with the affected central one (thus including the other central 3 but also the neighbouring less central points). Any treatment escalation triggered by worsening visual field loss required senior clinician verification to exclude retinal or neurological cause.

Optic disc progression

Worsening of disc damage was defined as a rate of neuro-retinal rim loss exceeding 1% of baseline rim area/year on a minimum of 5 repeat HRT images. This slope value was selected as approximately double that of age-related rim area loss (295) and gave a similar specificity to VF trend analyses. If the treating clinician suspected disc progression in the absence of HRT deterioration and or change in GPA (e.g. due to focal NRR notching) then the HRT images were reviewed (masked to treatment allocation and IOP data) by the TMG.

Resetting of Visual Field and Optic Disc Baselines

If treatment was escalated because of progressive glaucomatous damage as detected by either visual field or optic disc change then the 'baseline' against which future tests were compared was reset. The measurements taken on the visit at which treatment changes were instigated became the new baseline. Escalation due to failure to reach IOP target *alone* did not result in any change to HVF or HRT baselines.

Unreliable or Unavailable VF & HRT – dealing with missing data

If HRT data was unreliable (MPHSD high) or VF data was unreliable (False Positives > 15%), the algorithm dealt with that internally and discounted that data. However, in majority of patients, a repeat VF or HRT was attempted up to 3 times where clinically indicated, on the same or a separate visit within a month if deemed clinically appropriate/necessary. If assessments generated consistently poor quality data, the investigation could then be abandoned for future visits at the discretion of the treating clinician.

If disc HRT or VF was unable to be obtained (e.g. patients refused, were unwell or unreliable, or the machine was broken), the algorithm would then ignore HRT for that visit. If no VF was available (despite repeat VF), other data was used to determine treatment escalation (i.e. IOP with respect to target IOP and HRT if available).

Algorithm override

In the following cases the algorithm was overridden by the treating consultant:

- Where poor concordance was thought to be the contributing factor to failure to meet IOP target and was followed by patient education and a recall 8 weeks afterwards for an IOP check

- When it was felt that it was in the patient's best interest to override the algorithm's decision to either revise the target IOP (upwards or downwards) or to escalate treatment

  The reason for the override was recorded.

3.13 Follow-up procedure

Follow-up intervals were set at entry to the study, based on disease severity and lifetime risk of loss of vision, according to NICE guidance (296) and subsequently adjusted on the basis of IOP control, disease progression or adverse reactions. Disease stability, along with all available data, was taken into consideration, but testing for progression did not independently determine follow-up intervals. The routine schedule of appointments for patients who remained at or below target IOP without progression or treatment change and had no adverse reactions requiring earlier assessment is shown in Table 4. Additional VF tests were permissible at any visit, if clinically necessary to confirm possible progression. Variation in follow-up intervals was permitted to accommodate clinician's judgment and/or patient choice.

Disease Severity Category		**Routine follow-up intervals in months**						
	1st visit	2nd visit**	3rd	4th	5th	6th	7th	8th...
OHT	Randomisation & treatment	2	4	6	12	12	12	12 ...
Mild OAG		2	4	6	6	12	12	12 ...
Moderate OAG		2	4	6	6	6	6	6 ...
Severe OAG		1-2	4	6	6	6	6	6 ...

Table 4: Routine follow-up frequency for patients who remain at Target without progression or treatment change and have no adverse effects requiring earlier assessment. ** All patients are seen 2 months after randomisation and initial treatment. Patients treated with SLT are also seen 2 weeks post treatment for an IOP check (not shown in this Table). IOP: intra-ocular pressure, SLT: selective laser trabeculoplasty, OHT: Ocular Hypertension, OAG: Open Angle Glaucoma. Taken with permission from LiGHT Trial Protocol.

After SLT application the Laser-1st group were reviewed at 2 weeks and 8 weeks post-laser. Thereafter, and for all treatment changes in the Medicine-1st group,

the patients were reviewed at 2 months, followed by either treatment change (with consequent early assessment of response to 2nd Treatment) *or* entry into disease severity-tailored routine follow-up schedule. For Severe OAG the follow-up was at the discretion of the consultant ophthalmologist. If an eye showed 'possible progression' then the follow-up frequency was intensified to every 3-4 months, until progression was confirmed or ruled out with additional VF/HRT. Additional visits for IOP check alone after treatment changes were not associated with additional tests. All contacts with medical professionals and optometrists were captured for cost data. Contact with healthcare providers were collected via a CSRI, a validated method of collecting healthcare cost data (297).

The main factor for follow-up frequency was Treatment in Pursuit of Control (TPC). Disease stability was considered using all available data, but testing for progression did not independently determine follow-up. Patients who required medication changes or additional laser, patients who suffered adverse events or showed progression of glaucoma were seen sooner and reverted to schedule when stable. The worst or more unstable of each patient's two eyes determined follow-up interval, while treatment was individualised to the needs of each eye.

3.14 Follow-up clinical assessments

The schedule of assessments (all assessments were part of routine care) is shown in Table 5. After the full baseline assessment all patients underwent VF and HRT to assess progression at each follow-up visit. EQ-5D and other HRQL questionnaires were assessed at baseline and 6 monthly thereafter.

Investigation	Time of Follow Up*							
	Baseline	**1st Check***	**3rd visit (6 months)**	**1st year**	**18 months**	**2nd year**	**Patient Specific**	**3rd year**
Clinical Exam (incl. disc & IOP)	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
Dilated Fundus Examination	*Yes*	-	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
Gonioscopy	*Yes*	-	-	*Yes*	-	*Yes*	*Yes*	*Yes*
Visual Field Test	*Yes*	-	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
Optic Nerve Imaging (HRT)	*Yes*	-	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
EQ-5D	*Yes*	-	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
GUI	*Yes*	-	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
GSS	*Yes*	-	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
CSRI**	*Yes*	-	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*

Table 5: Schedule of assessments and questionnaires for the baseline and follow-up visits for patients who remain at Target without progression or treatment change and have no adverse effects requiring earlier assessment. Additional VF tests are permissible at any visit, if clinically necessary to confirm possible progression. Variation in follow-up intervals is permitted to accommodate clinician's judgment and/or patient choice. *1st follow-up visit will be at 2 weeks following SLT, followed by a visit at 2 months. 1st follow-up visit for the medication 1st pathway will be at 2 months. **modified CSRI questionnaire. HRT: Heidelberg Retinal Tomography, GUI: Glaucoma Utility Index, GSS: Glaucoma Symptom Scale, CSRI: Client Service Receipt Inventory.

3.15 Treatment Arms

Laser 1st pathway

SLT was delivered to 360º of the TM, with a 360° retreatment permitted as the first escalation of treatment, if required.

To ensure consistency of SLT treatment and to minimise variation between clinicians, standardisation was attempted by specifying a stringent protocol defining laser settings and technique including the range of acceptable powers. Pretreatment with Iopidine (0.5% or 1%) at least 15 minutes before laser was mandatory, unless contra-indicated for medical reasons when alternative medications such as oral acetazolamide could have been used. If no prophylaxis against IOP spikes was used close post-treatment monitoring of IOP for 2 hours was necessary.

One hundred non-overlapping shots (25 per quadrant) of a preset 3 nanoseconds duration and a preset 400μm spot size were used, with the laser energy varied from 0.3 to 1.4mJ by the clinician using any laser gonioscopy lens (as long as the appropriate magnification was observed. The desired end-point was the production of a few fine "champagne bubbles" at least 50% of the time. Pigmented TM would have required lower energy (from 0.3mJ to 1.2mJ) than non-pigmented TM. IOP was measured 60 minutes post treatment.

After SLT, patients were not instructed to use anti-inflammatory eye-drops routinely, but were provided with a bottle of topical non-steroidal anti-

inflammatory eye-drops for use only if they developed significant discomfort, despite simple oral analgesia such as paracetamol.

Any rise of IOP >10mmHg or that puts the patient at risk of visual loss was treated at the discretion of the treating clinician with an earlier recheck of IOP (e.g. at 2 hours, 1 day or 1 week) and/or a short-term course of topical or systemic aqueous suppressants as necessary. An IOP rise needing medical treatment or an extra visit alone would constitute an adverse event.

As described previously, first review following SLT was at 2 weeks for IOP check and assessment of potential side-effects. No re-intervention or treatment escalation decisions for non-response were made at this point; a further follow-up 6 weeks later was to allow time for the full effects of laser to occur. Patients at target IOP eight weeks after SLT were subsequently reviewed as per the interval determined by the severity category. Patients not at target IOP after a single SLT received another SLT treatment with re-evaluation after 2 weeks. After retreatment, a 6 week follow-up was given unless a dangerously high IOP posed a significant risk to vision in the opinion of the treating clinician, in which case earlier follow-up was allowed to avoid an unsafe delay in medical therapy.

If it was felt by the treating clinician that repeat SLT would not be safe (e.g. IOP spike following initial SLT), topical medication was started rather than repeating the SLT. Any immediate IOP rise above 40 mmHg despite pre-treatment iopidine or any rise of over 5 mmHg that persisted 8 weeks after laser would usually prevent further SLT treatment.

All treating clinicians were given training before recruitment. After two SLT treatments the Laser-1st pathway embarked on medical treatment and followed the Medicine-1st algorithms. If the participant subsequently underwent drainage surgery which failed during the course of the trial, the step-wise medical intervention algorithm began again with further SLT not being permitted.

Significant complications of laser treatment, if they occurred (e.g. corneal oedema, intra-ocular haemorrhage, severe uveitis, IOP spike greater than 15 mmHg, peripheral anterior synechiae), prevented a second treatment with SLT. Other new medical conditions (such as a new history of uveitis or rubeosis) also prevented repeat SLT.

Medicine 1st pathway

Topical medical treatment of glaucoma can involve several steps and potential treatment pathways due to the number of medications (available as a single drop or in combination with other medication in a single drop), number of medications (& thus drops) permitted by a treating protocol or tolerated by the patient ('maximum medical therapy') and rules for switching between or adding medications (& thus drops).

International best practice guidelines advocate changing medication if the target is not reached, with the addition or switching of medication (based on the magnitude of initial response) (292-294).

Choice of agent

No mainstream medications were prohibited, but drugs classes for 1st, 2nd, or 3rd line treatment were defined as per NICE and European Glaucoma Society (EGS) guidance

- 1st line: Prostaglandin analogue (PGA)
- 2nd line: Beta blocker (once in the morning or in a PGA combination)
- 3rd or 4th line: Topical carbonic anhydrase inhibitor (CAI) or alpha-agonist

Systemic CAIs were only permitted as a temporising measure while awaiting surgery and did not influence treatment escalation. Pilocarpine was not an accepted medication for OAG.

Adding/switching medication

The incremental escalation of treatment protocol defined stepwise increases in treatment. Patients were switched if the pre- and post- treatment IOP difference was no greater than measurement error. If there was a greater reduction but the eye was still not at target then the next medication was added. Progression of glaucoma optic neuropathy when at target IOP also triggered a stepwise increase of treatment and a lowering of the target.

Maximum Medical Therapy (MMT)

MMT was the most intensive combination of drops a given individual could reasonably, reliably and safely use. MMT varied between patients depending on co-morbidities, side effects and patient-specific compliance factors. NICE recommends offering surgery after only two drugs have failed to control IOP. In LiGHT, treatment with multiple different medications was limited and MMT was defined

in terms of the maximum number of drops (3 ‘drops’ – note – could contain up to 5 medications) and instillations per day (5 instillations). MMT was often less, due to drug intolerance, contra-indications and patient factors.

3.16 Questionnaires

The content of the questionnaires was determined by the use of a number of validated, widely accepted existing questionnaires:

- Euro-Qol 5D (EQ-5D)
- Glaucoma Utility Index (GUI)
- Glaucoma Symptom Score (GSS)
- Glaucoma Quality of Life 15 (GQL-15)

The EQ-5D questionnaire was chosen as the main quality of life outcome measure, as this was a stipulation from the study funding body, the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) Programme. It is validated and has been used to assess HRQL in studies across multiple medical specialties as well as being used in cost-effectiveness analyses (a secondary outcome of the LiGHT trial).

The remaining questionnaires were glaucoma specific. The GUI aimed to assess glaucoma specific treatment related quality of life. The GSS aimed to assess patient reported disease and treatment symptoms. The GQL-15 aimed to assess patient reported visual function.

Additionally, a modified CSRI was used and two questions regarding concordance.

3.17 Questionnaire delivery and follow-up

The Baseline questionnaires were self-administered, in a private room, at the time of enrolment, after informed consent had been given but before randomisation. Subsequent questionnaires were sent out by post for self-completion at 6 monthly intervals.

3.18 Adverse events and serious adverse events

An adverse event (AE) was defined as an unfavourable medical occurrence in a patient that was not necessarily caused by the treatment. AEs were classified as serious (SAE) according to GCP guidelines. AEs and SAEs were reported according to standard operating procedures and GCP guidelines, to achieve standardisation across sites and between treatment arms, with an annual safety report to the Research and Ethics Committee.

3.19 Outcome Measures

As previously outlined, the primary outcome of LiGHT was to determine whether there was a difference in HRQL (using the EQ5D questionnaire) at 36 months between primary SLT compared to primary medical treatment in treatment naïve OAG and OHT patients.

Whilst clearly HRQL outcomes formed a significant part of LiGHT, the main aim of the work presented in this thesis was to use clinical data derived from the trial to address important clinical questions related to the clinical efficacy and safety of primary SLT in OAG and OHT patients.

For this reason, the clinical outcome measures pertaining to SLT are reported and discussed first, followed by the HRQL PROMs. We acknowledge that the trial and specific fundamentals (such as power calculation and sample size) were calculated in consideration of the primary outcome measure.

The clinical outcome measures chosen are a combination of those that had already been defined as part of the original trial statistical analysis plan (280), as well as additional measures which were devised and defined post hoc, as part of this thesis, having taken into consideration the trial design and existing outcome measures.

3.19.1 Pre-defined Trial Clinical Outcome Measures

These outcome measures were objective measurements of clinical pathway effectiveness for IOP lowering and visual function preservation, since the 'Treat in Pursuit of Control' design was expected to lead to a different intensity of intervention in each treatment pathway.

These included:

- The proportion of eyes achieving Target IOP after each year of treatment.
- The number of clinic visits at 12, 24 and 36 months
- Number of clinical visits at target
- The intensity of treatment used to achieve Target IOP at 12, 24 and 36 months i.e. number of eyes with: multiple SLT treatments; multiple medications; number of treatment escalations in both treatment arms
- Numbers of cataract surgery at 36 months monitored by event reporting during the trial.
- Numbers of IOP lowering surgery (trabeculectomy/ tube surgery) at 36 months monitored by event reporting during the trial
- The number of eyes with confirmed deterioration of visual field or optic disc appearance in each group at 36 months
- Objective measures of visual function (Visual acuity, HVF (Mean Deviation, Pattern Standard Deviation)
- Objective safety measures of each pathway

3.19.2 Further Clinical Outcome Measures

These were:

- Initial ("early") IOP lowering response following primary SLT
- Baseline predictors of initial IOP lowering
- Achievement of drop free 'disease control': eyes meeting target IOP without disease progression or need for additional topical medication over 36 months following primary SLT.
- Baseline predictors of eyes achieving drop free 'disease control' at 36 months following single SLT
- IOP fluctuation
- IOP lowering after initial vs repeat SLT ('Repeatability Analysis')
- Duration of effect of initial vs repeat SLT ('Repeatability Analysis')

3.19.3 Summary of Clinical Outcome Measures

The clinical outcome measures were collated into groups, since the information they would provide answered different aspects of the clinical efficacy of SLT.

IOP control

- Initial ("early") IOP lowering response following primary SLT and topical medication
- The proportion of eyes achieving Target IOP after each year of treatment.
- Number of visits at target IOP
- IOP fluctuation
- Achievement of drop free 'disease control': eyes meeting target IOP without disease progression or need for additional topical medication over 36 months following primary SLT.

Treatment intensity

- Objective measures of visual function (Visual acuity, HVF (Mean Deviation, Pattern Standard Deviation)
- The number of clinic visits at 12, 24 and 36 months
- The intensity of treatment used to achieve Target IOP at 12, 24 and 36 months i.e. number of eyes with: multiple SLT treatments; multiple medications; number of treatment escalations in both treatment arms
- Numbers of cataract surgery at 36 months monitored by event reporting during the trial.
- Numbers of IOP lowering surgery (trabeculectomy/ tube surgery) at 36 months monitored by event reporting during the trial

Disease progression

- The number of eyes with confirmed deterioration of visual field or optic disc appearance in each group at 36 months

Predictors of IOP lowering & Achievement of Disease Control

- Baseline predictors of initial IOP lowering
- Baseline predictors of eyes achieving drop free 'disease control' at 36 months following single SLT

Repeatability

- IOP lowering after initial vs repeat SLT
- Duration of effect of initial vs repeat SLT

Safety

- Objective safety measures of each pathway

3.19.4 PROMS Analyses

The main aim of the LiGHT trial was to assess differences in HRQL in patients with POAG or OHT treated with initial SLT compared to with topical medication. Quality of life analysis was thus based around comparison of HRQL outcomes between treatment arms at 36 months.

The primary HRQL outcome of LiGHT was:

- General health related quality of life using EQ5D at 36 months

Secondary HRQL outcomes of the trial were:

- Glaucoma specific treatment-related quality of life using the GUI at 36 months
- Patient reported disease and treatment related symptoms using the GSS at 36 months
- Patient reported visual function using the GQL-15 at 36 months

3.19.5 Further PROMS Analyses

Further clinical analyses of quality of life (post-hoc performed as part of this thesis) related to primary SLT were also performed.

Outcome measures of these analyses were:

- Differences in general health (EQ5D) and glaucoma specific quality of life measures in 'drop free' patients vs. patients taking topical medication at 36 months
- Differences in general health (EQ5D) and glaucoma specific quality of life measures in patients with objective evidence of disease progression vs. patients with no objective evidence of progression at 36 months

3.20 Statistical Analysis Plan

Overall, the LiGHT statistical analysis plan detailed by Vickerstaff et al (280) was followed for reporting of trial outcomes including the pre-determined clinical analyses outlined in Section 3.19.1. These clinical outcomes were secondary outcomes and statistical analyses were not planned or outlined for these measures. This was adhered to in this thesis, to maintain consistency with the original SAP. The additional clinical analyses outlined in Section 3.19.2 were conceptualised after ('post hoc') the original LiGHT SAP had been drafted as part of a separate clinical outcomes SAP (See appendix). This will explain why statistical analyses are present for certain analyses and not for others in this thesis.

3.20.1 Clinical Analyses - Introduction

All patients (eyes) were analysed in the treatment arm to which they were randomised. Statistical significance was defined as a 2-sided P value <0.05. All analyses were performed in Stata, version 15 (StataCorp, 2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

Sample size

For the clinical analyses, the unit of analysis was the 'eye'. The sample size of eyes was the available number of eyes from the number of patients recruited to the study for the primary outcome. We recognise this is a limitation, since the sample size was not calculated around detecting a difference in a pre-specified *clinical* outcome. However, the sample of eyes used in this analysis represents one of the largest samples of treatment naïve eyes receiving primary SLT or primary medical

treatment to date. It is larger than in several previous studies that have performed similar clinical analyses to date.

Time points

Clinically, the LiGHT trial aimed to match real world clinical practice. Follow up appointments were scheduled by the decision support software in 'real time' at a patient's scheduled visit, taking into account their visual field, HRT, IOP, disease severity & objective evidence of progression.

Follow up intervals and frequency were influenced by disease severity (more frequent follow up for 'moderate' and 'severe' POAG), evidence of disease progression (more frequent follow up) and treatment stability (see Table 4). There were no predefined 'set' time points at which patients (eyes) were followed up, since each patient was following an individual follow up schedule generated by the computerised decision support software, taking into account ocular disease severity, achievement of target IOP and whether there was evidence of disease progression.

This presented a challenge for aspects of the clinical analysis. Calculation of certain clinical metrics required data for specific time points during the trial (e.g. 12, 24, 36 months). As these were not pre-defined 'absolute' time points at which patients were actually seen (e.g. 12, 24, 36 months) during the trial, a method of analysis was required to address this, whilst also ensuring that available clinical data was fully utilised and recall/selection bias was minimised.

A statistical analysis plan was devised prior commencing all aspects of the clinical analyses. For pre-specified time points needed for the clinical analysis, a method to find and use the closest appointment to that absolute time point within a permitted 'bracket window' (e.g. 36 months; 1095.75 days+/- 180 days) was used. If the patient (eye) was not seen within the permitted time frame, then the eye was not included in the analysis at that time point.

The size of the 'bracket window' took into consideration multiple factors related to the trial design and methodology. Firstly, the use of a 'narrow' window (e.g. +/- 30 days) would lead to capturing less clinical data at each time point since fewer eyes would be included in the analysis. Recall bias would also potentially be an issue, since eyes with more advanced disease (e.g. 'moderate' and 'severe' POAG) and less 'stable' eyes (e.g. requiring treatment escalation) were seen more frequently (due to trial methodology mirroring 'real world' clinical practice follow up schedules) and were thus more likely to be seen if a narrower time window to the absolute time point were to be used. Eyes with early or mild disease (e.g. OHT or 'mild' POAG) that were stable on their respective treatment (laser or topical medication) were seen less frequently and were on longer follow up intervals (up to 12 months). For these eyes, if their follow up appointment was not within the narrow window of the absolute time point, they would be excluded from the analysis leading to recall/selection bias of mainly unstable, more severe eyes.

The size of the 'bracket window' had to be balanced however, since conversely, use of a very large 'bracket window' would lead to collating information from a wide timeframe into a single time point which too could be misrepresentative.

With the above considered, the following 'bracketing' criteria were devised and agreed upon by the chief investigator and analysis team to be used for the clinical analyses. These criteria maximised data capture for all available eyes (taking into account follow up intervals of all eyes) whilst ensuring the same clinical data was not used for multiple time points. The same criteria were used for both treatment arms.

Clinical Time Point	Absolute time from Baseline Visit + 'Bracket Window' (days)
12 months	365.25 days +/- 180 days
24 months	730.5 days +/- 180 days
36 months	1095.75 +/- 180 days

Table 6: Bracketing criteria used to define time points at 12, 24, 36 months.

Cross sectional vs. Longitudinal Metrics

Certain clinical indices were cumulative metrics collated at the end of the 36-month trial period (e.g. total number of clinical visits, total number of treatment escalations, number of surgeries) and for these, an absolute cut-off of 36 months (1095.75 days) was used in both treatment arms.

Other clinical metrics (e.g. number of eyes at target following single SLT, repeat SLT vs. single medication, multiple medication) which provided information at certain points during the trial (e.g. at 12 months, 24 months, 36 months) required a 'cross-sectional' analysis at that specific time point. For this, the bracketing criteria (Table 6) were used in both treatment arms.

As explained previously, the above was a consequence of the pragmatic nature of the trial, where there were no 'set' absolute time points at which patients (eyes) were seen. For data analysis and presentation of results at required pre-specified

time points (12, 24, 36 months), this was agreed amongst the study team as the best means of obtaining meaningful data to analyse. Both arms had the same assumptions applied to minimise bias.

Analysis of missing data

Potential bias due to missing data was investigated by comparing the baseline characteristics of eyes with clinical data available for analysis at 36 months to those eyes that had incomplete follow-up or no outcome data.

Use of mixed models

For the clinical analyses, it was determined that 'all' available eyes should be used in the analyses where possible. This is because in both treatment arms, approximately 72% of patients had both eyes in the study. Using a one eye per patient approach (either randomly selected vs. worse eye vs. better eye) would be sub-optimal as clinical data from approximately 500 eyes across both groups would then not be utilised from one of the largest datasets of treatment naïve eyes receiving primary treatment to date. Moreover, due to the existing trial design of 'treating to target IOP' based on disease severity, selecting only the 'better' or 'worse' eye could give skewed results which could limit the generalisability of the findings.

With the above considered and acknowledging that utilisation of all eyes represented a large clustered dataset with several data points per eye and two eyes per person for ~72% of patients, mixed models were utilised for statistical analysis to account for non-independence/correlation within the data.

In the next section, we describe how the analyses were performed for each aspect of the clinical outcomes being assessed.

3.20.2 Clinical Analyses – IOP Control

Initial ("early") IOP lowering response of Primary SLT

For this analysis, the unit of analysis was the 'eye'. All eyes (patients) were analysed in the treatment arm to which they were randomised.

We evaluated the initial ("early") absolute IOP reduction at 2 months (60 days + 'bracket window' of +/- 30 days) for all eyes receiving primary SLT. This was the first scheduled visit (after 'safety' IOP check visit at 2 weeks post laser) following laser at baseline. A similar visit at 2 months was scheduled in the Medication 1st arm of the trial (following initiation of topical medication at baseline) permitting a comparison of the early absolute IOP lowering efficacy of primary SLT against topical medication. Beyond 2 months, the computerized decision support software would guide decisions based on 'pursuit of disease control and achievement of target IOP' with differing treatment intensities and so this would make interpretation of IOP lowering data beyond 2 months difficult.

To compare absolute IOP reduction at 2 months between OHT and POAG eyes, a mixed effects model using the eye as the unit of analysis and using patients as a random factor to adjust for correlation between paired eyes was performed. The model also controlled for pre-treatment baseline IOP and treating centre (to control for centre effects in a multicentre trial).

To compare absolute IOP reduction at 2 months between primary SLT vs topical medication, a similar mixed effects model was also used.

All eligible study eyes that received SLT at baseline were included in the analysis with appropriate measures taken to account for correlation amongst paired eyes within a subject. Statistical significance was defined as a 2-sided P value <0.05. All analyses were performed in Stata, version 15 (StataCorp, 2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

Eyes at Target at 12, 24, 36 months

Calculated by selecting the eyes that had available data at 12, 24 and 36 months timepoints using bracketing approach. The number of eyes at target/not at target were identified and the intensity of treatment each had received (e.g. Initial single SLT, repeat SLT vs initial single medication, two medications, three medications etc.) was collated.

Percentage of clinic visits at target by 36 months

Using an absolute cut off of 1095.75 days for 36 months, the number of scheduled visits when study eye at target divided by the total number of scheduled visits over the 36 month time period.

IOP fluctuation

Standard deviation of serial IOP measurements of study eye at all clinic visits over the 36 month time period, a method reported previously by Caprioli et al (298).

Achievement of drop free 'disease control': meeting target IOP without disease progression or need for additional topical medication over 36 months following primary SLT.

Following the 2-month appointment post SLT, the objective computerised decision support software utilised during this study tailored treatment for each eye based on achievement of "disease control" i.e. achievement of predefined target IOP with no objective evidence of disease of progression (detected using visual field and disc imaging analysis). We collated and evaluated drop-free "disease control" achieved by primary SLT at 12, 24 and 36 months.

3.20.3 Clinical Analyses – Treatment Intensity

Objective measures of visual function

Calculated by selecting the eyes that had available data at 36 months timepoint. The measures of visual function (visual acuity, mean deviation, pattern standard deviation, HRT rim area) were collated for each treatment arm.

Number of clinic visits by 36 months

Calculated by using an absolute cut off of 1095.75 days for 36 months and counting the total number of visits from baseline.

Intensity of treatment at 12, 24, 36 months

Calculated by selecting the eyes that had available data at 12, 24 and 36 months timepoints using bracketing approach. The number of eyes at target/not at target were identified and the intensity of treatment each had received (e.g. Initial single SLT, repeat SLT vs initial single medication, two medications, three medications etc.) was collated.

Number of eyes undergoing cataract surgery at 36 months

Calculated using an absolute cut off of 1095.75 days for 36 months, and the cumulative number of cataract surgeries were counted from baseline.

Number of eyes undergoing IOP lowering surgery at 36 months

Calculated using an absolute cut off of 1095.75 days for 36 months, and the cumulative number of IOP lowering surgeries (trabeculectomy, tube surgery) were counted from baseline.

3.20.4 Clinical Analyses – Disease progression

Number of eyes with confirmed visual field or disc progression at 36 months

Calculated using an absolute cut off of 1095.75 days for 36 months. Eyes that had objective evidence of visual field progression, disc progression (or both) detected by the computerized decision-support software, using previously described predefined criteria.

3.20.5 Clinical Analyses – Predictors of IOP lowering & drop free disease control

Predictors of initial ("early") IOP lowering response following primary SLT at 2 months

To examine baseline predictors of early absolute IOP reduction at 2 months in eyes receiving primary SLT, univariate mixed effect linear regression analyses were performed using the eye as the unit of analysis and using patients as a random factor to adjust for correlation between paired eyes.

Patient related baseline characteristics considered for univariable selection were age, gender, ethnicity, phakic status, baseline IOP, central corneal thickness (CCT), TM pigmentation, pseudoexfoliation (PXF), hypertension (HTN) & diabetes mellitus (DM). Laser related characteristics included total SLT power and total number of SLT shots of initial SLT at baseline. Covariates that achieved $p<0.10$ in the univariable selection regression analyses were entered in a mixed effect multivariable linear regression model controlling for LiGHT stratification factors (disease severity and treating centre). The regression model was then run, with non-significant variables removed one by one until only significant ($p<0.05$) variables remained.

Predictors of eyes achieving drop free 'disease control' at 36 months following single SLT

Logistic regression was used to look for predictors of drop-free 'disease control' at 36 months. For the logistic regression analysis, a modified success criterion was used to permit comparison with the pre-existing literature. The most commonly

defined measure of 'success' in the SLT literature is a minimum IOP reduction of ≥ 20% from baseline IOP following SLT at a specified time point without need for further intervention (299). In LiGHT, predefined target IOPs required a minimum IOP reduction of > 20% from baseline IOP for all disease severities.
Thus, eyes achieving target IOP at 36 months achieved a minimum IOP reduction of > 20% from baseline IOP.

Our outcome measure of 'success' for the regression analysis was thus defined as eyes that achieved drop-free "disease control" i.e. achievement of target IOP without disease progression or requiring topical medication at 36 months having undergone single initial SLT. This was a more stringent criterion than used elsewhere. We also considered the 2 month IOP to assess if this was a post treatment predictor of drop-free 'disease control' at 36 months.

3.20.6 Clinical Analyses – Repeatability of SLT

Repeatability of SLT analysis

We assessed whether the IOP lowering efficacy and duration of effect of Repeat SLT were comparable to Initial SLT in completely medication-naïve OAG and OHT eyes. We also investigated whether the timing of Initial SLT failure influenced the efficacy of repeat laser.

All eligible study eyes that received 2 SLTs within the first 18 months of the LiGHT trial were included in the analysis, such that eyes had an equivalent duration of follow up after initial and Repeat SLT.

For Initial SLT, baseline IOP was the pretreatment IOP measured on the date of the patient's baseline visit. For Repeat SLT, pre-retreatment IOP was the IOP at the clinical visit at which the decision support software recommended a treatment escalation (as confirmed by the treating clinician and when the decision to escalate treatment was made).

When eyes received retreatment, IOP values at time points subsequent to Repeat SLT laser were not included as part of Initial SLT values but as the part of "Repeat SLT". Similarly, for eyes started on topical medication following "Repeat SLT", IOP at time points subsequent to initiation of medication were not included as part of "Repeat SLT", since these were a reflection of SLT and medication combined and not SLT efficacy alone.

We present IOP at post-laser time points (2 months, 6 months, 12 months and 18 months). For these pre-specified time points, we found and used the closest appointment to the absolute time point within a permitted 'bracket window'. If the patient (eye) was not seen within the permitted time frame, then the eye was not included in the analysis at that time point.

The following 'bracketing' criteria were devised and agreed upon by the chief investigator and analysis team to be used for this analysis. These criteria maximised data capture for all available eyes (taking into account follow up intervals of all eyes) whilst ensuring the same clinical data was not used for multiple time points.

Clinical Time Point	Absolute time from Baseline Visit + 'Bracket Window' (days)
2 months	60.0 days +/- 30 days
6 months	182.6 days +/- 90 days
12 months	365.25 +/- 90 days
18 months	547.8 +/- 90 days

Table 7: Bracketing criteria used to define time points at 12, 24, 36 months

To demonstrate the IOP lowering efficacy of initial and Repeat SLT in this cohort of eyes receiving Repeat SLT due to early/medium-term failure, we focussed primarily on the 2-month timepoint. This was the first scheduled visit following laser, allowing time for the full laser effect to occur, whilst also being free from bias arising from censoring of IOP data due to introduction of additional treatment at later timepoints ('treatment escalations').

Mean IOP at 2 months (following initial and Repeat SLT) was compared with respective pretreatment IOPs using mixed model analysis with crossed random

effects. Random effects were used to adjust for correlation between paired eyes whilst also taking into account repeated measures within eyes.

Mixed model analysis with crossed random effects was also used for comparison of absolute IOP reduction and adjusted absolute IOP reduction between initial and Repeat SLT at 2 months. Beyond 2 months, eyes were censored if they underwent treatment escalation and so statistical comparison of IOP reduction between initial vs Repeat SLT at further timepoints was not performed.

We aimed to evaluate whether the treatment response of Initial SLT influenced the efficacy of Repeat SLT in this cohort of early/medium-term SLT failures receiving repeat treatment. We compared IOP lowering between eyes that demonstrated an initial (but insufficient) IOP-lowering response following Initial SLT ('Early Failures': Repeat SLT required following the first scheduled visit at 2 months and performed within 4 weeks) with eyes that demonstrated adequate initial IOP lowering after Initial SLT but in which the treatment effect subsequently diminished triggering Repeat SLT ('Later Failures': Repeat SLT performed beyond 2 months post Initial SLT).

To compare duration of effect between initial and Repeat SLT in this cohort of eyes receiving repeat laser, a Kaplan Meier plot of time to failure was constructed using a clinically relevant definition of success: IOP control (maintaining IOP 'at or below' Target IOP) after SLT without additional IOP lowering medications, further laser procedures or incisional glaucoma surgery (206). The maximum follow up period was 18 months (548 days) such that eyes had an equivalent duration of follow up after initial and Repeat SLT.

A sensitivity analysis using one eye chosen at random per patient (for subjects with both eyes in the original analysis) was also performed. A Kaplan Meier plot was also produced using one eye chosen at random (for subjects with both eyes in the original analysis) as a sensitivity analysis to establish whether inclusion of multiple eyes per patient in the original analysis altered the results.

3.20.7 Clinical Analyses – Safety

Objectives safety measures of each pathway at 36 months

Calculated using an absolute cut off of 1095.75 days for 36 months, and the cumulative number of adverse events (general health, laser related, drop related) was counted from baseline.

3.20.8 PROMS Analyses

Sample size

The sample size for the study was 718 participants. This number of participants was required to detect a difference of 0.05 in EQ5D between two arms at 36 months using a two sample t-test at the 5% significance level, with 90% power, assuming a common standard deviation of 0.19(300), and a 15% loss to follow-up.

Primary outcome

The primary outcome measure was HRQL measured using the EQ5D at 36 months. EQ5D score was analysed using a linear regression model with an adjustment for the randomisation factors (severity and centre), baseline IOP, the baseline value of EQ-5D and whether the patient had 1 or 2 eyes affected at baseline.

For the primary outcome, the unit of analysis was the patient. If the patient had both eyes in the study, the worst eye was used at baseline for severity and baseline IOP covariates. The worst eye was defined using the mean deviation (MD) at baseline, with the worse eye having the most negative MD.

Whilst it is noted that 'vision specific' HRQL is generally influenced by the 'better' eye, in this study, the 'worse' eye was chosen since the primary outcome measure was a general health related QoL instrument and the worse eye would potentially influence non vision related aspects of quality of life such as drop burden/discomfort, side effects and visit frequency (which would also be utilised in the cost-effectiveness analysis).

The primary analysis used outcome data measured at 36 months. If this was missing, we imputed this missing data using the outcome measured at 30 months.

Secondary outcomes

The secondary outcomes were analysed using similar regression methods. The models were also adjusted using the covariates mentioned above.

3.20.9 Statistical Analysis Plan for Additional PROMS Analyses

Further clinical analyses of quality of life (post hoc analyses as part of this thesis) related to primary SLT were also performed.

Difference in PROMS in 'drop free' patients vs 'on medication' at 36 months

Differences in general health (EQ5D) and glaucoma specific HRQL measures in 'drop free' patients vs. patients taking topical medication at 36 months

Difference in PROMS in patients with objective evidence of 'disease progression' vs no progression

Differences in general health (EQ5D) and glaucoma specific quality of life measures in patients with objective evidence of disease progression vs. patients with no objective evidence of progression at 36 months.

Section 4: Results

We present first the overall results of trial recruitment and the baseline characteristics of patients (and eyes) participating in the LiGHT trial. We then present the results of the clinical analyses and PROMS analyses.

4.1 Recruitment

A total of 16379 patients were assessed for eligibility; 15483 were excluded as they did not meet the inclusion criteria and a further 178 patients declined to participate in the study. Of the patients who declined to participate, 43 did not want to have SLT, 17 did not want to take part in research, 9 did not want to use drops, 3 did not want to receive any treatment, 1 did not want to travel to the hospital and 105 did not provide an explanation. Of the 896 patients that were eligible across the 6 participating NHS centres, a total of 718 patients (1235 eyes) were recruited.

4.2 Participants

718 patients (1235 eyes) were randomised: 356 patients (613 eyes) were allocated to initial SLT (Laser-1st pathway) and 362 patients (622 eyes) to initial medical treatment (Medicine-1st pathway). Two patients were randomized twice due to IT failure, where the initial randomisation was not visible. Subsequently, a second randomisation was carried out; one (1) of these patients was initially randomised to medication but was subsequently randomised to, and received SLT. The second patient was initially randomised to SLT but was later randomised to,

and received medication. Four patients did not meet the eligibility criteria were randomised in error and were subsequently removed from the study.

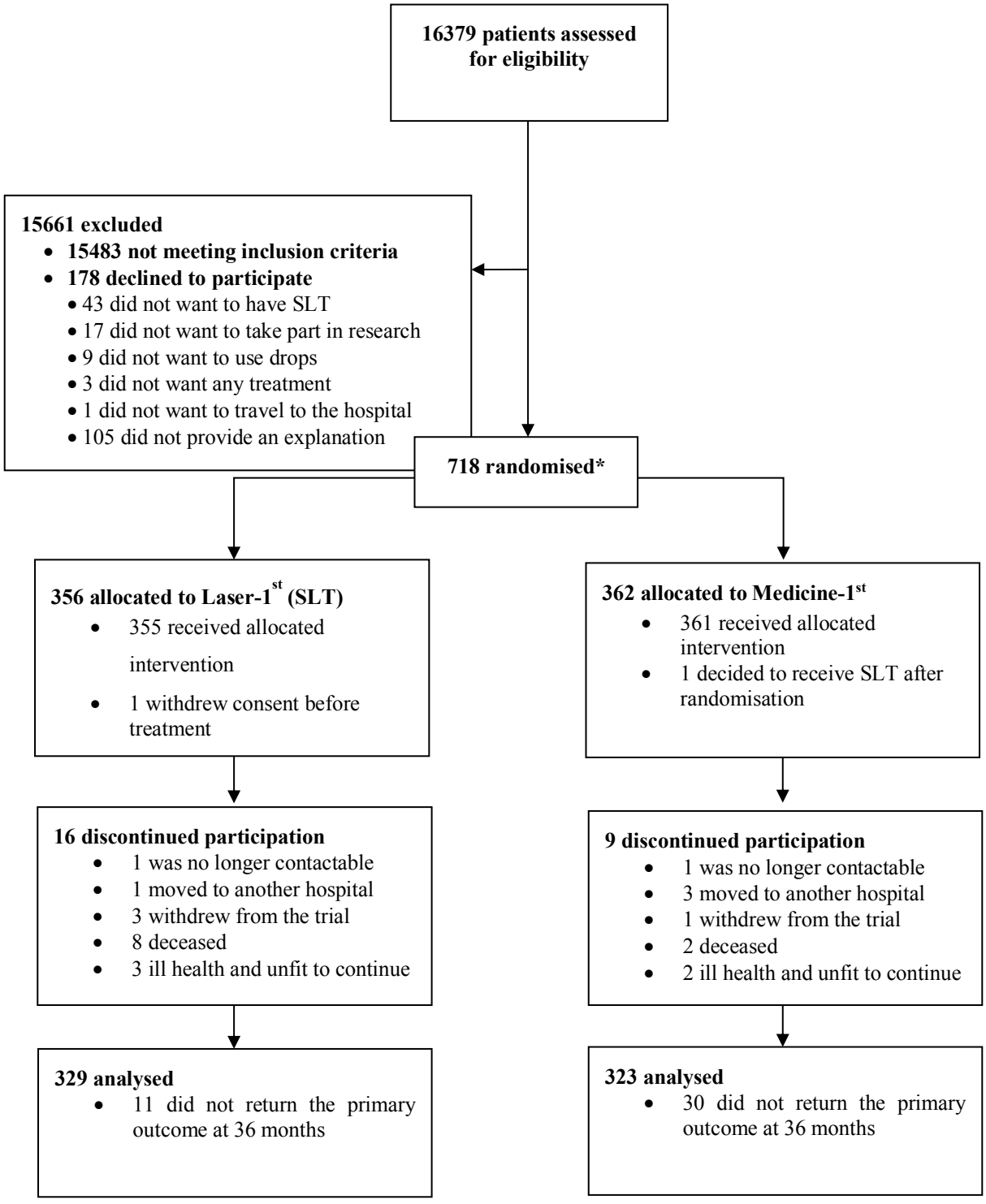


Figure 7: LiGHT trial profile. SLT: Selective Laser Trabeculoplasty. * Two (2) patients were randomized twice due to IT failure, where the initial randomisation was not visible and subsequently a second randomisation was carried out.

4.3 Baseline characteristics

	Total (N = 718)	Medicine-1st (N = 362)	Laser-1st (N = 356)
	N (%)	N (%)	N (%)
Centre			
Moorfields Eye Hospital	374 (52.1)	187 (51.7)	187 (52.5)
Huntingdon Hospital	82 (11.4)	41 (11.3)	41 (11.5)
Guy's and St Thomas' Hospital	106 (14.8)	55 (15.2)	51 (14.3)
Queen's University Belfast	30 (4.2)	15 (4.1)	15 (4.2)
Norfolk and Norwich University Hospital	89 (12.4)	46 (12.7)	43 (12.1)
York Hospital	37 (5.2)	18 (5)	19 (5.3)
Age (years), mean (SD)	63.1 (11.8)	62.7 (11.6)	63.4 (12.0)
Gender			
Males	397 (55.3)	197 (54.4)	200 (56.2)
Females	321 (44.7)	165 (45.6)	156 (43.8)
Ethnicity [a]			
Asian	51 (7.1)	28 (7.7)	23 (6.5)
Black	146 (20.3)	69 (19.1)	77 (21.6)
White/Caucasian	501 (69.8)	258 (71.3)	243 (68.3)
Other	20 (2.8)	7 (1.9)	13 (3.7)
Diagnosis			
OAG	555 (77.3)	282 (77.9)	273 (76.7)
OHT	163 (22.7)	80 (22.1)	83 (23.3)
Family Ocular History of Glaucoma [b]	214 (30)	107 (29.6)	107 (30.1)
Highest education achievement			
Degree or equivalent	216 (30.1)	106 (29.3)	110 (30.9)
Higher Education	94 (13.1)	39 (10.8)	55 (15.5)
A Level or equivalent	88 (12.3)	49 (13.5)	39 (11)
GCSEs	155 (21.6)	84 (23.2)	71 (19.9)
Other Qualifications	59 (8.2)	30 (8.3)	29 (8.2)
No Qualification	106 (14.8)	54 (14.9)	52 (14.6)

Table 8: Baseline patient characteristics. OAG: Open Angle Glaucoma, OHT: Ocular Hypertension a: Self defined ethnicity; 'Asian' ethnicity refers to Indian, Pakistani, Bangladeshi and any other Asian background, 'Black' ethnicity refers to Caribbean, African and any other black background, 'Other' ethnicity refers to Chinese and any other ethnic groups b: 1st degree relative

Overall, across both treatment arms, the mean age of the patients was 63.1 years (SD 11.8). There were more male patients recruited than females (55.3% males, 44.7% females). In total, approximately 70% of all participants were White/Caucasian, whilst the second largest ethnic group (20.3%) were Black/Afro-Caribbean patients. 30% of patients reported a family history of glaucoma affecting at least one 1st degree relative. Baseline patient characteristics were similar

between the two groups in terms of age, gender distribution, ethnicity and family history of glaucoma (see Table 8).

		All eyes (N = 1235)	Medicine-1st (N = 622)	Laser-1st (N = 613)
	N	N (%)		
Diagnosis, n (%)	1235			
OHT		380 (30.8)	185 (29.7)	195 (31.8)
Mild OAG		636 (51.5)	325 (52.3)	311 (50.7)
Moderate OAG		144 (11.7)	77 (12.4)	67 (10.9)
Severe OAG		75 (6.1)	35 (5.6)	40 (6.5)
			Mean (SD)	
Refractive Error (Spherical D)	1225	-0.2 (3.0)	-0.2 (2.7)	-0.3 (3.2)
Visual acuity	1235	0.1 (0.1)	0.1 (0.1)	0.1 (0.2)
VF MD (dB)	1233	-3.0 (3.5)	-3.0 (3.6)	-3.0 (3.4)
HRT Rim Area	1128	1.2 (0.4)	1.1 (0.4)	1.2 (0.4)
IOP (mmHg)	1233	24.5 (5.1)	24.4 (5.0)	24.5 (5.2)
PXF, n (%)	1233	17 (1.4)	12 (1.9)	5 (0.8)
Pseudophakia, n (%)	1233	72 (5.8)	33 (5.3)	39 (6.4)
CCT (µm)	1229	551.1 (37.2)	551.6 (36.3)	550.7 (38.1)

Table 9: Baseline eye characteristics. OHT: Ocular Hypertension; OAG: Open Angle Glaucoma, VF MD: Visual field Mean Deviation; VF PSD: visual field pattern standard deviation; HRT: Heidelberg Retina Tomograph; IOP: Intraocular pressure; CCT: Central corneal thickness; PXF: pseudoexfoliation; SD: standard deviation

Eye characteristics were also similar between the two treatment arms. Overall, approximately 80% of study eyes in both treatment arms had 'early' disease comprising of OHT or mild OAG. The proportion of eyes with each disease severity was similar between groups. Visual acuity, VF MD, HRT optic disc rim area, IOP and CCT also all appeared comparable between the two treatment arms (see Table 9).

	Overall (n=717)	Medicine-1st (n=362)	Laser-1st (n=355)
		Mean (SD)	
EQ-5D-5L Index	**0.91 (0.13)**	**0.92 (0.13)**	**0.91 (0.13)**
Glaucoma Utility index[a]	**0.89 (0.12)**	**0.89 (0.11)**	**0.89 (0.12)**
Glaucoma Symptom Scale[b]	**82.4 (16.9)**	**83.3 (16.6)**	**81.4 (17.2)**
Subscales:			
Symptom	**80.2 (19.7)**	**81.2 (19.4)**	**79.1 (20.1)**
Function	**85.6 (17.6)**	**86.4 (17.3)**	**84.8 (17.8)**
Glaucoma Quality of life-15[a]	**18.8 (6.1)**	**18.7 (5.6)**	**18.9 (6.6)**
Subscales:			
Central	**2.5 (1)**	**2.5 (1)**	**2.5 (1)**
Peripheral	**8.5 (3.1)**	**8.4 (2.9)**	**8.5 (3.4)**
Dark	**7.9 (2.9)**	**7.9 (2.8)**	**7.9 (3)**
Outdoor	**1.1 (0.4)**	**1.1 (0.4)**	**1.1 (0.4)**

Table 10: Baseline questionnaire scores.

The baseline scores for HRQL (EQ5D, GSS, GUS and GQL15) are shown in Table 10. The two treatment arms had similar mean EQ-5D (Medicine-1st 0.9 (SD 0.1); Laser-1st 0.9 (SD 0.1), GUI (Medicine-1st 0.9 (SD 0.1); Laser-1st 0.9 (SD 0.1) and GQL-15 (Medicine-1st 18.7 (SD 5.6; Laser-1st 18.9 (SD 6.6) scores at baseline. The Medicine-1st arm showed slightly higher average GSS scores at baseline compared to the Laser-1st arm (Medicine-1st 83.3 (SD 16.6); Laser-1st 81.4 (SD 17.2).

4.4 Clinical Analyses

Primary SLT arm

356 patients (613 eyes) were randomized to the Laser 1st arm of LiGHT. One patient (2 eyes) withdrew consent prior to receiving SLT at the baseline visit and thus 355 patients (611 eyes) received primary SLT.

At 36 months, 536 eyes of 314 patients were available for analysis. Of the 75 remaining eyes, 22 eyes (of 13 patients) were formally lost to follow up (withdrew, died, illness, or moved) during the course of the 3-year trial. The remaining 53 eyes (of 28 patients) were still returning HRQL questionnaires in the main LiGHT study, but clinical data were not available at the 36-month time-point.

Analysis comparing baseline demographics of eyes available vs unavailable to analyse at 36-months (536 eyes vs 77 eyes) demonstrated no clinically or statistically significant differences in age, baseline IOP, ethnicity, gender, disease severity and VF mean deviation. A statistically but not clinically significant difference in baseline visual acuity (~3 letters) was noted between groups (mean difference LogMAR -0.06 ,95% CI, -0.1 to -0.01, p=0.02) (see Appendix).

Baseline Characteristics

Baseline demographic data of the 611 eyes that received primary SLT are given in Table 11. There was a greater proportion of males compared to females (56.1% vs 43.9%) at baseline. The most common ethnicities were White European (68.2%) and Black (21.7%). 72.1% of patients had both eyes in the study, 13.8% had only the right eye and 14.1% had only the left eye in the study; 31.9% of eyes had a diagnosis of OHT (195 eyes) compared to 68.1% of eyes with OAG (416 eyes). This is reflected in the average mean deviation (MD) value of -3.0 decibels (dB). Mean baseline IOP was 24.5mmHg (SD 5.2) for all eyes but was greater in OHT eyes (26.5mmHg (SD 3.5)) vs OAG eyes (23.5mmHg (SD 5.6)). During initial SLT, mean total power delivered was 90.4 (SD 23.5) mJ via a mean treatment of 99.2 (SD 5.1) shots.

Characteristics	Value
Age (years), mean (SD)	63.4 (12.1)
Gender (patients), (%)	
Male	199 (56.1%)
Female	156 (43.9%)
Race/ Ethnicity (patients), (%)	
White European	242 (68.2%)
Black	77 (21.7%)
Asian	23 (6.5%)
Other	13 (3.7%)
Laterality (patients), (%)	
Bilateral Eyes	256 (72.1%)
Right Eye	49 (13.8%)
Left Eye	50 (14.1%)
Hypertension (patients), (%)	
Yes	131 (36.9%)
No	224 (63.1%)
Diabetes Mellitus (patients), (%)	
Yes	41 (11.6%)
No	314 (88.5%)
Disease Severity (eyes), (%)	
OHT	195 (31.9%)
'Mild' OAG	309 (50.6%)
'Moderate' OAG	67 (11.0%)
'Severe' OAG	40 (6.5%)
Mean Deviation (dB), mean (SD)	-3.0 (3.4)
Pattern Standard Deviation (dB), mean (SD)	3.7 (2.9)
Mean HRT area (mm2), mean (SD)	1.2 (0.4)
Baseline IOP (mmHg), mean (SD)	
Overall	24.5 (5.2)
OHT	26.5 (3.5)
OAG	23.5 (5.6)
Average Trabecular Pigmentation Grade (eyes), (%)	243 (39.8%)
0 -None	264 (43.2%)
1- Mild	101 (16.5%)
2-Moderate	1 (0.2%)
3-Dense	2 (0.4%)
Unknown	
Habitual VA (Logmar), mean (SD)	0.10 (0.2)
CCT (microns), mean (SD)	550.6 (38.1)
PXF (eyes), (%)	
Yes	5 (0.8%)
No	606 (99.2%)
Target IOP (mmHg)	
OHT	21.1 (2.4)
'Mild' OAG	17.9 (3.1)
'Moderate' OAG	15.9 (2.6)
'Severe' OAG	13.9 (1.6)

Table 11: Baseline characteristics of Primary SLT arm. OAG: Open Angle Glaucoma, OHT: Ocular Hypertension. Self-defined ethnicity; 'Asian' ethnicity refers to Indian, Pakistani, Bangladeshi and any other Asian background, 'Black' ethnicity refers to Caribbean, African and any other black background, 'Other' ethnicity refers to Chinese and any other ethnic groups.

4.4.1 IOP Control of Primary SLT

Early IOP lowering efficacy of Primary SLT

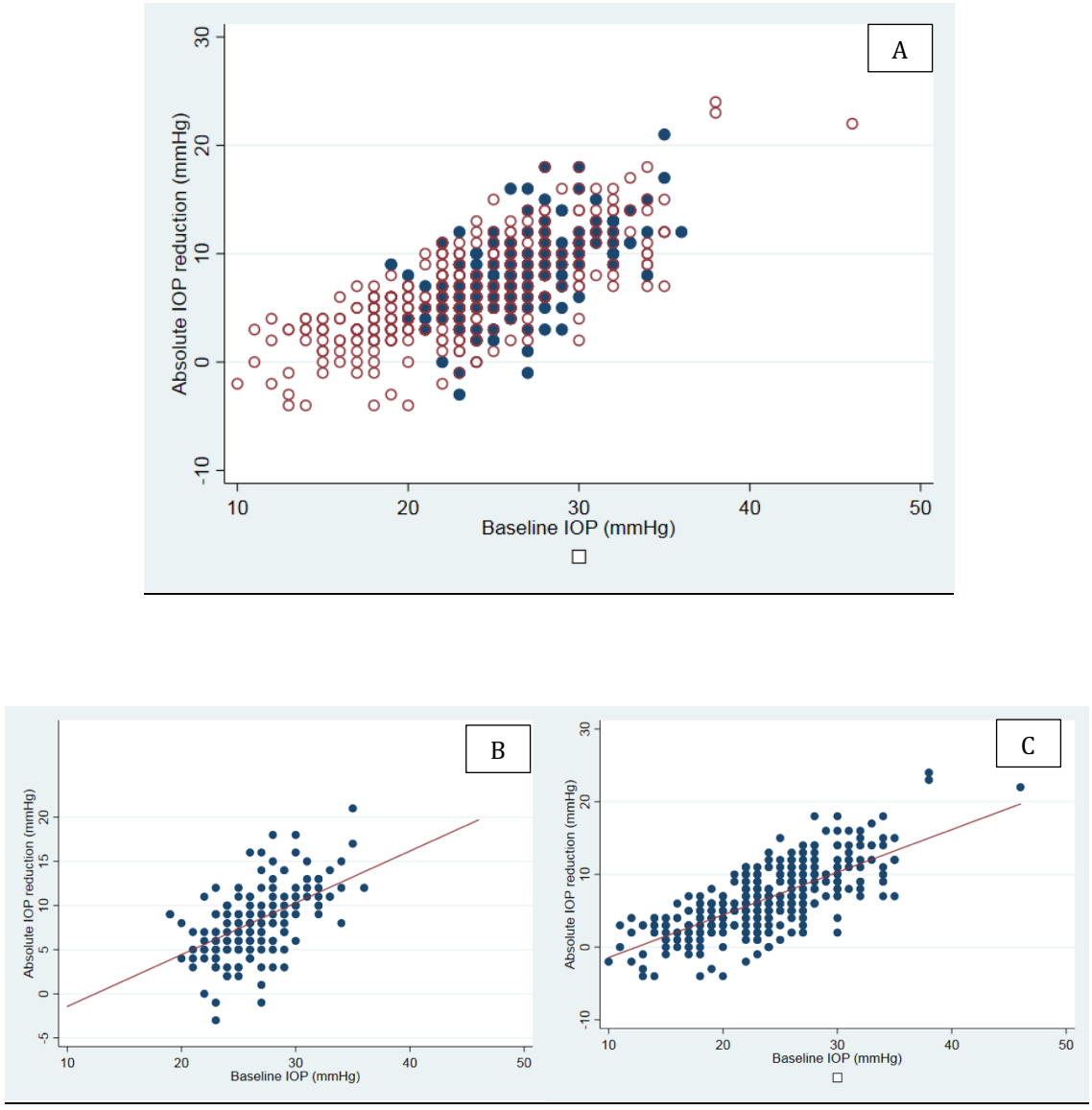


Figure 8: (A) Scatter plot of absolute IOP reduction vs. baseline IOP in all eyes (559 eyes) at 2 months following initial SLT- Filled circles: OHT, Hollow circles: OAG, (B) OHT eyes only – Filled circles (C) OAG eyes only – Filled circles.

**Due to overlap of several data points, scatterplots appear less populated than actual number of eyes.*

559 eyes (out of 611 eyes at baseline) were available for analysis at the 2-month time point in the primary SLT arm having undergone initial SLT at baseline (see Figure 8). Mean initial IOP lowering at 2 months was 8mmHg (SD 4.0) in OHT eyes and 6.5mmHg (SD 4.3) in OAG eyes. Mean percentage IOP reduction was 29.7%

(SD 13.1) in OHT eyes and 26.1% (SD 14.7) in OAG eyes respectively. A clear trend was noted towards increasing absolute IOP reduction with higher baseline IOP in both OHT and OAG eyes (see Figure 8) but there was no significant difference in early absolute IOP lowering between OHT and OAG eyes having controlled for pre-treatment baseline IOP and centre effects (adjusted mean difference = -0.05mmHg; 95% confidence interval (CI) -0.6 to 0.5mmHg; p=0.85).

For comparison, 594 eyes (out of 622 eyes at baseline) were available for analysis in the Medication 1st arm at 2 months. Of these, 99.3% (590 eyes) were on a single medication (96.1% on topical prostaglandin, 1.9% on beta blocker, 0.3% on carbonic anhydrase inhibitor, 0.3% on alpha agonist, 0.7% on two medications). Mean initial IOP lowering at 2 months was 7.6mmHg (SD 4) in OHT eyes and 6.8mmHg (SD 4.4) in OAG eyes. Mean (SD) percentage IOP reduction was 27.9% (13.5) in OHT eyes and 27.9% (14.4) in OAG eyes respectively.

Overall, absolute IOP reduction at 2 months was no different between topical medication and primary SLT (adjusted mean difference = -0.1mmHg; CI -0.6 to 0.4mmHg; p= 0.67). There was no difference in absolute IOP reduction for OHT eyes (adjusted mean difference = 0.4mmHg; CI -0.4 to 1.2mmHg; p=0.31) or OAG eyes (adjusted mean difference = -0.2mmHg; CI -0.8 to 0.3mmHg; p=0.36) between the two treatment groups.

Eyes at Target at 12, 24, 36 months & IOP fluctuation

For the trial clinical analyses, we present the number of available eyes at each time point (12, 24, 36 months). The number of eyes available for analyses was similar between treatment arms at all time points. The median difference in interval from absolute time point was also similar between both treatment arms at all time points. There was a greater difference in interval from absolute time point in both arms at 24 months and 36 months compared to 12 months. This is likely to be a reflection of the increasingly individualised follow up pathway of each eye generated by the computerised decision support software following the initial standardised 2-3 visits of the first 12 months, when reference data for serial visual field analysis and HRT disc analysis was being gathered for the algorithm.

Time point	Eyes available for analysis Medicine-1st	Median difference in interval from absolute time point Medicine-1st (days)	Eyes available for analysis Laser-1st	Median difference in interval from absolute time point Laser-1st (days)
12 months	606	20.75 days (IQR 6.75 – 47.75)	608	18.75 days (IQR 6.75 – 49.25)
24 months	564	47.5 days (IQR 18.5 – 109.5)	576	50.5 days (IQR 17.5 – 102.5)
36 months	536	46.25 days (IQR 17.25 – 93.25)	536	45.25 days (IQR 17.75 – 93.75)

Table 12: Eyes available for analysis at each timepoint

	Medicine-1st	Laser-1st
% of visits at target IOP over 36 months	**91.3%**	**93.0%**
Eyes at target IOP at 12 months	**96.2% (583)**	**94.7% (576)**
OHT	**97.6% (166)**	**95.3% (183)**
Mild OAG	**96.4% (320)**	**95.6% (301)**
Moderate OAG	**96.5 % (55)**	**90.7% (49)**
Severe OAG	**91.3% (42)**	**91.5% (43)**
Eyes at target IOP at 24 months	**94.1% (531)**	**96.0% (553)**
OHT	**92.8% (142)**	**98.3% (171)**
Mild OAG	**94.5% (294)**	**95.9% (281)**
Moderate OAG	**95.3% (61)**	**95.7% (66)**
Severe OAG	**89.5% (34)**	**87.5% (35)**
Eyes at target IOP at 36 months	**93.1% (499)**	**95.0% (509)**
OHT	**92.0% (127)**	**95.6 % (151)**
Mild OAG	**94.6% (261)**	**96.3 % (259)**
Moderate OAG	**94.5% (69)**	**96.5% (55)**
Severe OAG	**85.7% (42)**	**84.6% (44)**
IOP fluctuation over 36 months (SD)	**2.5mmHg**	**2.3 mmHg**

Table 13: Control of IOP over 12, 24 and 36 months. a: out of a total of 615 eyes for Medicine-1st and 605 eyes for Laser-1st

Over 36 months, 93·0% of Laser-1st visits were at target IOP compared to 91·3% of Medicine-1st visits (see Table 13). At serial time points (12 months, 24 months, 36 months), the overall percentage of eyes achieving target IOP was similar between the two treatment arms. Differences were noted within the disease severities however, with the percentage of eyes with 'severe' POAG achieving target IOP being lower compared to milder disease severities (e.g. OHT, 'mild POAG') at serial time points across both treatment arms. IOP fluctuation across serial visits over the 36 month trial period were similar between the 2 treatment arms.

Eyes achieving Target IOP at 36 months

	1 SLT per eye	1 SLT per eye + on medication	2 SLT per eye	2 SLT per eye + on medication	3 SLT per eye	IOP lowering surgery
At Target	**321 (59.9%)**	**48 (9.0%)**	**97 (18.1%)**	**42 (7.8%)**	**1 (0.2%)**	**-**
Not at Target	**10 (1.9%)**	**6 (1.1%)**	**8 (1.5%)**	**3 (0.6%)**	**0 (0%)**	**-**

Table 14: Achievement of Target IOP at 36 months in Laser-1st Arm

95% of the eyes treated with Laser-1st (n=509) were at target IOP at 36 months. Target IOP was achieved without IOP medication in 78·2% of the eyes (n=419) treated with Laser-1st (Table 14). 59.9% of eyes achieved target IOP following single initial SLT at 36 months. Of the Laser-1st patients, 74·2% (n=233, 95% CI 69.3% to 78.6%) were drop-free at 36 months. 18.5% (n=99) eyes were on medication at 36 months despite receiving 1 or 2 SLT.

	Nil Medication	1 Medication	2 Medications	3 Medications	4 Medications	IOP lowering surgery + Nil medication	IOP lowering surgery + Medication
At Target	**8 (1.5%)**	**346 (64.6%)**	**98 (18.3%)**	**35 (6.5%)**	**3 (0.6%)**	**8 (1.5%)**	**1 (0.2%)**
Not at Target	**1 (0.2%)**	**21 (3.9%)**	**10 (1.9%)**	**3 (0.6%)**	**0 (0%)**	**1 (0.2%)**	**1 (0.2%)**

Table 15: Achievement of Target IOP at 36 months in Medication-1st Arm. 18 eyes on nil meds at 36 months – 9 of these had undergone IOP lowering Surgery (Trabeculectomy). A further 7 eyes were in post-operative phase following cataract surgery where IOP lowering drops amended/ceased temporarily. 2 eyes were from a single patient who was randomised to Medication-1st arm but received SLT within 12 months (patient choice) but kept in Medication-1st arm on intention to treat basis.

Of the eyes that received Medicine-1st, 93·1% (n=499) were at target IOP at 36 months. 64·6% (n=346) of these eyes were using a single medication, 18.3% (n=98) using 2 medications and 6.5% eyes (n=35) using 3 medications (Table 15).

Achievement of drop free 'disease control': meeting target IOP without disease progression or need for additional topical medication over 36 months following primary SLT.

Eyes that met target IOP without disease progression or need for topical IOP lowering medication were deemed to have achieved drop-free "disease-control". At 12 months, 85.2% of eyes (518 eyes) achieved drop-free 'disease-control' after 1 or 2 SLTs. At 24 months and 36 months, 79.2% of eyes (456 eyes) and 74.6% of eyes (400 eyes) respectively, continued to achieve drop-free 'disease-control' (see Table 16). At all time points, drop-free 'disease-control' was achieved in a higher percentage of OHT and 'mild OAG' eyes compared to 'moderate' and 'severe' OAG eyes.

Disease Severity	12 months Total eyes available for analysis (n)	12 months Eyes achieving drop-free 'disease-control' % (n)	24 months Total eyes available for analysis (n)	24 months Eyes achieving drop-free 'disease-control'% (n)	36 months Total eyes available for analysis (n)	36 months Eyes achieving drop-free 'disease-control'% (n)
ALL EYES	**608**	**85.2% (518)**	**576**	**79.2% (456)**	**536**	**74.6% (400)[a]**
OHT	**192**	**92.7% (178)**	**174**	**92% (160)**	**158**	**88.6% (140)**
'Mild' OAG	**315**	**87.3% (275)**	**293**	**81.2% (238)**	**269**	**76.6% (206)**
'Moderate' OAG	**54**	**63% (34)**	**69**	**56.5% (39)**	**57**	**56.1% (32)**
'Severe' OAG	**47**	**65.9% (31)**	**40**	**47.5% (19)**	**52**	**42.3% (22)**

Table 16: Eyes achieving drop-free "disease-control" using 1 or 2 SLT. a: one eye was protocol deviation - received 3 SLT

Assessing drop-free 'disease-control' achieved by *initial single SLT at baseline*, 75.5% of eyes (459 eyes) achieved this at 12 months, 66.5% of eyes (383 eyes) at 24 months and 58.2% of eyes (312 eyes) at 36 months. At all time points, drop-free

'disease-control' *after single initial SLT* was achieved in a higher percentage of OHT and 'mild OAG' eyes compared to 'moderate' and 'severe' OAG eyes (see Table 17).

Disease Severity	12 months Total eyes available for analysis (n)	12 months Eyes achieving drop-free 'disease-control' after single SLT % (n)	24 months Total eyes available for analysis (n)	24 months Eyes achieving drop-free 'disease-control' after single SLT % (n)	36 months Total eyes available for analysis (n)	36 months Eyes achieving drop-free 'disease-control' after single SLT % (n)
ALL EYES	**608**	**75.5% (459)**	**576**	**66.5% (383)**	**536**	**58.2% (312)**
OHT	**192**	**85.9% (165)**	**174**	**80.5% (140)**	**158**	**72.8% (115)**
'Mild' OAG	**315**	**79.4% (250)**	**293**	**70.6% (207)**	**269**	**64.3% (173)**
'Moderate' OAG	**54**	**46.3% (25)**	**69**	**42% (29)**	**57**	**33.3% (19)**
'Severe' OAG	**47**	**40.4% (19)**	**40**	**17.5% (7)**	**52**	**9.6% (5)**

Table 17: Eyes achieving drop-free 'disease-control' after single, initial SLT at baseline

Overall at 36 months, mean absolute IOP reduction in the 312 eyes achieving drop-free "disease-control" following single initial SLT at baseline was 8.1mmHg (SD 4.1). Mean absolute IOP reduction was similar between all disease severities (see Table 18).

	Drop-free 'disease-control' using single SLT at 36 months (eyes)	Mean(SD) absolute IOP reduction (mmHg)	Mean (SD) % IOP reduction from baseline
ALL EYES	**312**	**8.1 (4.1)**	**31.4 (11.7)**
OHT	**115**	**8.8 (3.6)**	**32.7 (11.5)**
'Mild' OAG	**173**	**7.5 (4.3)**	**29.9 (11.7)**
'Moderate' OAG	**19**	**8.6 (3.9)**	**36.4 (11.7))**
'Severe' OAG	**5**	**8.2 (4.6)**	**34.4 (13.1)**

Table 18: Mean IOP reduction and Percentage IOP reduction at 36 months in eyes achieving drop-free "disease-control" after single initial SLT

4.4.2 Treatment Intensity

Objective measures of visual function

At 36 months, 536 eyes (87·7%) of 314 patients in the Laser-1st arm and 536 eyes (86·2%) of 312 patients in the Medicine-1st arm were available for analysis of clinical outcomes. The Laser-1st and Medicine-1st arms had comparable mean endpoint visual acuity, mean deviation, pattern standard deviation, disc HRT and IOP measurements (see Table 19).

	Medicine-1st	Laser-1st
	Mean (SD)	
Visual acuity (LogMAR) at 36 months	**0.1 (0.2)**	**0.1 (0.2)**
OHT	**0.1 (0.2)**	**0.0 (0.1)**
Mild OAG	**0.1 (0.2)**	**0.1 (0.2)**
Moderate OAG	**0.1 (0.2)**	**0.1 (0.2)**
Severe OAG	**0.2 (0.2)**	**0.2 (0.2)**
VF MD (dB) at 36 months	**-3.2 (3.8)**	**-3.2 (3.9)**
OHT	**-0.9 (1.9)**	**-1.1 (2.0)**
Mild OAG	**-2.1 (2.0)**	**-2.0 (1.9)**
Moderate OAG	**-7.2 (1.9)**	**-8.0 (2.0)**
Severe OAG	**-10.5 (5.0)**	**-10.2 (4.9)**
VF PSD (dB) at 36 months	**4.0 (3.3)**	**3.9 (3.2)**
OHT	**2.0 (1.2)**	**2.1 (1.3)**
Mild OAG	**3.0 (1.9)**	**2.8 (1.6)**
Moderate OAG	**7.6 (2.9)**	**8.4 (3.0)**
Severe OAG	**10.4 (2.8)**	**9.6 (2.6)**
Disc HRT at 36 months	**1.1 (0.4)**	**1.1 (0.4)**
OHT	**1.3 (0.3)**	**1.3 (0.4)**
Mild OAG	**1.1 (0.3)**	**1.1 (0.4)**
Moderate OAG	**1.0 (0.3)**	**0.9 (0.4)**
Severe OAG	**0.9 (0.5)**	**1.0 (0.4)**
IOP (mmHg) at 36 months	**16.3 (3.9)**	**16.6 (3.6)**
OHT	**18.7 (3.7)**	**18.2 (3.7)**
Mild OAG	**15.7 (3.5)**	**16.4 (3.2)**
Moderate OAG	**14.7 (3.5)**	**14.4 (3.1)**
Severe OAG	**15.5 (4.2)**	**15.5 (4.2)**

Table 19: Visual acuity, MD, PSD, HRT and IOP at 36 months.

Treatment Intensity

	Medicine-1st	Laser-1st
Total number of clinic visits	**2907**	**3441**
Total number of clinic visits excluding 2 week IOP check	**2907**	**2976**
Treatment escalations[a]	**348**	**299**
Number of SLT treatments per eye at 36 months [b]	**6 [a]**	**770**
1 SLT treatment	**6**	**453 (74%)**
2 SLT treatments	**0**	**157 (26%)**
3 SLT treatments [c]	**0**	**1 (0.2%)**
Number of medications per eye at target IOP at 36 months [d]		
No medication	**3.0% (16)**	**78.2% (419)**
1 medication	**64.6% (346)**	**12.0% (64)**
2 medications	**18.5% (99)**	**3.9% (21)**
3 medications	**6.5% (35)**	**0.8 % (4)**
4 medications	**0.6% (3)**	**0.2% (1)**
IOP target revisions	**38**	**41**
Upward IOP target revisions	**22**	**26**
Downward IOP target revisions	**16**	**15**
Ocular surgeries during the trial		
Phacoemulsification	**25**	**13**
Trabeculectomy	**11**	**0**
Trabeculectomy Revision	**7 (5 eyes)**	**0**

Table 20: Intensity of treatment. a: Escalations initiated by the algorithm and the clinicians b: 3 patients (6 eyes) in the Medication-1st arm wanted SLT at a treatment escalation, c: Protocol deviation, d: Includes eyes that had undergone trabeculectomy, e: Conversion of OHT to OAG required a DSS derived sign of progression and verification by a consultant ophthalmologist

Overall, the total number of clinic visits at 36 months was greater in the Laser-1st arm (3441 visits) vs the Medicine-1st arm (2907 visits). The treatment protocol of the Laser-1st arm included a safety IOP check visit at 2 weeks following each SLT, which was not needed for the Medicine-1st arm. If the 2-week safety check visits (465 visits) were excluded, the total number of clinic visits was similar between treatment arms (2907 vs 2976 visits).

More treatment escalations took place in the Medicine-1st arm (n=348) compared to the Laser-1st arm (n=299). 38 eyes of 33 patients had their target IOP revised

during the 36 month duration of the trial in the Medicine-1st arm (total 38 IOP revisions) compared to 38 eyes of 37 patients in the Laser-1st arm (total 41 IOP revisions) (see Table 24). There were 31 downward IOP revisions (16 in the Medicine-1st arm and 15 in the Laser-1st arm), where there were objective signs of disease deterioration/progression, despite the IOP target being met. The vast majority of the downward target IOP revisions happened for eyes with OAG (28 out of 31 downward target IOP revisions).

Additionally, there were 48 revisions (22 in the Medicine-1st arm and 26 in the Laser-1st arm) where the IOP target was revised upwards, as despite the initial IOP target not having been met repeatedly there was no evidence of disease deterioration/progression. There were proportionately more upward target IOP revisions in eyes with mild OAG (8 out of 22 in the Medicine-1st arm and 14 out of 26 in the Laser-1st arm). 11 eyes (1.8%) required IOP-lowering surgery (trabeculectomy) in the Medicine-1st arm compared to none in the Laser-1st.

4.4.3 Disease Progression

	Medicine-1st	Laser-1st
Disease progression during the trial	**5.8% (36)**	**3.8% (23)**
From OHT to OAG[e]	**(3)**	**(2)**
OAG progression	**(33)**	**(21)**
Algorithm defined VF progression	**(27)**	**(18)**
Algorithm defined optic disc progression	**(3)**	**(2)**
Algorithm defined VF & disc progression	**(3)**	**(1)**

Table 21: Disease progression over 36 months

36 eyes in the Medicine-1st arm showed algorithm-confirmed disease deterioration (3 eyes converted from OHT to OAG and in 33 eyes OAG progressed) compared to 23 eyes in the Laser-1st arm (2 eyes showed OHT conversion to OAG and in 21 eyes OAG worsened) (see Table 21).

4.4.4 Predictors of IOP lowering & drop free disease control

Predictors of initial ("early") IOP lowering response following primary SLT at 2 months

For the predictors of initial IOP lowering response, covariates that achieved $p<0.10$ in the initial variable selection regression analyses were baseline IOP ($p<0.001$), gender ($p=0.002$) and age ($p=0.05$). Within group (OHT vs OAG) sub-analysis demonstrated that the trend noted towards increasing absolute IOP reduction with higher baseline IOP (see Figure 8) was significant in both OHT (Coefficient 0.68, 95% CI, 0.55 to 0.81; $p<0.001$) and OAG (Coefficient 0.58, 95% CI, 0.53 to 0.64; $p<0.001$). The final multivariable linear regression model showed that baseline IOP ($p<0.001$) and gender ($p=0.04$) were predictors of initial absolute IOP reduction.

Variable	Coefficient	95% confidence Interval	P-value
Baseline IOP (mmHg)	**0.59**	**(0.54, 0.64)**	**<0.001***
Race/ Ethnicity			**0.17**
Black	**1.18**	**(0.08, 2.29)**	
Asian	**0.89**	**(-0.87, 2.66)**	
Other	**0.70**	**(-1.75, 3.15)**	
****reference White European***			
Sex			
Female	**-1.42**	**(-2.29, -0.54)**	**0.002***
Age (years)	**-0.04**	**(-0.08, 0.00)**	**0.05***
CCT (microns)	**0.01**	**(0.00, 0.02)**	**0.15**
PXF (Y/N)			
No	**-1.62**	**(-4.94, 1.69)**	**0.34**
Average TM Pigmentation Grade			**0.12**
1- Mild	**-0.12**	**(-1.04, 0.81)**	
2-Moderate	**0.03**	**(-1.16, 1.23)**	
3-Dense	**6.51**	**(1.06, 12.0)**	
****reference No Pigmentation***			
Phakic Status (Y/N)			
Phakic	**0.70**	**(-0.90, 2.29)**	**0.39**
Hypertension (Y/N)			
No	**0.05**	**(-0.87, 0.96)**	**0.92**
Diabetes Mellitus (Y/N)			
No	**0.82**	**(-0.51, 2.15)**	**0.22**
Total Power 1st SLT (mJ)	**0.01**	**(-0.01, 0.03)**	**0.29**
Total Number of shots 1st SLT (shots)	**0.04**	**(-0.03, 0.11)**	**0.26**

Table 22: Univariable Linear Regression Analysis for Absolute IOP Reduction

**Covariates that achieved p<0.10 in the initial variable selection linear regression analyses were: baseline IOP (p<0.001), gender (p=0.002) and age (p=0.05)*

Variable	Coefficient	95% confidence Interval	P-value
Baseline IOP (mmHg)	**0.58**	**(0.53, 0.63)**	**<0.001**
Sex			
Female	**-0.63**	**(-1.23, -0.02)**	**0.04**

Table 23: Multivariable Logistic Regression Analysis for Absolute IOP reduction

Predictors of drop-free 'disease-control' at 36 months

312 eyes achieved drop-free "disease-control" at 36 months following initial single SLT (Table 8). These eyes achieved >20% IOP reduction from baseline IOP and thus were a treatment 'success' (using conventional 'IOP lowering >20% from baseline IOP' definition of success). Baseline covariates that achieved $p<0.10$ in the mixed effects univariable logistic regression analyses were: total power of 1st SLT ($p=0.08$) and age ($p=0.09$) (see Table 24). Two month IOP ($p<0.001$) was a 'post' treatment covariate that achieved $p<0.10$ in the univariable logistic regression analysis. The final mixed effects multivariable logistic regression model of baseline factors showed that total power of 1st SLT (see Table 25) was a predictor of achieving drop-free "disease-control" at 36 months following single initial SLT (adjusted odds ratio 1.02, 95% CI, 1.01 to 1.04, $p=0.01$). Two month IOP was also a 'post' treatment predictor of drop-free 'disease-control' at 36 months when controlling for the other significant baseline factors (adjusted odds ratio 0.66, 95% CI, 0.57 to 0.79, $p<0.001$) (see Table 25).

Variable	Odds Ratio	95% confidence Interval	P-value
Baseline IOP (mmHg)	**1.01**	**(0.95, 1.09)**	**0.69**
Race/ Ethnicity ***Black*** ***Asian*** ***Other*** ***reference White European***	 **1.55** **0.74** **1.78**	 **(0.57, 4.20)** **(0.16, 3.41)** **(0.23, 13.64)**	**0.74**
Sex **Female**	 **0.57**	 **(0.26, 1.28)**	 **0.17**
Age (years)	**0.97**	**(0.94, 1.00)**	**0.09***
CCT (microns)	**1.00**	**(0.99, 1.01)**	**0.62**
PXF Status ***Nil PXF***	 **18.9**	 **(0.28, 1294.66)**	 **0.17**
Average TM Pigmentation Grade **1- Mild** **2-Moderate** **3-Dense** ***reference No Pigmentation***	 **1.1** **1.1** **1[a]**	 **(0.47, 2.57)** **(0.34, 3.26)**	**0.98**
Phakic Status ***Phakic***	 **0.52**	 **(0.10, 2.67)**	 **0.44**
Hypertension(Y/N) ***No***	 **0.63**	 **(0.28, 1.43)**	 **0.27**
Diabetes Mellitus (Y/N) ***No***	 **1.07**	 **(0.30, 3.80)**	 **0.91**
Total Power 1st SLT (mJ)	**1.01**	**(1.00, 1.03)**	**0.08***
Total Number of shots 1st SLT (shots)	**1.02**	**(0.96, 1.10)**	**0.41**
2 month IOP post treatment (mmHg)	**0.71**	**(0.61, 0.82)**	**<0.001***

Table 24: Univariable Selection Logistic Regression Analysis

**Covariates that achieved p<0.10 in the initial variable selection logistic regression analyses were: total power of 1st SLT (p=0.08) and age (p=0.09)*
[a]model unable to converge due to insufficient data

Variable	Odds Ratio	95% confidence Interval	P-value
Total Power 1st SLT (mJ)	**1.02**	**(1.01, 1.04)**	**0.01**
***2 month IOP post treatment (mmHg)**	**0.66**	**(0.57, 0.79)**	**<0.001**

Table 25: Multivariable Logistic Regression Analysis Result of Baseline Factors

** 2 month IOP is a post treatment predictor*

4.4.5 Repeatability of SLT

115 eyes of 90 patients had undergone 2 SLTs by 18 months into the LiGHT trial and were included in this analysis of Repeat SLT. Additionally, 43 eyes had been started on topical medication following Initial SLT (and did not undergo Repeat SLT). 20 of these eyes were started on topical medication following the first scheduled visit at 2 months and were judged by treating clinicians to have had 'no' treatment effect from Initial SLT. A further 23 eyes were started on topical medication *beyond* the first scheduled visit and did not undergo Repeat SLT. The decision to start medication instead of Repeat SLT in these 23 eyes was made jointly by the local treating clinician and patients. At 18 months, 453 eyes were still successfully maintaining IOP control following single, initial baseline SLT and had not required additional treatment.

Background Characteristics

The demographics of the 90 patients with the study sample of 115 eyes are presented in Table 26. The distribution of glaucoma severities was similar in the sensitivity analysis using one eye randomly selected per patient (see Appendix).

Characteristics	Value
Age (years), mean (SD)	**63.5 (13.1)**
Gender (patients), (%)	
Male	**52 (57.8%)**
Female	**38 (42.2%)**
Ethnicity (patients), (%)	
White European	**63 (70.0%)**
Black	**17 (18.9%)**
Asian	**6 (6.7%)**
Other	**4 (4.4%)**
Disease Severity (eyes), (%)	
OHT	**22 (19.1%)**
'Mild' OAG	**46 (40.0%)**
'Moderate' OAG	**27 (23.5%)**
'Severe' OAG	**20 (17.4%)**
Baseline IOP (mmHg), mean (SD)	**24.5 (6.6)**

Table 26: Baseline characteristics of study sample

IOP lowering efficacy of Initial and Repeat SLT

	Initial SLT				Repeat SLT				Initial vs Repeat SLT	
	Number of eyes (n)	**Mean IOP (SD) (mmHg)**	**Mean absolute IOP reduction (mmHg; 95% CI)**	**Mean % IOP reduction (95% CI)**	**Number of eyes (n)**	**Mean IOP (SD) (mmHg)**	**Mean absolute IOP reduction (mmHg; 95% CI)**	**Mean % IOP reduction (95% CI)**	**Mean difference in absolute IOP reduction (mmHg; 95% CI)**	***Adjusted* mean difference in absolute IOP reduction (mmHg; 95% CI)**
Pre-treatment	**115**	**24.5** ** **(6.6)**			**115**	**21.0** ** **(4.2)**				
2 months	**97**[a,b]	**19.1 (3.9)**	**5.3* (4.5 to 6.0)**	**21.6 (18.4 to 24.5)**	**104**[c,d]	**16.3 (3.3)**	**4.6* (4.0 to 5.2)**	**21.9 (19.0 to 24.8)**	**1.0 (0.2 to 1.8)**	**-1.1 (-1.7 to -0.5)**
6 months	58[a,b]	18.8 (4.1)	4.5 (3.6 to 5.4)	18.4 (14.7 to 22.0)	88[c,d]	17.0 (3.4)	4.0 (3.4 to 4.6)	19.0 (16.2 to 21.9)	0.3 (-0.8 to 1.3)	-1.1 (-1.9 to -0.2)
12 months	26[a,b]	21.0 (4.9)	2.4 (1.2 to 3.7)	9.8 (4.9 to 15.1)	76[c,d]	17.2 (4.0)	3.8 (3.1 to 4.5)	18.1 (14.8 to 21.4)	-1.0 (-2.7 to 0.7)	-2.4 (-3.9 to -0.9)
18 months	0 [b]	-	-	-	62 [c,d]	16.7 (3.8)	3.8 (3.1 to 4.5)	18.1 (14.8 to 21.4)	-	-

Table 27: Summary of Mean IOP between Initial SLT and Repeat SLT.

a: IOP data missing: 15 eyes at 2 months, 2 eyes at 6 months, 1 eye at 12 months for Initial SLT.
b: IOP data censored (no longer at target, treatment escalated): 3 eyes at 2 months, 55 eyes at 6 months, 88 eyes at 12 months, 115 eyes at 18 months for Initial SLT.

c: IOP data missing: 9 eyes at 2 months, 6 eyes at 6 months, 8 eyes at 12 months, 15 eyes at 18 months for Repeat SLT.
d: IOP data censored (no longer at target, treatment escalated: 2 eyes at 2 months, 21 eyes at 6 months, 31 eyes at 12 months, 38 eyes at 18 months for Repeat SLT.

**Significant reduction in mean absolute IOP reduction from baseline at 2-month time point for initial and Repeat SLT (p<0.001)*
*** Significant difference in pre-treatment IOP between initial and Repeat SLT (mean difference: 3.4, 95% CI 2.6 to 4.3, mmHg; p<0.001)*

Mean IOP values at each post laser time point for initial and Repeat SLT are given in Table 27. Pre-treatment IOP prior to Initial SLT was significantly higher than the pre-retreatment IOP prior to Repeat SLT (mean difference: 3.4mmHg, 95% CI, 2.6 to 4.3mmHg; p<0.001). Comparison of absolute IOP reduction at 2-months between initial and repeat SLT demonstrated a greater reduction following initial

SLT which was statistically, and probably clinically, significant (mean difference: 1.0, 95% CI 0.2 to 1.8, mmHg; p=0.02). Adjusting for the corresponding pre-treatment IOP ('adjusted absolute IOP reduction'), the adjusted absolute IOP reduction at 2-months was greater following Repeat SLT (adjusted mean difference: -1.1, 95% CI -1.7 to -0.5, mmHg; p=0.001). Sensitivity analysis using one eye randomly selected per patient also demonstrated similar results (see Appendix). Beyond 2 months, eyes were censored if they underwent treatment escalation and so statistical comparison of IOP reduction between Initial vs Repeat SLT was not performed.

Mean (SD) total power of Initial SLT was 89.1mJ (27.5) and total number of applications was 98.9 (4.6) shots. Mean (SD) total power of Repeat SLT was 100.5mJ (24.9) and total number of applications was 99.5 (4.6) shots. The difference in total power of SLT between Initial vs Repeat SLT was both clinically and statistically significant (mean difference: 11.6mJ, 95% CI 7.7mJ to 15.6mJ; p<0.001). There was no significant difference in the total number of applications (mean difference: 0.6 shots, -0.5 shots to 1.7 shots; p=0.266).

	'Early failures' who underwent Repeat SLT	'Later failures' who underwent Repeat SLT	'Early failures' started on topical medication without Repeat SLT	'Later failures' started on topical medication without Repeat SLT	Single SLT treatment still successful at 18 months, no additional treatment
Disease Severity: Eyes (n) / (%) OHT 'Mild' OAG 'Moderate' OAG 'Severe' OAG	 3 (8.8) 15 (44.1) 8 (23.5) 8 (23.5)	 19 (23.5) 31 (38.3) 19 (23.5) 12 (14.8)	 4 (20.0) 10 (50.0) 5 (25.0) 1 (5.0)	 1 (4.4) 12 (52.2) 4 (17.4) 6 (26.1)	 168 (37.1) 241 (53.2) 31 (6.8) 13 (2.9)
Mean IOP reduction required to achieve Target IOP (mmHg; 95% CI) Eyes (n)	9.7 (7.7 to 11.6) 34	6.5 (5.8 to 7.2) 81	5.4 (4.6 to 6.1) 20	6.1 (4.9 to 7.4) 23	5.7 (5.5 to 5.9) 453
Mean pre-treatment IOP prior to Initial SLT (SD) (mmHg) Eyes (n)	26.1 (7.8) 34	23.8 (5.9) 81	22.6 (4.4) 20	22.1 (4.6) 23	24.7 (4.8) 453
Mean IOP at 2 months post initial SLT (SD) (mmHg) Eyes (n)	21.6 (3.9) 32	17.8 (3.4) 65	21.1 (4.0) 20	16.8 (2.9) 21	16.7 (2.3) 414
Mean absolute IOP reduction at 2 months after initial SLT (mmHg; 95% CI) Eyes (n)	4.4 (2.6 to 6.2) 32	5.7 (4.9 to 6.5) 65	1.3 (-0.2 to 2.7) 20	5.1 (3.7 to 6.4) 21	7.9 (7.6 to 8.2) 414
Mean pre-retreatment IOP prior to repeat SLT (SD) (mmHg) Eyes (n)	21.6 (3.7) 34	20.7 (4.3) 81	-	-	-
Mean IOP at 2 months post repeat SLT (SD) (mmHg) Eyes (n)	17.5 (3.0) 29	15.9 (3.4) 75	-	-	-
Mean absolute IOP reduction at 2 months after repeat SLT (mmHg; 95% CI) Eyes (n)	4.1 (2.8 to 5.4) 29	4.8 (4.1 to 5.4) 75	-	-	-
Mean IOP reduction at 2 months after LAST SLT (mmHg; 95% CI) Eyes (n)	17.5 (3.0) 29	15.9 (3.4) 75	21.1 (4.) 20	16.8 (2.9) 21	16.7 (2.3) 414
Mean total absolute IOP reduction at 2 months from pre-treatment IOP after LAST SLT (mmHg; 95% CI) Eyes (n)	9.1 (6.4 to 11.8) 29	7.7 (6.6 to 8.8) 75	1.3 (-0.2 to 2.7) 20	5.1 (3.7 to 6.4) 21	7.9 (7.6 to 8.2) 414

Table 28: Early IOP lowering of Eyes following Initial SLT and Repeat SLT

A further sub-analysis of the 115 eyes requiring Repeat SLT within the first 18 months is presented in Table 28. 34 eyes required Repeat SLT at 2 months ('Early Failures') vs 81 eyes required Repeat SLT later ('Later Failures). IOP lowering data at 2 months for 'Early' and 'Later' Failures is presented, alongside for reference, the 2 month IOP lowering data for the 43 eyes started on topical medication following initial SLT and the 453 eyes that were maintaining successful IOP control following initial SLT.

Overall, in both the 'Early Failures' and 'Late Failures' Repeat SLT eyes, there was a greater proportion of eyes with 'moderate' and 'severe' POAG compared to the group of eyes controlled on a single SLT at 18 months. They also had a greater required absolute IOP reduction to achieve 'Target IOP' compared to eyes controlled on a single SLT at 18 months.

Comparison of pre-treatment IOP prior to initial SLT for the 'Early Failures' vs 'Later Failures' who underwent repeat SLT demonstrated a significantly higher pre-treatment IOP in the 'Early Failures' eyes (mean difference: 3.0mmHg, 95% CI, 0.3 to 5.8mmHg; p=0.033). Absolute IOP reduction at 2 months following initial SLT was not statistically or clinically significantly different between 'Early Failures' and 'Later Failures' (mean difference: 0.6 mmHg, 95% CI, -1.4 to 2.6; p=0.551). There was no significant difference in pre-retreatment IOP prior to Repeat SLT between 'Early Failures' vs 'Later Failures' eyes (mean difference: 1.2 mmHg, 95% CI, -0.5 to 3.0 mmHg; p=0.169), with no significant difference in absolute IOP reduction following Repeat SLT at 2 months between 'Early Failures' vs 'Later Failures' (mean difference 0.3mmHg, 95% CI, -1.1 to 1.8mmHg; p=0.655).

For reference, mean absolute IOP reduction at 2 months following Initial SLT (95% CI) in the 20 eyes which then immediately started on topical medication ('no' treatment effect from Initial SLT – as judged by clinician) was 1.3mmHg (-0.2 to 2.7mmHg). Mean absolute IOP reduction (95% CI) at 2 months in the 23 eyes which started on topical medication beyond the first scheduled visit but did not undergo Repeat SLT was 5.1mmHg (3.7 to 6.1mmHg). Mean absolute IOP reduction (95% CI) at 2 months in the 453 eyes successfully maintaining IOP control to 18 months following single Initial SLT was 7.9mmHg (7.6 to 8.2mmHg). The mean IOP at 2 months in eyes following repeat SLT, in both 'Early Failures' and 'Late Failures', was similar to the 2 month IOP in eyes following single SLT and not requiring a repeat treatment.

Duration of Effect

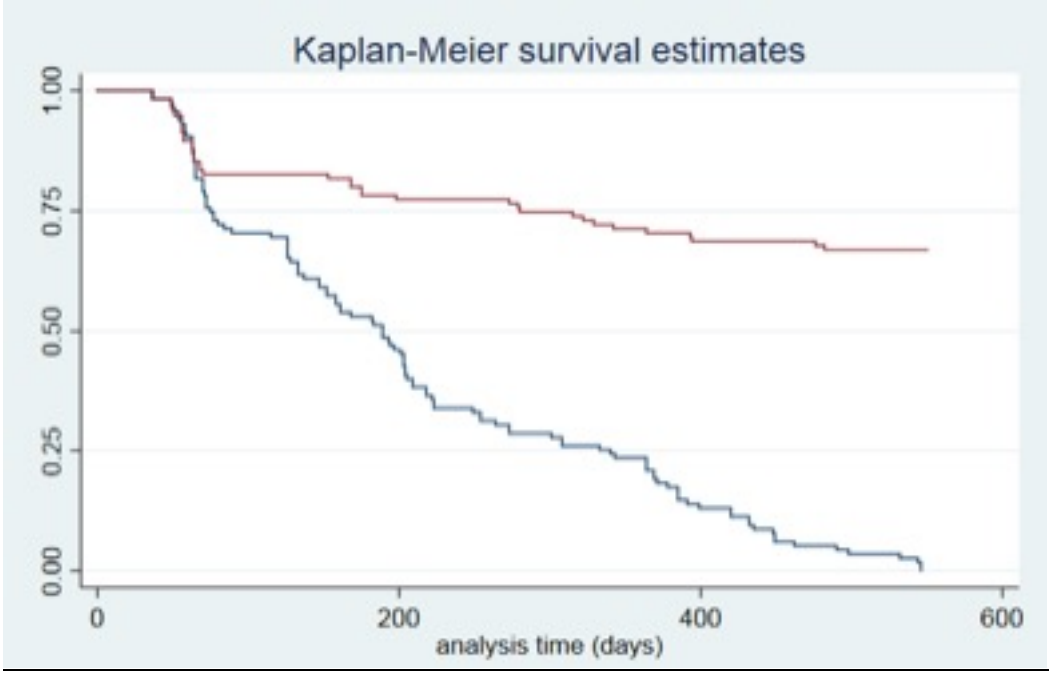


Figure 9: Kaplan Meier Plot for 115 eyes: Initial SLT (blue line) vs Repeat SLT (red line)

In this analysis, the duration of Repeat SLT effect (and restoration of IOP control) lasted at least as long as after the Initial SLT. For this sample of patients requiring Repeat SLT within 18 months of Initial SLT, using 'no further IOP lowering interventions following Initial SLT' as a definition of success, Kaplan Meier analysis of Initial SLT survival demonstrated a median duration of effect of 189 days (Interquartile range (IQR): 75 – 340 days), see Figure 9. We could not determine overall median duration of effect for Repeat SLT, as 50% of these eyes did not reach the endpoint within the 18 months follow up period, though our results show that it is at least 18 months. Two eyes in the study sample underwent cataract surgery for visually significant cataract during the study period (following Repeat SLT) and were included in this analysis. If these 2 eyes are excluded from the analysis or treated as Repeat SLT failures, the results and conclusions are unchanged.

Thirty eight of 115 eyes (33%) receiving Repeat SLT within the first 18 months had commenced medical treatment ('Repeat SLT failures') in the 18 months following the Repeat SLT. Approximately 60% of these eyes had a baseline disease severity of either 'moderate' OAG (12 eyes, 31.6%) or 'severe' OAG (11 eyes, 29%), with fewer OHT (1 eye, 2.6%) or 'mild' OAG (14 eyes, 36.8%). In these 38 'Repeat SLT failure' eyes, 20 were 'early failures' and 18 were 'later failures' following Initial SLT.

The remaining 67% of eyes (77 of 115) did not require further intervention in the subsequent 18 months. Approximately 68% of these eyes had a baseline disease severity of either 'OHT' (21 eyes, 27.3%) or 'mild' OAG (32 eyes, 41.6%), with

fewer 'moderate' OAG (15 eyes, 19.5%) or 'severe' OAG (9 eyes, 11.7%). Survival estimates taking one randomly-selected eye per patient were similar (see Appendix).

Of the 115 eyes requiring Repeat SLT following Initial SLT, the indication for Repeat SLT in 98.3% (113 eyes) of eyes was due to the IOP not being at target. Of the 2 remaining eyes, 1 eye required Repeat SLT due to IOP not being at target and concurrent visual field progression and the other eye due to visual field progression alone. Of the 38 eyes requiring additional treatment escalation following Repeat SLT (i.e. started on medication), 92.1% (35 eyes) of these eyes were escalated due to the IOP not being at target. Of the 3 remaining eyes, 1 eye required additional treatment due to the IOP not being at target and concurrent visual field progression whilst 2 eyes had visual field progression alone.

Safety

We found no evidence of harm caused by SLT during the LiGHT trial (301, 302); no IOP spikes >5mmHg from pre-treatment IOP at 60 minutes post procedure were seen after Repeat SLT. There were no sight threatening adverse events related to initial or Repeat SLT. All laser-related adverse events (e.g. discomfort, headaches, hyperaemia, transient blurred vison) were self-limiting and resolved within 8 weeks following SLT.

4.4.6 Safety

Overall, there were a greater number of adverse events (AEs) in the Medicine 1st arm compared to the Laser 1st arm (1196 vs 900).

Systemic adverse events

Systemic AEs were similar overall between the two treatment arms (Table 29). Medication-related systemic AEs were reported more often and by more patients in the Medicine-1st arm (148 events reported by 52 patients (14·4%) compared to 87 events reported by 23 patients (6·5%) in the SLT arm). Pulmonary problems and cardiac events were few and balanced between the two arms.

	Medicine-1st		Laser-1st	
	Number of events	N (%) of Patients	Number of events	N (%) of Patients
Systemic Adverse Events/Symptoms	298	115 (31.8)	236	98 (27.6)
Pulmonary problems	23	14 (3.9)	24	12 (3.4)
Cardiac events	6	5 (1.4)	8	5 (1.4)
Heart Block	1	1 (0.3)	0	0 (0)
Cardiac Arrhythmia	5	4 (1.1)	8	5 (1.4)
Drug related events	148	52 (14.4)	87	23 (6.5)
Impotence	10	3 (0.8)	7	4 (1.1)
Depression	18	9 (2.5)	14	4 (1.1)
Somnolence/Tiredness	60	31 (8.6)	34	17 (4.8)
Nightmares	21	11 (3)	15	4 (1.1)
Generalised Skin Rash	18	11 (3)	13	8 (2.3)
Taste Disturbance	21	18 (5)	4	3 (0.8)
Other [b]	121	82 (22.7)	117	78 (22)

Table 29: Systemic Adverse events

Ophthalmic adverse events

There were more ophthalmic drop related AEs reported by patients in the Medicine-1st arm (150 aesthetic side effects and ocular allergic reactions reported by 73 patients) compared to the Laser-1st arm (30 equivalent events reported by 20 patients). In both arms, one patient developed reactivation of herpes keratitis. There was also a greater frequency of conjunctival injection, ocular irritation, itching reported in the Medicine-1st arm compared to the Laser-1st arm (see Table 30).

	Medicine-1st		Laser-1st	
	Number of events	N (%) of Patients	Number of events	N (%) of Patients
Ophthalmic Adverse events	809	241 (66.6)	492	188 (53)
Aesthetic drop side effects	117	56 (15.5)	12	7 (2.0)
Change in Iris Colour	6	4 (1.1)	1	1 (0.3)
Peri-ocular Pigmentation	24	16 (4.4)	4	4 (1.1)
Excessive Lash Growth	87	48 (13.3)	7	5 (1.4)
Ophthalmic allergic reactions	33	17 (4.7)	18	13 (3.7)
Peri-ocular skin rash	16	10 (2.8)	5	5 (1.4)
Allergy	17	11 (3)	13	8 (2.3)
Uveitis	1	1 (0.3)	2	2 (0.6)
Reactivation of Herpes	1	1 (0.3)	1	1 (0.3)
Other	744	118 (32.6)	459	117 (33)
Conjunctival Injection	109	61 (16.9)	33	25 (7)
Ocular Irritation, Discomfort or Dry Eye	239	125 (34.5)	147	97 (27.3)
Itching	103	51 (14.1)	73	44 (12.4)
Stinging on Instillation	89	53 (14.6)	18	11 (3.1)
Optic disc haemorrhage	4	4 (1.1)	8	7 (2)
Macular haemorrhage	0	0 (0)	0	0 (0)
Sub-conjunctival haemorrhage	9	8 (2.2)	2	2 (0.6)
Cataract	14	13 (3.6)	19	17 (4.8)
Blurred vision	19	18 (5)	12	12 (3.4)
Change in vision	16	14 (3.9)	9	9 (2.5)
Floater(s)	5	5 (1.4)	11	8 (2.3)
Flashes	4	4 (1.1)	8	7 (2)
Conjunctivitis	8	8 (2.2)	6	5 (1.4)
Watery eye	8	7 (1.9)	13	11 (3.1)
Glare	4	4 (1.1)	6	5 (1.4)
Pain/Sore eye	10	10 (2.8)	8	8 (2.3)
Blepharitis	6	6 (1.7)	0	0 (0)
Swollen eye(s)	3	3 (0.8)	1	1 (0.3)
Photophobia	4	4 (1.1)	4	3 (0.8)
CRVO	2	1 (0.3)	0	0 (0)
BRVO	1	1 (0.3)	2	1 (0.3)
Diabetic retinopathy	0	0 (0)	1	1 (0.3)
Diabetic macular oedema	0	0 (0)	3	2 (0.6)

Table 30: Ophthalmic Adverse events

Laser related adverse events

There were no sight threatening adverse events related to primary SLT (initial or repeat SLT) during or after the procedure (see Table 31). 6 eyes (of 6 patients) experienced immediate post laser IOP spike (>5mmHg from pre-treatment IOP) at 60 minutes following initial SLT, but only one of these eyes required medical treatment. No IOP spikes >10mmHg from pre-treatment IOP at 60 minutes post procedure were reported. There were no IOP spikes reported immediately post repeat SLT. In 4 patients (1.1%), there was difficulty in visualizing the angle and in 3 patients (0.9%) fewer laser applications than required by the protocol were reported to have been used. Following SLT, symptoms including ocular discomfort, headache, blurred vision and photophobia were reported by 34.4% of patients (122 patients). These were of a transient nature and self-limiting; all had resolved by the first scheduled visit. No IOP spikes (>5mmHg from Baseline IOP) were detected at the 2-week safety check visit post SLT; 6.2% of eyes (38 eyes) were noted to have a higher IOP at 2-week safety visit compared to baseline.

Adverse Events during SLT	Total Number of Events (n=20)	Total Number of Patients reporting (N=19) (5.4%)
Discomfort (Ocular and/or Headache)	6	6 (1.7%)
IOP spike (>5mmHg)	6	6 (1.7%)
Other (specify): Fewer shots Visualization of angle	 3 5	 3 (0.9%) 4 (1.1%)
Adverse Events post SLT	Total Number of Events Total (n=172)	Total Number of Patients reporting (N=122) (34.4%)
Discomfort (Ocular and/or Headache)	92	82 (23.1%)
Blurred/ altered vision	23	21 (5.9%)
Change in Refraction	5	4 (1.1%)
Inflammation post SLT	1	1 (0.3%)
Other (specify): Photophobia Hyperaemia	51 21 3	47 (13.2%) 20 (5.6%) 3 (0.8%)

Table 31: Laser related Adverse events

Serious adverse events

SAEs were overall balanced between the two treatment arms (see Table 32); there were 97 events in the Medicine-1st arm reported by 69 patients and 107 events reported by 64 patients. The most common ocular SAEs were vascular occlusions, retinal detachments, choroidal neovascularisation and angle closure. In terms of systemic SAEs, Pulmonary problems requiring hospitalisations were balanced between the Medicine-1st and Laser-1st arms (3 compared to 2, respectively), as were cardiac events (7 compared to 9, respectively). There were few and balanced cerebrovascular accidents (1 in the Medicine-1st arm compared to 2 in the Laser-1st arm). There were more cancer diagnoses (15 events) and deaths (8) in the Laser-1st arm compare to the Medicine-1st arm (9 and 2 events, respectively).

	Medicine-1st		**Laser-1st**	
Total number of events	**97**		**107**	
Total number of patients reporting	**69**		**64**	
	N of events	**N (%)**	**N of events**	**N (%)**
Ocular	**9**	**6**	**10**	**8**
CRVO/BRVO	**1**	**1**	**1**	**1**
Retinal detachment	**1**	**1**	**3**	**2**
Anterior chamber surgery	**1**	**1**	**0**	**0**
Posterior segment surgery	**1**	**1**	**0**	**0**
Corneal ulcer	**1**	**1**	**0**	**0**
CNV	**2**	**2**	**3**	**3**
Angle closure requiring intervention	**2**	**1**	**2**	**1**
Post-traumatic uveitis	**0**	**0**	**1**	**1**
Pulmonary problems [a]	**3**	**3**	**2**	**2**
Cerebrovascular accidents	**1**	**1**	**2**	**2**
Cardiac events [a]	**7**	**7**	**9**	**8**
Cancer	**9**	**8**	**15**	**13**
Death	**2**	**2**	**8**	**8**
Other Systemic	**66**	**50**	**61**	**43**

Table 32: Serious adverse events. a: requiring hospitalisation

4.5 Quality of Life Analyses

In this section, the results of the quality of life PROMS analyses from LiGHT are described. Dr Vicki Vickerstaff – a principal member of the LiGHT trial statistical team, performed the statistical analyses of the HRQL outcome measures, as well as providing guidance related to the further PROMs analyses carried out as part of this thesis. Her contribution has been acknowledged at the start of this thesis.

4.5.1 Primary Outcome Measure: EQ5D

A total of 652 patients returned the primary outcome at the trial's end point at 36 months (overall return rate was 91%: 92% for the SLT arm and 89% for the Medicine-1st arm), and were included in the intention to treat analysis. An additional 21 patients supplied 30-month data, which was used to impute their missing 36-month data, such that 673 patients were included in the primary ITT analysis.

A total of 16 patients in the Laser-1st arm and 9 patients in the Medicine-1st arm discontinued participation. In total, 2 patients were lost to follow-up and were no longer contactable, 4 patients moved to a different hospital, 4 patients withdrew from the trial, 5 patients could not continue participation owing to ill health and 10 patients died.

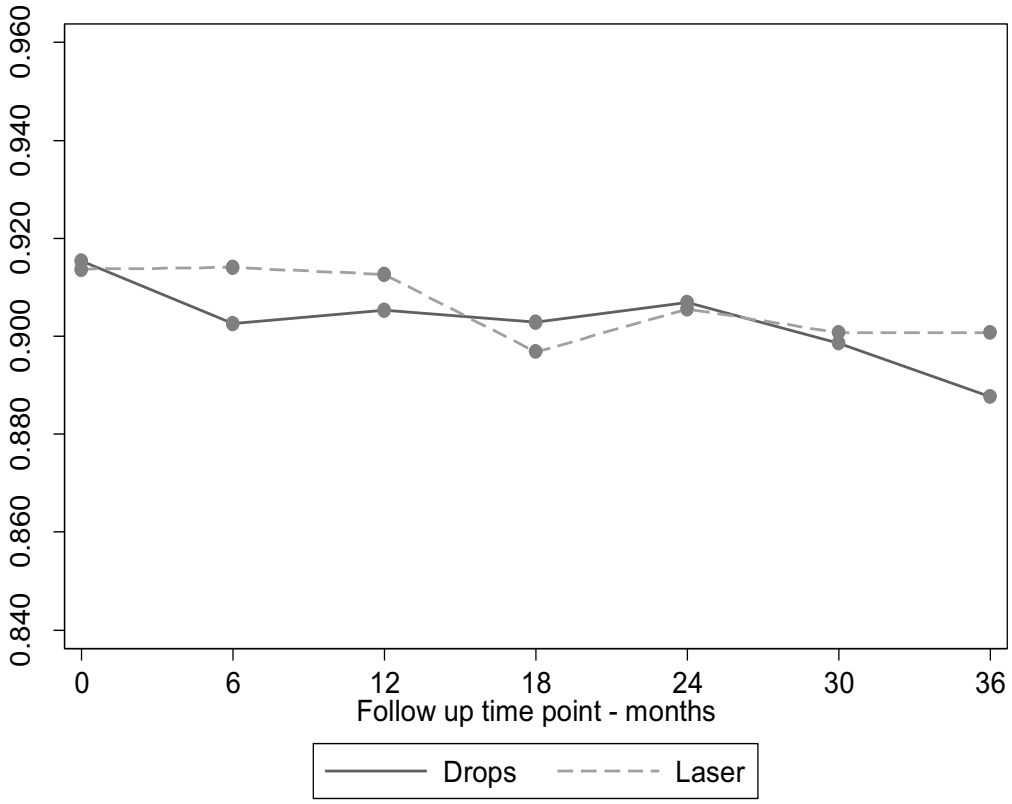


Figure 10: Mean EQ5D scores at each time point across 36 months. Time-point '0' refers to pre-treatment. Higher score indicates better HRQL

At 36 months, the Laser 1st arm had an average EQ-5D-5L score of 0.90 (SD 0.16), compared with 0.89 (SD 0.18) in the Medicine-1st arm, suggesting little difference between the two treatment arms [adjusted mean difference (Laser-1st – Medicine-1st): 0.01, 95% CI –0.01 to 0.03; p = 0.23). Repeated measures analysis across 36 months also demonstrated no significant difference between both treatment groups across all time points (see Table 33).

	Medicine 1st		Laser 1st			
	n	Mean (SD)	n	Mean (SD)	Adjusted mean difference	95% CI
Baseline	**362**	**0.92 (0.13)**	**355**	**0.91 (0.13)**		
6 months	**332**	**0.90 (0.15)**	**330**	**0.91 (0.13)**	**0.01**	**–0.01 to 0.03**
12 months	**327**	**0.91 (0.14)**	**327**	**0.91 (0.14)**	**0.01**	**–0.01 to 0.02**
18 months	**329**	**0.90 (0.16)**	**325**	**0.90 (0.16)**	**0.00**	**–0.02 to 0.02**
24 months	**326**	**0.91 (0.14)**	**326**	**0.91 (0.14)**	**0.00**	**–0.02 to 0.02**
30 months	**320**	**0.90 (0.15)**	**317**	**0.90 (0.15)**	**0.00**	**–0.01 to 0.02**
36 months	**323**	**0.89 (0.18)**	**329**	**0.90 (0.16)**	**0.02**	**–0.01 to 0.03**

Table 33: EQ5d: Repeated measures analysis across 36 months

4.5.2 Secondary outcomes: GUI, GQL-15, GSS

Glaucoma Utility Index

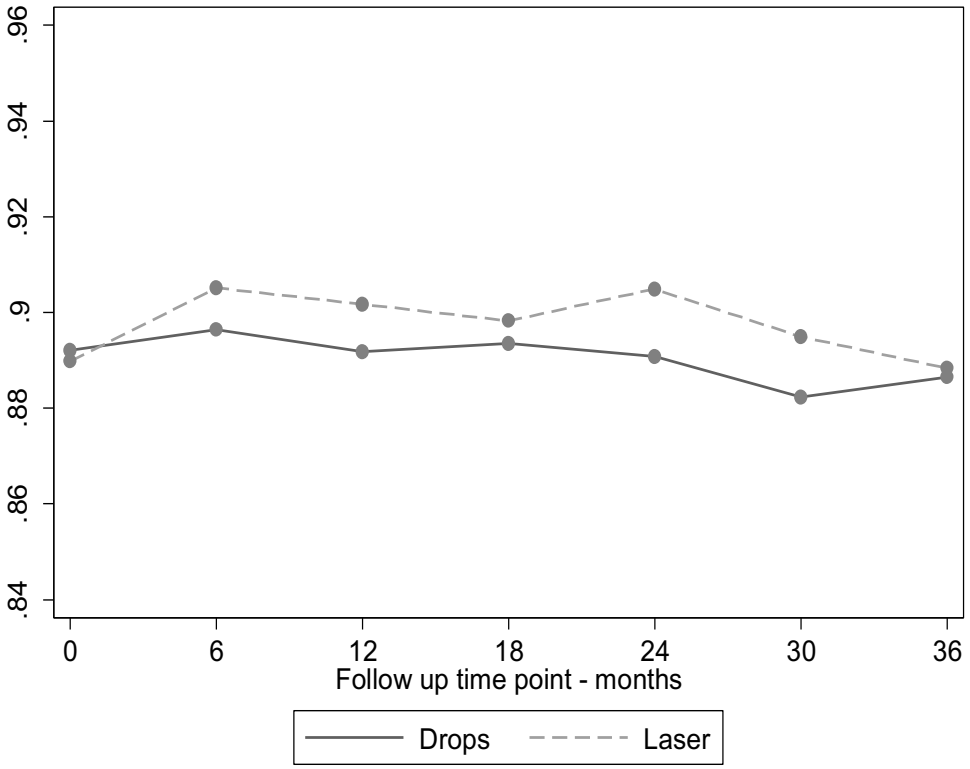


Figure 11: Mean GUI scores at each time point across 36 months. Time-point '0' refers to pre-treatment. Higher score indicates better HRQL

The Laser 1st arm scored an average of 0.89 (SD 0.13) for the GUI compared to 0.89 (SD 0.13) for the Medicine-1st group at 36 months, suggesting no difference between the two treatment arms (adjusted mean difference 0.01, 95% CI: -0.01, 0.02). Repeated measures analysis across 36 months also demonstrated no significant difference between both treatment groups across all time points (see Table 34), despite the trend of the Laser 1st arm appearing to demonstrate better HRQL scores throughout all the preceding time points post baseline.

	Medicine 1st		Laser 1st			
	n	Mean (SD)	n	Mean (SD)	Adjusted mean difference	95% CI
Baseline	361	0.89 (0.11)	355	0.89 (0.12)		
6 months	330	0.90 (0.11)	329	0.91 (0.10)	0.01	–0.00 to 0.03
12 months	315	0.89 (0.12)	320	0.91 (0.11)	0.01	–0.00 to 0.03
18 months	305	0.89 (0.12)	303	0.90 (0.13)	0.01	–0.01 to 0.02
24 months	298	0.89 (0.12)	305	0.90 (0.11)	0.02	0.00 to 0.03
30 months	299	0.88 (0.12)	291	0.89 (0.12)	0.02	0.00 to 0.03
36 months	300	0.89 (0.13)	303	0.89 (0.13)	0.01	–0.01 to 0.02

Table 34: GUI: Repeated measures analysis across 36 months.

Glaucoma Quality of Life-15

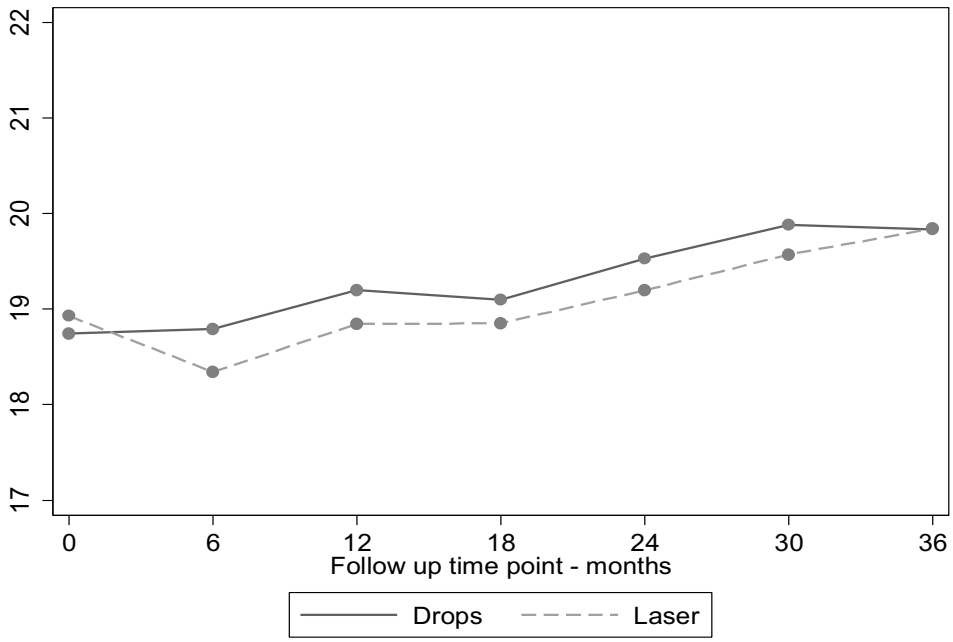


Figure 12: Mean GQL-15 scores at each time point across 36 months. Higher score indicates worse HRQL

Mean GQL-15 scores at 36 months were similar between the two arms (19.8 for Laser-1st and 19.8 Medicine-1st, adjusted mean difference -0.4, 95% CI: -1.2,0.4). Repeated measures analysis across 36 months also demonstrated no significant difference between both treatment groups across all time points (see Table 35). This is despite the trend demonstrating that the Medication 1st arm appeared to have worse HRQL scores throughout the preceding time points post baseline.

	Medicine 1st		**Laser 1st**			
	n	**Mean (SD)**	**n**	**Mean (SD)**	**Adjusted mean difference**	**95% CI**
Baseline	**361**	**18.7 (5.6)**	**355**	**18.9 (6.6)**		
6 months	**323**	**18.8 (5.6)**	**324**	**18.3 (5.4)**	**–0.8**	**–1.6 to 0.0**
12 months	**314**	**19.2 (7.2)**	**318**	**18.8 (6.6)**	**–0.5**	**–1.4 to 0.3**
18 months	**302**	**19.1 (6.4)**	**298**	**18.9 (6.5)**	**–0.6**	**–1.4 to 0.2**
24 months	**289**	**19.5 (7.3)**	**298**	**19.2 (6.7)**	**–0.5**	**–1.3 to 0.4**
30 months	**293**	**19.9 (7.1)**	**287**	**19.6 (7.9)**	**–0.3**	**–1.1 to 0.5**
36 months	**298**	**19.8 (7.8)**	**304**	**19.8 (7.2)**	**–0.4**	**–1.2 to 0.4**

Table 35: GQL-15: Repeated measures analysis across 36 months.

Glaucoma Symptom Score

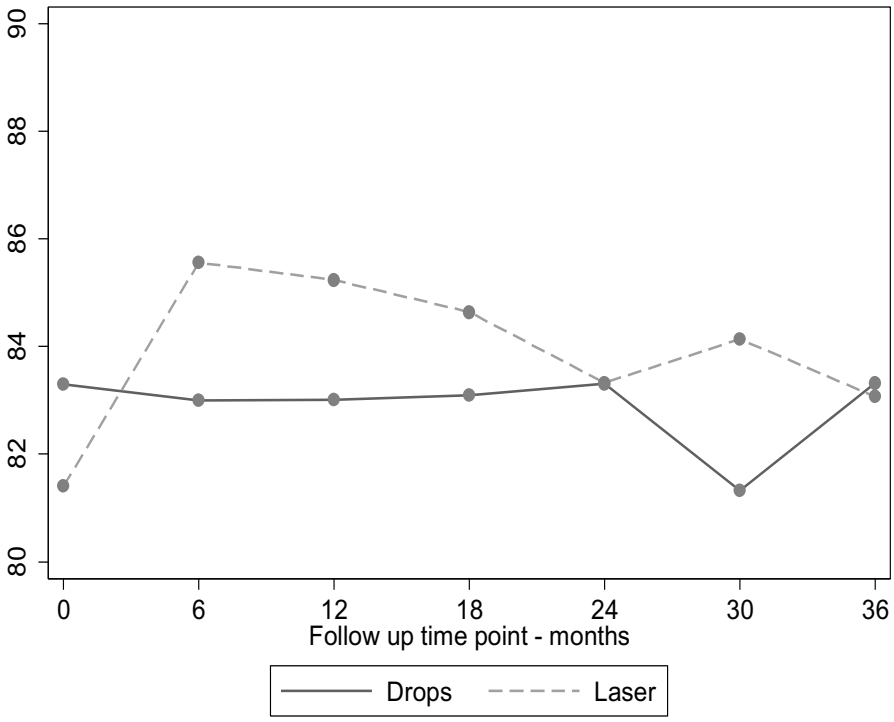


Figure 13: Mean GSS scores at each time point across 36 months. Higher score indicates better HRQL

For GSS, the Laser-1st group had a mean score of 83.3 (SD 17.3) at 36 months, compared to 83.1 (SD 17.7) for the Medicine-1st group (adjusted mean difference 1.6, 95% CI: -0.8, 4.0), suggesting no difference between the two treatment arms. Interestingly, repeated measures analysis across 36 months demonstrated worse scores in the Medicine-1st group in 5 out of the 6 timepoints across 36 months (see Table 36).

	Medicine 1st		Laser 1st			
	n	**Mean (SD)**	**n**	**Mean (SD)**	**Adjusted mean difference**	**95% CI**
Baseline	**357**	**83.3 (16.6)**	**353**	**81.4 (17.2)**		
6 months	**321**	**83.0 (16.3)**	**320**	**85.6 (14.9)**	**4.0**	**2.0 to 6.0**
12 months	**310**	**83.0 (17.6)**	**309**	**85.2 (15.4)**	**2.9**	**0.8 to 4.9**
18 months	**295**	**83.1 (16.8)**	**294**	**84.6 (15.8)**	**2.8**	**0.7 to 4.8**
24 months	**287**	**83.3 (16.4)**	**290**	**83.3 (16.3)**	**1.4**	**–0.7 to 3.5**
30 months	**288**	**81.3 (17.6)**	**276**	**84.1 (16.7)**	**3.5**	**1.5 to 5.6**
36 months	**282**	**83.3 (17.3)**	**296**	**83.1 (17.7)**	**2.2**	**0.1 to 4.2**

Table 36: Mean GSS scores at each time point across 36 months.

Overall, the primary HRQL (EQ5D-5L) and secondary HRQL outcomes (GUI, GSS, GQL-15) generally suggested better HRQL for the Laser-1st cohort, but these were not statistically significant (see Table 33).

		Medicine-1st		**Laser-1st**	**Adjusted mean difference** [a]	**95% CI**	**P-Value**
	N	Mean (SD)	N	Mean (SD)			
Primary analysis at 36 months							
EQ-5D	336	0.89 (0.18)	337	0.90 (0.16)	0.01	-0.01, 0.03	0.230
GUI	299	0.89 (0.13)	303	0.89 (0.13)	0.01	-0.01, 0.03	0.413*
GSS	281	83.3 (17.3)	294	83.1 (17.7)	1.6	-0.8, 4.0	0.196*
GQL-15	297	19.8 (7.8)	304	19.8 (7.2)	-0.4	-1.3, 0.6	0.549*

Table 37: Analysis of HRQL questionnaires at 36 months. Mean difference is adjusted for baseline score, severity, centre, baseline IOP, and number of eyes affected at baseline.

*p- values calculated post-hoc

4.5.3 Further PROMs Analyses

'Drop free' vs 'On topical medication' at 36 months within Primary SLT arm

		'Drop free'		'On topical medication'	Adjusted mean difference	95% CI
	N	Mean (SD)	N	Mean (SD)		
EQ-5D	243	0.90 (0.16)	67	0.88 (0.16)	0.01	-0.02, 0.06
GUI	222	0.89 (0.13)	61	0.86 (0.15)	0.03	-0.00, 0.06
GSS	216	83.7 (18.2)	61	80.7 (16.6)	2.53	-2.2, 7.3
GQL-15	223	19.6 (7.1)	61	20.7 (7.9)	-0.4	-2.3, 1.4

Table 38: Analysis of HRQL questionnaires at 36 months. Mean difference is adjusted for baseline score, severity, centre, baseline IOP, and number of eyes affected at baseline.

Comparing the HRQL measures across 'drop free' patients vs. those on 'topical medication' within the primary SLT arm at 36 months, whilst there was a general trend for all of the QoL scores to be 'better' in the 'drop free' group, there appeared to be no significant difference between the two groups.

‘Disease progressors’ vs ‘No evidence of progression’ at 36 months within Primary SLT arm

		‘Progression’		‘No progression’	Adjusted mean difference	95% CI
	N	Mean (SD)	N	Mean (SD)		
EQ-5D	22	0.88 (0.14)	288	0.90 (0.17)	0.00	-0.06, 0.06
GUI	22	0.82 (0.19)	261	0.89 (0.13)	-0.06	-0.11, -0.01
GSS	21	74.0 (24.2)	256	83.8 (17.1)	-5.6	-12.6, 1.3
GQL-15	22	24.6 (11.7)	262	19.4 (6.6)	3.3	0.7, 5.8

Table 39: Analysis of HRQL questionnaires at 36 months. Mean difference is adjusted for baseline score, severity, centre, baseline IOP, and number of eyes affected at baseline.

Comparing the HRQL measures across ‘disease progression’ patients vs. ‘non progression’ patients within the primary SLT arm at 36 months, there was a general trend of all the QoL scores to be ‘better’ in ‘non progression’ patients.

Section 5: Discussion

In this section, the results of the study will be discussed and their meaning interpreted in the context of the existing evidence in the literature. The strengths and limitations of the work are evaluated. Conclusions about the efficacy of primary SLT are drawn from the findings of the study. Suggestions for further areas of development in future studies are also made.

5.1 IOP Control

5.1.1 IOP Lowering of Primary SLT

Following initial primary SLT, mean initial IOP lowering at 2 months was greater in OHT eyes compared to OAG eyes (8mmHg vs 6.5mmHg), as was mean percentage IOP reduction (29.7% vs 26.1%). This difference was unlikely to be due to varying response of SLT to the two different disease entities, but rather due to OHT eyes having a higher baseline IOP compared to OAG eyes (26.5mmHg vs 23.5mmHg).

If pre-treatment baseline IOP and centre effects were controlled for, there was no significant difference in early absolute IOP lowering between OHT and OAG eyes (adjusted mean difference = -0.05mmHg; 95% confidence interval (CI) -0.6 to 0.5mmHg; p=0.85). This confirms that the observed difference was likely to be related to baseline IOP and not disease entity. This is also reflected in NTG studies, where baseline IOPs are lower and both absolute IOP reductions and success rates are also lower compared to other disease subtypes (212, 213).

There was no significant difference in early absolute IOP lowering at 2 months between topical medication and primary SLT (adjusted mean difference = -

0.1mmHg, CI -0.6 to 0.4mmHg, p= 0.67) At this timepoint, 99.3% of Medication 1st eyes were on a single medication, with the majority (96.1%) on a topical prostaglandin. Previous studies comparing IOP lowering efficacy of SLT and topical prostaglandins have also found no significant difference between the two treatments (181).

A post-hoc power calculation for this IOP lowering analysis was not conducted, since limitations have been reported with such calculations (303). Instead, the narrow (<1mmHg) confidence intervals for our pointwise estimates of differences in early IOP lowering between OHT vs OAG eyes and primary SLT vs topical medication suggest that the study had an adequate sample size to detect a clinically important difference if it exists (304).

Due to the 'Treat to Target IOP' study design of LiGHT, beyond 2 months the computerised decision support software escalated treatment if eyes met escalation criteria. Reporting IOP lowering beyond 2 months would therefore have been confounded by differing treatment intensities based on achievement of target IOP set by the underlying disease severities of each study eye. Whilst this approach was a strength in emulating 'real world' clinical practice, it makes it harder to establish the long term IOP lowering efficacy of primary SLT, which requires observation only at further time points following initial SLT at baseline. Despite this, our logistic regression analysis on "disease control" did demonstrate that lower IOP at 2 months was predictive of achieving "disease-control" at 36 months following initial single SLT at baseline. This suggests that despite being early in the trial, the 2 month timepoint was an important and sensitive marker of disease course for the duration of the trial.

There was no placebo arm in LiGHT to ascertain fully the regression to the mean, but a previous study has demonstrated a ~ 1.4mmHg (SD 3.1) absolute IOP reduction at first visit post placebo compared to 5mmHg (SD 3.6) in the topical latanoprost group (44). Our study design minimised the effects of regression to the mean on IOP lowering: qualifying IOP measurements were made on a separate day to baseline assessments, and IOP level was an entry criterion only for OHT eyes (31.9% of eyes at baseline).

5.1.2 IOP Control

Overall, IOP was at target for 93% of the Laser-1st visits, compared with 91% of the Medicine-1st visits over the 36-month duration of the trial. This high percentage in both arms was due to the 'Treat to Target IOP' design of the trial, whereby the computerised decision support software evaluated whether study eyes were at target IOP at each scheduled visit and escalated treatment if necessary.

The slightly lesser percentage in the Medicine-1st arm could be related to patient compliance with topical treatment, though self-reported concordance was very high in this trial. SLT has previously been suggested to provide better diurnal IOP stability, due to its continuous effect on the TM, in contrast to the episodic administration of medication (180). This trial showed a comparable IOP fluctuation between Medicine-1st and Laser-1st (2.5 mmHg and 2.3 mmHg, respectively). This minimal difference, could again be due to the high self-reported concordance in the trial patient population.

By 36 months, 78.2% (95% CI 74.7% to 81.4%) of the eyes treated in the Laser-1st arm were at target without the need for any topical IOP-lowering medication ("IOP control") (see Table 14). In the Medicine-1st arm for comparison, 64.6% of eyes were at target IOP with only a single medication (see Table 15). This is likely to be a reflection of the study population, which was predominantly OHT and mild OAG eyes. Taking this further, the results also show that at 36 months follow up, 74.6% of eyes (400 eyes) treated with primary SLT achieved drop-free "disease-control" (achievement of Target IOP i.e. "IOP control" and absence of disease progression), with 58.2% of eyes (312 eyes) doing so following a single initial SLT. All these eyes achieved IOP reduction > 20% from baseline IOP (see Tables 16 and 17).

IOP reduction >20% from baseline has been previously reported as occurring in between 38-74% of treated eyes at 36 months (163, 171, 184, 185). In this study, eyes with more advanced glaucoma had to meet more stringent target IOPs set according to previous published guidelines: 'moderate' or 'severe' disease had to achieve a minimum 30% reduction from baseline IOP to continue without further intervention (281). Thus, more severely affected eyes achieving >20% but <30% IOP reduction following first SLT would have undergone a further treatment (2nd SLT or medication if non-response to 1st SLT). This is reflected in our results with only 58.2% of eyes not receiving additional therapy. The relative proportion of eyes achieving drop-free "disease-control" at 36 months after initial single SLT at baseline (Table 17) was greater in OHT and 'mild OAG' eyes (with less stringent targets) than 'moderate' and 'severe OAG' eyes (with lower target IOPs), despite similar mean absolute IOP reductions for all levels of disease severity (Table 18). This does not mean SLT was ineffective in more advanced disease, merely insufficient in isolation.

Primary SLT gave drop-free IOP control for at least 36 months to 74.2% of patients (95% CI 69.3% to 78.6%) following 1 or 2 SLTs; substantially higher than reported in previous studies that used less stringent success criteria and which used SLT exclusively as the primary treatment (180-182). Prior treatment has been suggested to reduce the magnitude of IOP lowering with SLT (182) possibly explaining the results of this trial in treatment-naive patients.

In this analysis, despite no clinically or statistically significant differences in gender or ethnicity being noted in eyes available vs unavailable to analyse at 36-months, relatively more females and black patients had eyes unavailable for analysis. Studies have shown disparities in the utilization of eye care services among different racial minorities, with socio-economic deprivation and differences in access to healthcare implicated as contributory to this (305, 306).

Direct comparison between SLT studies is difficult. Differences in study design exist between studies, including patient demographics, disease subtypes investigated (OHT vs OAG), variations in topical IOP lowering medication usage prior to SLT (treatment-naïve vs medication washout period prior to SLT vs adjunct SLT in uncontrolled eyes on maximum tolerated medical therapy), differences in SLT treatment parameters (180-degree vs 360-degree treatments, variability in numbers of shots fired), variability in follow up intervals, total duration of follow up and variable definitions of success.

5.2 Treatment Intensity

5.2.1 Objective measures of visual function

The Laser-1st and Medicine-1st arms had comparable mean endpoint visual acuity, mean deviation, pattern standard deviation, disc HRT and IOP measurements (see Table 19). This was expected, due to the 'Treat to Target IOP' design of the trial, whereby the same escalation criteria were being used by an objective computerised decision support software to guide treatment decisions across both treatment arms.

5.3.2 Treatment Intensity

Overall, the total number of clinic visits at 36 months was greater in the Laser-1st arm (3441 visits) vs the Medicine-1st arm (2907 visits). The treatment protocol of the Laser-1st arm included a safety IOP check visit at 2 weeks following each SLT, which was not needed for the Medicine-1st arm. If the 2-week safety check visits (465 visits) were excluded, the total number of clinic visits was similar between treatment arms (2907 vs 2976 visits).

Upwards (22 in the Medicine-1st arm and 26 in the Laser-1st arm) and downwards (16 in the Medicine-1st arm and 15 in the Laser-1st arm) target IOP revisions were overall balanced between the two treatment arms. Again, this was expected, since the same computerised decision support software tool, with the same escalation criteria was being used across both treatment arms.

By 36 months, 78.2% (95% CI 74.7% to 81.4%) of the eyes treated in the Laser-1st arm were at target without the need for any topical IOP-lowering medication ("IOP

control") (see Table 20). In the Medicine-1st arm for comparison, 64.6% of eyes were at target IOP with only a single medication and a further 18.3% of eyes were at target IOP with two medications. This was likely to be a reflection of the study population of predominantly OHT and mild OAG eyes across both treatment arms, with resultant higher target IOPs, that were more achievable with less intensive treatment in both arms. It is likely that had the study population included a greater proportion of patients with more advanced disease, that the treatment intensity across both arms would have been 'shifted' further along the treatment paradigm in both arms. Indeed, whilst this may be the case, for patients with advanced glaucoma who require achievement of low target IOPs, primary SLT is generally not a favoured first line treatment choice. In such patients, early glaucoma filtration surgery is usually favoured to achieve the sustained, low IOP required. The Treatment of Advanced Glaucoma Study (TAGS) is a multi-centre RCT currently in progress which is comparing topical treatment vs trabeculectomy to address which treatment modality is best for newly diagnosed advanced glaucoma patients (307).

By 36 months, fewer cataract surgeries had been performed in the Laser-1st arm vs the Medication-1st arm (13 vs 25). Whilst this is noteworthy, the overall numbers in both arms are low and so limited conclusions can be made about whether the difference in treatment arms had any influence on cataract formation.

By 36 months, 11 eyes in the Medicine-1st arm, but none in the Laser-1st arm, had required IOP-lowering surgery. This difference is likely to be due to the trial study design. In the Laser-1st arm, if initial and repeat laser were unsuccessful, patients

were then started on topical medication. This would in essence, defer the need for interventional IOP lowering surgery as compared to the Medication-1st arm, where following unsuccessful IOP control using topical treatment, the next step was incisional glaucoma surgery.

Since the study design did not permit Medication-1st eyes to receive SLT following unsuccessful topical treatment, we are unable to make any inferences from the 36 month results of this trial about the ability of SLT to act as an adjunct treatment to eyes on maximally tolerated medical treatment with regards to additional IOP lowering or ability to defer the need for surgery.

5.3 Disease Progression

By 36 months, rates of disease deterioration were higher in the Medicine-1st arm than in the Laser-1st arm [5.8% (36 eyes) vs. 3.8% (23 eyes), respectively], despite the 'treat to target' study design, tailoring treatment intensity to disease severity and treatment response. The vast majority of disease progression happened in eyes with OAG (33 out of 36 eyes in the Medicine-1st arm and 21 out of 23 eyes in the Laser-1st arm). Additionally, there were more treatment escalations over 36 months in the Medicine-1st arm (348, compared with 299 in the Laser-1st arm). This suggests that overall, primary SLT achieved better disease control with less treatment intensity, compared to topical medication.

Across both treatment arms, an important point must be noted about the notion of 'treatment escalations'. In this study, a treatment escalation was suggested by the

computerised decision support software tool based on the pre-defined escalation criteria. Treatment escalations were either topical treatment (or addition of further topical medication as required), further laser or surgery. It must be recognised however, as is the case in clinical practice, that not all treatment escalations are 'equal', especially for patients. For example, a treatment escalation for inadequate IOP control involving incisional glaucoma surgery such as trabeculectomy is much more 'involved' (in terms of risk of complications, potential for harm, discomfort/pain and visual loss) compared to starting a topical medication. This difference was not 'measurable' in the trial, but as such, the fewer number of treatment escalations, incisional glaucoma surgeries and surgical procedures overall in the Laser-1st arm compared to the Medication-1st arm is an important finding to note.

5.4 IOP Predictors of IOP lowering & Disease Control

It was found that higher baseline IOP was a predictor of early absolute IOP lowering at 2 months in a mixed effects linear regression model. Increasing baseline IOP has already been reported as being associated with increased IOP lowering (218) and was also demonstrated in this study, in which OHT eyes had greater IOP lowering from baseline compared to OAG eyes. This association between a greater degree of IOP lowering and higher baseline IOP has also been observed in untreated glaucoma eyes receiving topical medication (308, 309). This suggests that irrespective of initial treatment modality, patients with higher untreated IOPs are more likely have a greater IOP lowering response compared to those with lower IOPs. Lower baseline IOPs are closer to the physiological 'floor' that exists within eyes due to ocular episcleral venous pressure (~13-14mmHg)

and so are likely to have a lesser IOP lowering response compared to starting baseline IOPs which are further away from this 'floor'.

In this analysis, female gender was associated with lesser initial IOP lowering, not a commonly reported predictor of IOP lowering (299). Further studies are needed to investigate whether this is indeed a consistent association or specific to the study population in this trial.

For the predictors of drop-free disease control mixed effects logistic regression model, it was taken into account that more advanced disease severities required greater IOP reductions to achieve target IOP. Terms for baseline disease severity and site (to control for centre effects) were used, whilst using the eye as the unit of analysis and using patients as a random factor to adjust for correlation between paired eyes. The logistic regression model suggested a statistically significant but small increase in odds of achieving drop-free "disease-control" at 36 months with higher total power of 1st SLT (adjusted odds ratio 1.02, 95% CI 1.01 to 1.04, p=0.01). For the logistic regression analysis, there were sufficient events based on the rule of thumb that 10-15 'events per variable' are required to develop an adequate prediction model (310).

On further analysis, mean total power of 1st SLT in 'success' eyes was 92.6mJ (SD 21.8) vs 87.7mJ (SD 25.6) in 'non-success' eyes (adjusted mean difference = 2.37mJ, 95% CI -0.5, 5.2 mJ). The modest effect and overlap in treatment parameters between 'success' and 'non-success' eyes means that response prediction was not possible. The trend to a greater response with more power delivered would need confirmation in future studies.

There is mixed evidence regarding the optimum power settings for SLT treatment. Tang et al compared 39 patients receiving 100 shots of 360^0 SLT using low energy settings (0.3-0.5mJ) with 35 patients who received 100 shots of 360^0 SLT using standard energy settings (0.6-1.0mJ) (152). No difference in IOP lowering between groups at all time points up to 1 year was noted. Furthermore, there was reduced incidence of adverse events in the lower energy group. Realini found total laser power *not* to be a significant predictor of 12-month success, with a mean (SD) of 86.0 (21.1) mJ in right eye and 87.7 (20.6) mJ in left (311) compared to a mean (SD) of 90.4 (23.5) mJ in our study (312). In contrast, Lee et al found greater total SLT energy was associated with a greater IOP lowering, but that study was limited by small sample size, short follow up (1 month) (153) and total energy powers that were considerably higher than those in this study ("optimum" total reported as 226.1mJ). Habib et al divided 360 degree SLT treatment patients into those who received low (<85 mJ), medium (85–105 mJ), or high (>105 mJ) energy SLT. At all time points up to 36-month follow-up, there was a significant positive correlation between greater energy and IOP lowering (154).

It was sought to establish whether IOP at first scheduled visit post SLT at 2 months was predictive of achieving "disease-control" at 36 months following initial single SLT at baseline. In the trial protocol, the 2-month time point was the first scheduled visit (aside from the 2 week safety check) at which patients were seen. This allowed sufficient time for the laser to take effect whilst also permitting comparison with the IOP lowering of the Medication 1^{st} arm eyes which were also first schedulted to be reviewed at 2 months post initiation of topical medication. A previous study found that the only significant predictor of IOP lowering at 12 months across all eyes was time, with maximum IOP reduction seen at 3 months

followed by a slow decline in effect subsequently (311). In this study, successful eyes achieving drop-free “disease-control” following initial single SLT at 36 months had a lower mean IOP at 2 months (16.5mmHg (SD 3.2) compared to non-successful eyes (18.5mmHg (SD 3.9). Whilst this difference was statistically significant in a mixed model (adjusted mean difference = -1.9mmHg; 95% CI, -1.4 to -2.3mmHg), the potential overlap between the standard deviations of the two groups suggests that there may not be enough specificity in this observation to be helpful in the individual case.

5.5 Repeatability of SLT

The aim of this analysis was to determine and characterise the efficacy of Repeat SLT in eyes requiring retreatment (within 18 months) following Initial SLT. Mean IOP following both Initial and Repeat SLT was clinically and statistically significantly reduced from the corresponding pre-treatment IOP at 2 months ($p<0.001$), confirming Repeat SLT to be effective (see Table 27). This supports results from other studies which have suggested effective IOP reduction following Repeat SLT (204-207, 209).

Furthermore, compared to Initial SLT (controlling for difference in pre-treatment IOPs), adjusted absolute IOP reduction was statistically significantly greater following Repeat SLT at the 2 month timepoint than at the same time post-laser following the first treatment. It is possible that this demonstrates an additive effect of Repeat SLT. An alternative explanation is that this may be inflated by superimposed effects of regression to the mean: LiGHT was a pragmatic trial primarily designed to evaluate quality of life and cost-effectiveness and patients were not recalled to define a second baseline IOP prior to Repeat SLT. However, the longer duration of effect for Repeat SLT suggested by fewer failures ('reinterventions') over an equivalent 18 months follow up window supports the idea of a greater, additive IOP lowering after re-treatment. Histological studies have demonstrated that SLT causes minimal TM damage (136, 313) and this also fits with the repeatability of IOP lowering as demonstrated in our results.

Following Initial SLT, there was a trend for mean IOP to increase over time. By the nature of the patient selection for this analysis, this was more rapid than in the LiGHT trial overall (301), since we specifically selected patients requiring

retreatment within 18 months. Our trial protocol mandated that more advanced disease had to achieve more stringent targets with greater IOP reductions (minimum 30% reduction vs minimum 20% for mild OAG or OHT eyes) (281) and were thus more likely to need treatment escalation to achieve these lower targets. This is reflected in the greater proportion of 'moderate' OAG or 'severe' OAG (47/115 = 40.9%) eyes in the Repeat SLT study sample compared to those eyes controlled on single SLT at 18 months (44/453 = 9.7%) and the greater IOP reduction required to achieve the target IOP (Table 4), especially in the 'early failure' group.

Similar to other studies (204-207), the pre-treatment baseline IOP of Initial SLT was significantly higher than that prior to Repeat SLT (mean difference: 3.4mmHg, 95% confidence interval (CI), 2.6 to 4.3mmHg; $p<0.001$). This is because Repeat SLT was delivered prior to the full treatment effect of the Initial SLT wearing off, in contrast to the treatment-naïve baseline IOP. This mirrors clinical practice where repeat treatment escalations (medication, laser or surgery) are usually not delayed to allow IOP to return to pre-treatment levels. Higher starting baseline IOP has been found to be a predictor of greater absolute IOP lowering (299) and hence mean absolute IOP reduction was expected to be less for Repeat SLT compared to Initial SLT (e.g. at 2 month timepoint, mean difference 1.0mmHg, 95% CI 0.2 to 1.8mmHg; $p<0.001$). The greater adjusted absolute IOP reduction after Repeat SLT, controlling for the difference in pre-treatment IOP, suggests that further laser may be additive to the initial treatment. This is also suggested by the cumulative treatment effect measured at 2 months after Repeat SLT being similar to the treatment effect achieved after the Initial SLT in those not requiring re-treatment (see Table 28). Overall, our results suggest that in eyes demonstrating at least a

'partial' response to initial SLT, repeat SLT should be considered and may be effective at achieving and maintaining target IOP for the short to intermediate term in treatment naïve OAG/OHT eyes. This has important clinical implications for the patient because it potentially delays the need to start topical treatment, avoiding the side-effects and compliance issues associated with this.

Mean (SD) total power of Initial vs Repeat SLT was both clinically and statistically significantly different (mean difference: 11.6mJ, 95% CI 7.7mJ to 15.6mJ; $p<0.001$) whereas there was no clinically or statistically significant difference in the number of applications (mean difference: 0.6 shots, -0.5 shots to 1.7 shots; $p=0.266$). The greater total power used for Repeat SLT could be due to several reasons. Firstly, greater energy per shot may have been required during Repeat SLT to generate the 'observable bubble formation at least 50% of the time' as mandated by our SLT treatment protocol. Histological studies in cadaveric eyes have demonstrated the SLT causes minimal ultrastructural damage to the TM compared to ALT (136). Nonetheless, transmission electron microscopy has shown cracked extracellular pigment granules within TM tissue post SLT (137). Whether in vivo, such pigment could potentially disperse out of the TM rendering it 'less' pigmented (and thus requiring more laser energy to reach the 'observable bubble formation' threshold) is possible, but no studies exist to correlate this. Indeed, there are no studies investigating the long-term pigmentary changes in the angle of patient post SLT. An alternative explanation is that there may also have been treatment bias by the clinicians who may have increased the energy per shot, having recognised that Initial SLT (with a lower total power) had not been as effective, by virtue of the patient receiving Repeat SLT.

It was investigated whether 'early' treatment failure compared to 'later' treatment failure of Initial SLT predicted the response to Repeat SLT. The results show that Early Failures of Initial SLT had higher pre-treatment baseline IOPs and less initial IOP lowering compared to Later Failures of Initial SLT, but that Repeat SLT provided a meaningful additional IOP lowering effect. The greater number of 'moderate' and 'severe' OAG eyes in the Early Failure compared to Later Failure group, also meant that the Early Failure group required greater absolute IOP reductions to achieve target IOP (and similarly compared to those eyes controlled on a single SLT at 18 months) – see Table 4.

In the Kaplan Meier analysis, a clinically-relevant and robust definition of success: IOP control (IOP at or below target IOP) maintained after Initial SLT without additional IOP lowering medications, further laser procedures or incisional glaucoma surgery (206)was used. The Kaplan Meier analysis shows that Repeat SLT can have a longer duration of IOP-lowering than the first laser. Thus, even after a waning of effect within 18 months, repeat treatment may work for longer and thus be worthwhile. Other studies have also suggested that Repeat SLT could have a longer duration of clinical benefit than Initial SLT (206, 207). Of the eyes that failed following Repeat SLT, the majority had a baseline disease severity of either 'moderate' OAG (12 eyes, 31.6%) or 'severe' OAG (11 eyes, 29%). This could partly explain the greater proportion of 'early failure' eyes failing Repeat SLT (20/34 = 58.8%) compared to 'later failures' (18/81 = 22.2%) as the increased relative proportion of 'moderate' and 'severe' OAG eyes compared to 'later failures' necessitated a greater absolute IOP reduction to achieve target IOP.

Direct comparison of these results with other studies is difficult due to differences in study design, patient demographics and concurrent use of topical medication at the time of SLT. However, mean absolute IOP reduction in this study for both initial and Repeat SLT was comparable with what has been previously reported (205-207, 314). Where variations exist, this could be due to higher baseline IOPs (for both Initial and Repeat SLT) in this study, since eyes in this analysis were not on concurrent topical medication at the time of either Initial or Repeat SLT in contrast to other studies (204-206, 209, 314). Differences in SLT treatment protocol such as number of spots and degree of TM treated could also be contributory (207). In this study, treatment was escalated when patients failed to reach pre-defined indvidualised target IOPs following both Initial and Repeat SLT; thus there are fewer eyes available for analysis at later time-points due to censoring of IOP data from medication-treated eyes, which means caution should be exercised in interpreting mean IOP outcomes beyond 2 months.

Certain other cautions should be noted. There is a selection bias in several of the retrospective SLT repeatability studies and also in our study, where eyes included were those having Repeat SLT following an initial response to the first SLT (judged by the treating clinician). During the LiGHT trial, by 18 months, 43 eyes out of original 611 eyes treated with SLT (7.0%) had been started on topical medication following Initial SLT rather than receiving Repeat SLT. Twenty of these eyes were started on topical medication following the first scheduled visit at 2 months and were judged by treating clinicians to have had 'no' treatment effect from Initial SLT. There were also too few eyes (n=15 eyes) that underwent Repeat SLT after 'no' initial response (less than a 10% change in IOP after first SLT) to be able to draw meaningful conclusions about the effects of a Repeat SLT when the first gave

no IOP lowering response. This means it is difficult to comment on the overall efficacy of Repeat SLT entirely irrespective of Initial SLT response from this analysis. Furthermore, this analysis comprises a sample of the original 611 eyes receiving SLT at baseline who then required Repeat SLT *within the first 18 months* of the trial, so that duration of follow-up would be at least as long (18.8%, 115 eyes). It does not include those eyes in the trial that received single SLT and subsequently maintained IOP control until the end of the trial at 36 months. It is therefore important to note that the median duration of survival for Initial SLT presented in this analysis is for eyes that required Repeat SLT *within the first 18 months of the trial* and not for *all* eyes following Initial SLT, or for eyes that had retreatment *beyond* the initial 18 months of the study.

Compared to previous SLT repeatability studies, this study has several strengths. The LiGHT trial was multi-centre and conducted prospectively. Eyes were treated to pre-defined target IOPs based on disease severity with pre-defined treatment escalation criteria and SLT treatment parameters in treatment-naive subjects (281). Limitations include the post-hoc (albeit pre-specified) nature of this analysis. Despite this, this analysis used one of the largest datasets of RCT-collected clinical data on Repeat SLT in treatment-naïve OAG/OHT patients. Whilst the analyses performed are exploratory, they are clinically valuable and add to the body of evidence supporting the use of Repeat SLT in medication-naive eyes that have undergone previous primary SLT.

5.6 Safety

Overall, both treatment pathways were safe throughout the study period. Rates of systemic AEs were balanced between the two treatment arms. As might be expected, drop-related systemic and ophthalmic AEs were reported by more patients in the Medicine-1st arm. As has previously been discussed, topical treatment can be associated with local and systemic side-effects (2). The greater proportion of patients taking topical treatment in the Medication-1st arm compared to the Laser-1st group would explain the higher frequency of reported local and systemic side effects .

SLT was found to be safe during the study period. It was well tolerated, with no sight threatening adverse events and only 6 eyes (1% of total eyes receiving SLT) having an IOP spike (>5mmHg) immediately after SLT. This compares favourably with other studies, which have reported IOP spikes (≥5mmHg) occurring between 0- 28% of eyes (218). Our results could be due to several factors. Firstly, our treatment protocol mandated pre-treatment with topical iopidine (0.5% or 1%) atleast 15 minutes prior to laser, whereas in other studies reporting higher frequencies of IOP spikes, eyes were not given a pre-treatment of IOP lowering medication (149). In addition, other studies may have had a higher proportion of PXF and PDS eyes in their smaller study samples (159, 215, 272), giving rise to a larger reported percentage of IOP spikes, whereas in our study, we had a larger cohort of predominantly OAG/OHT eyes with a low proportion of PXF/PDS eyes (0.8% of eyes). Post SLT, 34.4% of patients described mild laser related adverse events including ocular discomfort, headache, blurred vision and photophobia. These were of a transient nature and self-limiting. Anterior chamber inflammation

is common post SLT with up to 83% of eyes demonstrating some degree of inflammation (235). Considering the biological changes that SLT induces (108), some regard transient self-limiting inflammation to be a predictable consequence of SLT, explaining the symptoms of ocular redness, photophobia and pain that patients may report. The IOP check conventionally done 2 weeks after SLT did not change management for any of the patients and consequently appears unnecessary.

Regarding serious adverse events, differences in the rates of cancer diagnoses and deaths between the two treatment arms are attributable to chance, with no medical link between the treatments that were administered and the events that took place.

5.7 Quality of Life

5.7.1 Primary outcome: EQ5D

The Laser-1st and Medicine-1st treatment arms showed comparable EQ-5D-5L scores at the 36 months trial end point. The trial's protocol, whereby each eye was treated to an eye-specific IOP target, led to minimal disease-related differences such as visual function outcomes (see Table 19). In the trial patient population of predominantly OHT and mild OAG eyes receiving treatment, manifest visual loss or visual comorbidity was infrequent at 36 months in both treatment arms. HRQL was therefore unlikely to be significantly affected by differences in visual loss or function. Considering the 'burden' of the two treatments, approximately 2/3 of eyes in the Medication-1st arm were on a single topical medication at 36 months compared to approximately 75% of eyes being drop-free in the Laser-1st arm. Administration of a single drop (compared to instilling 'no drop') may not have been sufficiently troublesome or limiting to the majority of the Medication-1st arm study cohort to cause a 'manifest' statistically significant difference in general HRQL at 36 months. It is possible that had patients with more advanced disease been investigated (i.e. with more advanced visual field deficits and/or requiring more intense treatment e.g. multiple drops and/or glaucoma filtration surgery vs no drops) for a longer duration, then perhaps the quality of life differences between the two treatment arms may have become more evident.

It is also important to consider whether the EQ-5D-5L was sensitive enough to detect glaucoma-specific effects on HRQL. A previous trial evaluating PROMs in a

glaucoma RCT, found EQ-5D-5L to not be sensitive enough to function as a primary endpoint outcome measure (259).

5.7.2 Secondary outcomes: GUI, GSS, GQL-15

There was no significant difference in the GUI and GQL-15 at 36 months between the two treatment arms. Glaucoma-specific instruments (e.g. GUI and GQL-15) have been shown to be better at capturing differences in glaucoma severity rather than the effect of treatment side-effects on patients' HRQL. More specifically, the quality of life of patients with glaucoma has been related to the extent of VF loss when using the GQL-15 (315), whilst the GUI attributes less weight to local side effects and provides generic health outcome measures and measures of glaucoma severity (284). In this study, each eye was treated to target IOP and stringent controls over disease progression minimised any substantial differences in disease severity. With minimal differences in disease severity between groups, it is therefore reasonable that minimal differences in GUI and GQL-15 scores were detected between the two treatment arms.

There was also no significant difference in GSS scores between the 2 treatment arms at 36 months. This is despite repeated-measures analysis showing worse GSS scores for the Medicine-1st arm at five out of six time points over the course of the 36 months of the trial (see Figure 13). The GSS evaluates both visual and ocular comfort-related domains. The six symptoms evaluating the ocular comfort domain (burning/smarting/stinging, tearing, dryness, itching, soreness/tiredness and a feeling of something in the eye) are related to treatment side effects and their

measures. The GSS has been shown to correlate well with traditional measures of visual function (such as VA and VF) (285) which in this study's end points were comparable between the two treatment arms. As previously discussed, at 36 months approximately 2/3 of eyes in the Medication-1st arm were on a single topical medication compared to approximately 75% of eyes being drop-free in the Laser-1st arm. Administration of a single drop (compared to instilling 'no drop') may not have been sufficiently troublesome or limiting in terms of the visual and ocular comfort domains utilised in the GSS to cause a detectable difference at 36 months. It is possible that had patients with more advanced disease been investigated (i.e. with more advanced visual field deficits and/or requiring more intense treatment at 36 months e.g. multiple drops and/or glaucoma filtration surgery vs no drops) for a longer duration, then perhaps the quality of life difference between the two treatment arms may have become more evident.

The additional post hoc analyses demonstrated no significant difference in HRQL between 'drop free' patients and those 'on topical medication' at 36 months in the primary SLT arm. This could be explained similarly as above in the previous paragraph whereby in the absence of any significant visual comorbidity, the administration of a drop (compared to instilling 'no drop') was not sufficiently troublesome or limiting in terms of visual or ocular comfort domains for patients within the primary SLT arm. Furthermore, the patients who demonstrated evidence of 'disease progression' appeared to have worse HRQL measures compared to those with 'non progression' patients. It should be noted however that in both post-hoc analyses, there were large differences in the numbers of patients between both respective groups, which could skew the data and the

results. Whilst interesting and potentially hypothesis generating, in the absence of further robust HRQL studies aiming to specifically investigate differences between such groups, the conclusions that can be made are limited.

5.8 Strengths & Limitations

The analyses presented in this thesis have several strengths. They utilise data derived from a prospective multi-centre RCT with broad entry criteria that maximize the generalisability of the results. This study mirrored pragmatic clinical practice by tailoring treatment to the patient. Eyes were treated to pre-defined target IOPs based on disease severity with pre-defined treatment escalation criteria and SLT treatment parameters (281). The 'treat-to-target' design with computerised decision-supported treatment interventions and follow-up intervals captured the complexity of real-life clinical decision-making, but also allowed objective and unbiased decisions based on clinical observations.

There are limitations. Whilst the LiGHT trial was designed to be pragmatic and mirror clinical practice as much as possible, certain aspects of the trial methodology could affect its' applicability. The study excluded patients with very advanced glaucoma, secondary glaucoma as well as those with other active ocular comorbidities requiring treatment. The computerised decision software which was critical to the trial methodology and utilised to aid clinical decision making is not currently commercially available for use across the NHS for glaucoma care providers. If such a tool could be validated and made widely available, it could have significant benefits in standardising glaucoma care. The assessment of HRQL in glaucoma patients is also not part of standard clinical care and so how closely HRQL measures from the patient cohort in a clinical trial would match 'real world' patients is also not known. Analysis of the demographics of the patients that declined participation from the trial was also not performed. Knowledge of this would have helped determine further the generalisability of the study.

Furthermore, some of the clinical analyses performed were post-hoc, whilst the sample size of LiGHT was determined based on a power calculation to analyse the primary outcome of HRQL. This has implications for whether the sample size was large enough to detect differences for the different clinical parameters which were investigated. Whilst post hoc power calculations were not performed, since limitations have been reported with such calculations (303), the narrow confidence intervals for some of the pointwise estimates suggest that the study had an adequate sample size to detect a clinically important difference for some of these parameters.

Whilst this study has investigated the efficacy of primary SLT and topical treatment in the initial 36-month period for newly diagnosed OHT or OAG, both are chronic conditions frequently requiring lifelong treatment. Further long-term follow up research is required to assess the clinical efficacy and safety of primary SLT compared to topical treatment beyond 3 years. In addition, since the trial focused only on patients with OHT and/or mild or moderate OAG that had received no prior treatment; the results should be interpreted with caution in relation to the efficacy of SLT in advanced OAG stages, or in eyes previously treated with topical IOP lowering medication. The efficacy of adjunct SLT in eyes treated with topical medication is reported in the literature, but encompasses a wide range of clinical scenarios which limits the accuracy of the conclusions can be made about its' efficacy. In a retrospective analysis of 87 eyes, McIlraith et al showed that the IOP lowering response in medically treated eyes that underwent adjunct SLT following a 4-week washout period was statistically significantly less compared to treatment naïve eyes that received primary SLT (182). In a retrospective analysis of 206

patients, Woo et al investigated the effects of concurrent topical medication on the efficacy of first time adjunct SLT (185) and found no significant interactions between number of medications and post-treatment IOP response over time, though the study was limited by a large loss to follow up, which could affect the overall validity of the results. Lee et al performed a RCT of 41 medically controlled POAG patients evaluating the effect of adjuvant SLT vs. medication alone (179). At 6 months follow up, the average IOP in the SLT group was 7.6% lower than the medication only group ($p=0.03$) and the SLT group required significantly fewer anti-glaucoma medications compared with the medication only group ($p=0.02$), but again the sample size was small.

Overall, we can infer that adjunct SLT in POAG patients already on topical treatment can be effective at IOP lowering, but the degree of IOP lowering may be less compared to treatment naïve patients. Furthermore, in patients with uncontrolled IOPs despite medical therapy, adjunct SLT may be effective in maintaining an eye at a specific target IOP (based on disease severity). In eyes with already controlled IOP, it may permit reduction in the number of concurrent glaucoma medications needed to control IOP following treatment (182-184). Large scale prospective randomised studies are required to definitively ascertain the effect of adjunct SLT in patients receiving topical treatment.

Regarding HRQL, the EQ-5D-5L questionnaire, a generic tool eliciting utility values in multiple settings, may not have been the most sensitive tool to investigate HRQL in the two treatment arms for a 3-year trial, but was a requirement for a NICE cost–utility analysis. OAG can be asymptomatic, even at levels sufficient to make driving unsafe. Although potentially associated with significant visual impairment

over longer periods, only small changes in vision occurred over the 36 months duration of the trial, and this finding may be related to the lack of a difference in the primary outcome at 36 months.

Despite this, these clinical analyses utilised data from one of the largest datasets of treatment naïve OHT/OAG patients receiving primary SLT to date. The analyses are exploratory, but the results are clinically valuable and add to the limited body of evidence on primary SLT in treatment-naïve OAG and OHT, supporting its' use as an effective and safe initial treatment for such conditions.

Section 6: Conclusions

In summary, the work presented in this thesis shows that primary SLT is an effective and safe treatment for newly diagnosed OHT and OAG patients. It can provide predominantly drop-free IOP control over a minimum of 36 months, with less intense treatment, fewer adverse events and reduced need for ocular surgery, with a similar effect on patients' general and glaucoma specific HRQL.

There are important implications of this work. Alongside the health economic analysis carried out demonstrating primary SLT to be more cost-effective compared to topical treatment at 36 months (301), the clinical and patient reported outcomes of primary SLT suggest that it can be offered as a first line treatment to newly diagnosed OHT and OAG patients and supports a change in practice. This also has implications for health care provision in resource-poor health-care settings, where access to medication is a major barrier to glaucoma treatment.

For a clinician, choosing a treatment for a newly diagnosed OHT or OAG patient still requires careful consideration of both disease and patient related factors. The risks vs benefits of any treatment should be discussed with the patient and they should be appropriately counselled. The evidence from this work and the LiGHT trial overall supports primary SLT to be a safe, clinically efficient and cost-effective alternative to topical treatment that can be offered as a first-line treatment to patients with OAG or OHT in need of IOP reduction.

REFERENCES

1. Chauhan BC, Mikelberg FS, Artes PH, Balazsi AG, LeBlanc RP, Lesk MR, et al. Canadian Glaucoma Study: 3. Impact of risk factors and intraocular pressure reduction on the rates of visual field change. Archives of ophthalmology (Chicago, Ill : 1960). 2010;128(10):1249-55.
2. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. Annals of internal medicine. 1990;112(2):120-5.
3. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. Jama. 2014;311(18):1901-11.
4. Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary open-angle glaucoma. The New England journal of medicine. 2009;360(11):1113-24.
5. Gordon MO, Kass MA, for the Ocular Hypertension Treatment Study G. The ocular hypertension treatment study: Design and baseline description of the participants. Archives of Ophthalmology. 1999;117(5):573-83.
6. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. The British journal of ophthalmology. 2006;90(3):262-7.
7. Budenz DL, Barton K, Whiteside-de Vos J, Schiffman J, Bandi J, Nolan W, et al. Prevalence of glaucoma in an urban West African population: the Tema Eye Survey. JAMA ophthalmology. 2013;131(5):651-8.
8. Hennis A, Wu SY, Nemesure B, Honkanen R, Leske MC. Awareness of incident open-angle glaucoma in a population study: the Barbados Eye Studies. Ophthalmology. 2007;114(10):1816-21.
9. Tham Y-C, Li X, Wong TY, Quigley HA, Aung T, Cheng C-Y. Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040. Ophthalmology. 121(11):2081-90.
10. Weinreb RN, Khaw PT. Primary open-angle glaucoma. The Lancet.363(9422):1711-20.
11. Quigley HA, Addicks EM, Green WR, Maumenee AE. Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. Archives of ophthalmology (Chicago, Ill : 1960). 1981;99(4):635-49.
12. Fechtner RD, Weinreb RN. Mechanisms of optic nerve damage in primary open angle glaucoma. Survey of ophthalmology. 1994;39(1):23-42.
13. Burgoyne CF, Downs JC, Bellezza AJ, Suh JK, Hart RT. The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. Progress in retinal and eye research. 2005;24(1):39-73.
14. Wang L, Cioffi GA, Cull G, Dong J, Fortune B. Immunohistologic evidence for retinal glial cell changes in human glaucoma. Investigative ophthalmology & visual science. 2002;43(4):1088-94.
15. Rojas B, Gallego BI, Ramirez AI, Salazar JJ, de Hoz R, Valiente-Soriano FJ, et al. Microglia in mouse retina contralateral to experimental glaucoma exhibit multiple signs of activation in all retinal layers. Journal of neuroinflammation. 2014;11:133.
16. Yucel YH, Zhang Q, Gupta N, Kaufman PL, Weinreb RN. Loss of neurons in magnocellular and parvocellular layers of the lateral geniculate nucleus in glaucoma. Archives of ophthalmology (Chicago, Ill : 1960). 2000;118(3):378-84.
17. Sample PA, Bosworth CF, Blumenthal EZ, Girkin C, Weinreb RN. Visual function-specific perimetry for indirect comparison of different ganglion cell populations in glaucoma. Investigative ophthalmology & visual science. 2000;41(7):1783-90.
18. Ju WK, Kim KY, Lindsey JD, Angert M, Duong-Polk KX, Scott RT, et al. Intraocular pressure elevation induces mitochondrial fission and triggers OPA1 release in glaucomatous optic nerve. Investigative ophthalmology & visual science. 2008;49(11):4903-11.
19. Ren R, Jonas JB, Tian G, Zhen Y, Ma K, Li S, et al. Cerebrospinal fluid pressure in glaucoma: a prospective study. Ophthalmology. 2010;117(2):259-66.
20. Ren R, Zhang X, Wang N, Li B, Tian G, Jonas JB. Cerebrospinal fluid pressure in ocular hypertension. Acta ophthalmologica. 2011;89(2):e142-8.
21. Wilkinson CH, van der Straaten D, Craig JE, Coote MA, McCartney PJ, Stankovich J, et al. Tonography demonstrates reduced facility of outflow of aqueous humor in myocilin mutation carriers. Journal of glaucoma. 2003;12(3):237-42.
22. Rezaie T, Child A, Hitchings R, Brice G, Miller L, Coca-Prados M, et al. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. Science (New York, NY). 2002;295(5557):1077-9.
23. Thorleifsson G, Walters GB, Hewitt AW, Masson G, Helgason A, DeWan A, et al. Common variants near CAV1 and CAV2 are associated with primary open-angle glaucoma. Nature genetics. 2010;42(10):906-9.
24. Wiggs JL, Yaspan BL, Hauser MA, Kang JH, Allingham RR, Olson LM, et al. Common variants at 9p21 and 8q22 are associated with increased susceptibility to optic nerve degeneration in glaucoma. PLoS genetics. 2012;8(4):e1002654.
25. Khawaja AP, Cooke Bailey JN, Wareham NJ, Scott RA, Simcoe M, Igo RP, Jr., et al. Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma. Nature genetics. 2018;50(6):778-82.
26. Drance S, Anderson DR, Schulzer M. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. American journal of ophthalmology. 2001;131(6):699-708.
27. Williams PA, Harder JM, Foxworth NE, Cochran KE, Philip VM, Porciatti V, et al. Vitamin B(3) modulates mitochondrial vulnerability and prevents glaucoma in aged mice. Science (New York, NY). 2017;355(6326):756-60.
28. Williams PA, Harder JM, John SWM. Glaucoma as a Metabolic Optic Neuropathy: Making the Case for Nicotinamide Treatment in Glaucoma. Journal of glaucoma. 2017;26(12):1161-8.
29. The Advanced Glaucoma Intervention Study (AGIS): 4. Comparison of treatment outcomes within race. Seven-year results. Ophthalmology. 1998;105(7):1146-64.
30. Wolfs RC, Klaver CC, Ramrattan RS, van Duijn CM, Hofman A, de Jong PT. Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. Archives of ophthalmology (Chicago, Ill : 1960). 1998;116(12):1640-5.
31. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Family history and risk of primary open angle glaucoma. The Baltimore Eye Survey. Archives of ophthalmology (Chicago, Ill : 1960). 1994;112(1):69-73.
32. Perera SA, Wong TY, Tay WT, Foster PJ, Saw SM, Aung T. Refractive error, axial dimensions, and primary open-angle glaucoma: the Singapore Malay Eye Study. Archives of ophthalmology (Chicago, Ill : 1960). 2010;128(7):900-5.
33. Nagaoka N, Jonas JB, Morohoshi K, Moriyama M, Shimada N, Yoshida T, et al. Glaucomatous-Type Optic Discs in High Myopia. PloS one. 2015;10(10):e0138825.
34. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Archives of ophthalmology (Chicago, Ill : 1960). 2002;120(6):714-20; discussion 829-30.
35. Zhang X, Beckles GL, Chou CF, Saaddine JB, Wilson MR, Lee PP, et al. Socioeconomic disparity in use of eye care services among US adults with age-related eye diseases: National Health Interview Survey, 2002 and 2008. JAMA ophthalmology. 2013;131(9):1198-206.
36. Quigley HA, Dunkelberger GR, Green WR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. American journal of ophthalmology. 1989;107(5):453-64.
37. Quigley HA, Katz J, Derick RJ, Gilbert D, Sommer A. An evaluation of optic disc and nerve fiber layer examinations in monitoring progression of early glaucoma damage. Ophthalmology. 1992;99(1):19-28.
38. Hee MR, Izatt JA, Swanson EA, Huang D, Schuman JS, Lin CP, et al. Optical coherence tomography of the human retina. Archives of ophthalmology (Chicago, Ill : 1960). 1995;113(3):325-32.
39. Bussel, II, Wollstein G, Schuman JS. OCT for glaucoma diagnosis, screening and detection of glaucoma progression. The British journal of ophthalmology. 2014;98 Suppl 2(Suppl 2):ii15-9.
40. Schulze A, Lamparter J, Pfeiffer N, Berisha F, Schmidtmann I, Hoffmann EM. Diagnostic ability of retinal ganglion cell complex, retinal nerve fiber layer, and optic nerve head measurements by Fourier-domain optical coherence tomography. Graefes archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2011;249(7):1039-45.
41. Yang Z, Tatham AJ, Zangwill LM, Weinreb RN, Zhang C, Medeiros FA. Diagnostic ability of retinal nerve fiber layer imaging by swept-source optical coherence tomography in glaucoma. American journal of ophthalmology. 2015;159(1):193-201.
42. Polo V, Larrosa JM, Pinilla I, Perez S, Gonzalvo F, Honrubia FM. Predictive value of short-wavelength automated perimetry: a 3-year follow-up study. Ophthalmology. 2002;109(4):761-5.
43. Landers JA, Goldberg I, Graham SL. Detection of early visual field loss in glaucoma using frequency-doubling perimetry and short-wavelength automated perimetry. Archives of ophthalmology (Chicago, Ill : 1960). 2003;121(12):1705-10.
44. Garway-Heath DF, Crabb DP, Bunce C, Lascaratos G, Amalfitano F, Anand N, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. Lancet (London, England). 2015;385(9975):1295-304.
45. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Archives of ophthalmology (Chicago, Ill : 1960). 2002;120(6):701-13; discussion 829-30.
46. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Archives of ophthalmology (Chicago, Ill : 1960). 2002;120(10):1268-79.
47. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. American journal of ophthalmology. 1998;126(4):487-97.
48. Damji KF, Behki R, Wang L. Canadian perspectives in glaucoma management: setting target intraocular pressure range. Canadian journal of ophthalmology Journal canadien dophtalmologie. 2003;38(3):189-97.
49. Owen CG, Carey IM, De Wilde S, Whincup PH, Wormald R, Cook DG. The epidemiology of medical treatment for glaucoma and ocular hypertension in the United Kingdom: 1994 to 2003. The British journal of ophthalmology. 2006;90(7):861-8.
50. Robin AL, Novack GD, Covert DW, Crockett RS, Marcic TS. Adherence in glaucoma: objective measurements of once-daily and adjunctive medication use. American journal of ophthalmology. 2007;144(4):533-40.
51. Tsai JC. A comprehensive perspective on patient adherence to topical glaucoma therapy. Ophthalmology. 2009;116(11 Suppl):S30-6.
52. Tsai JC, McClure CA, Ramos SE, Schlundt DG, Pichert JW. Compliance barriers in glaucoma: a systematic classification. Journal of glaucoma. 2003;12(5):393-8.
53. Tsai JC. Medication adherence in glaucoma: approaches for optimizing patient compliance. Current opinion in ophthalmology. 2006;17(2):190-5.
54. Nordstrom BL, Friedman DS, Mozaffari E, Quigley HA, Walker AM. Persistence and adherence with topical glaucoma therapy. American journal of ophthalmology. 2005;140(4):598-606.
55. Balkrishnan R, Bond JB, Byerly WG, Camacho FT, Anderson RT. Medication-related predictors of health-related quality of life in glaucoma patients enrolled in a medicare health maintenance organization. The American journal of geriatric pharmacotherapy. 2003;1(2):75-81.
56. Rahman MQ, Montgomery DM, Lazaridou MN. Surveillance of glaucoma medical therapy in a Glasgow teaching hospital: 26 years experience. The British journal of ophthalmology. 2009;93(12):1572-5.
57. Broadway D, Grierson I, Hitchings R. Adverse effects of topical antiglaucomatous medications on the conjunctiva. The British journal of ophthalmology. 1993;77(9):590-6.
58. Broadway DC, Grierson I, OBrien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. Archives of ophthalmology (Chicago, Ill : 1960). 1994;112(11):1446-54.
59. Weinreb RN, Toris CB, Gabelt BT, Lindsey JD, Kaufman PL. Effects of prostaglandins on the aqueous humor outflow pathways. Survey of ophthalmology. 2002;47 Suppl 1:S53-64.
60. Weinreb RN, Kashiwagi K, Kashiwagi F, Tsukahara S, Lindsey JD. Prostaglandins increase matrix metalloproteinase release from human ciliary smooth muscle cells. Investigative ophthalmology & visual science. 1997;38(13):2772-80.
61. Grierson I, Pfeiffer N, Cracknell KP, Appleton P. Histology and fine structure of the iris and outflow system following latanoprost therapy. Survey of ophthalmology. 2002;47 Suppl 1:S176-84.
62. Toris CB, Camras CB, Yablonski ME. Acute versus chronic effects of brimonidine on aqueous humor dynamics in ocular hypertensive patients. American journal of ophthalmology. 1999;128(1):8-14.
63. Kirwan JF, Nightingale JA, Bunce C, Wormald R. Beta blockers for glaucoma and excess risk of airways obstruction: population based cohort study. BMJ (Clinical research ed). 2002;325(7377):1396-7.
64. Li G, Torrejon KY, Unser AM, Ahmed F, Navarro ID, Baumgartner RA, et al. Trabodenoson, an Adenosine Mimetic With A1 Receptor Selectivity Lowers Intraocular Pressure by Increasing Conventional Outflow Facility in Mice. Investigative ophthalmology & visual science. 2018;59(1):383-92.
65. Myers JS, Sall KN, DuBiner H, Slomowitz N, McVicar W, Rich CC, et al. A Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of 2 and 4 Weeks of Twice-Daily Ocular Trabodenoson in Adults with Ocular Hypertension or Primary Open-Angle Glaucoma. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics. 2016;32(8):555-62.
66. Liebmann JM, Lee JK. Current therapeutic options and treatments in development for the management of primary open-angle glaucoma. The American journal of managed care. 2017;23(15 Suppl):S279-s92.
67. Ren R, Li G, Le TD, Kopczynski C, Stamer WD, Gong H. Netarsudil Increases Outflow Facility in Human Eyes Through Multiple Mechanisms. Investigative ophthalmology & visual science. 2016;57(14):6197-209.
68. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. Journal of glaucoma. 2015;24(1):51-4.
69. Kiel JW, Kopczynski CC. Effect of AR-13324 on episcleral venous pressure in Dutch belted rabbits. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics. 2015;31(3):146-51.
70. Serle JB, Katz LJ, McLaurin E, Heah T, Ramirez-Davis N, Usner DW, et al. Two Phase 3 Clinical Trials Comparing the Safety and Efficacy of Netarsudil to Timolol in Patients With Elevated Intraocular Pressure: Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2). American journal of ophthalmology. 2018;186:116-27.
71. Lewis RA, Levy B, Ramirez N, Kopczynski CC, Usner DW, Novack GD. Fixed-dose combination of AR-13324 and latanoprost: a double-masked, 28-day, randomised, controlled study in patients with open-angle glaucoma or ocular hypertension. The British journal of ophthalmology. 2016;100(3):339-44.
72. Garcia GA, Ngai P, Mosaed S, Lin KY. Critical evaluation of latanoprostene bunod in the treatment of glaucoma. Clinical ophthalmology (Auckland, NZ). 2016;10:2035-50.
73. Cavet ME, Vittitow JL, Impagnatiello F, Ongini E, Bastia E. Nitric oxide (NO): an emerging target for the treatment of glaucoma. Investigative ophthalmology & visual science. 2014;55(8):5005-15.
74. Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J. Latanoprostene Bunod 0.024% versus Timolol Maleate 0.5% in Subjects with Open-Angle Glaucoma or Ocular Hypertension: The APOLLO Study. Ophthalmology. 2016;123(5):965-73.
75. Medeiros FA, Martin KR, Peace J, Scassellati Sforzolini B, Vittitow JL, Weinreb RN. Comparison of Latanoprostene Bunod 0.024% and Timolol Maleate 0.5% in Open-Angle Glaucoma or Ocular Hypertension: The LUNAR Study. American journal of ophthalmology. 2016;168:250-9.
76. Kawase K, Vittitow JL, Weinreb RN, Araie M. Long-term Safety and Efficacy of Latanoprostene Bunod 0.024% in Japanese Subjects with Open-Angle Glaucoma or Ocular Hypertension: The JUPITER Study. Advances in therapy. 2016;33(9):1612-27.
77. Watson PG, Barnett F. Effectiveness of trabeculectomy in glaucoma. American journal of ophthalmology. 1975;79(5):831-45.
78. Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD, Budenz DL. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. American journal of ophthalmology. 2012;153(5):789-803.e2.
79. Gedde SJ, Feuer WJ, Shi W, Lim KS, Barton K, Goyal S, et al. Treatment Outcomes in the Primary Tube Versus Trabeculectomy Study after 1 Year of Follow-up. Ophthalmology. 2018;125(5):650-63.
80. Gedde SJ, Feuer WJ, Lim KS, Barton K, Goyal S, Ahmed IIK, et al. Treatment Outcomes in the Primary Tube Versus Trabeculectomy Study after 3 Years of Follow-up. Ophthalmology. 2020;127(3):333-45.
81. Budenz DL, Barton K, Gedde SJ, Feuer WJ, Schiffman J, Costa VP, et al. Five-Year Treatment Outcomes in the Ahmed Baerveldt Comparison Study. Ophthalmology. 2015;122(2):308-16.
82. OBrart DPS, Rowlands E, Islam N, Noury AMS. A randomised, prospective study comparing trabeculectomy augmented with antimetabolites with a viscocanalostomy technique for the management of open angle glaucoma uncontrolled by medical therapy. The British journal of ophthalmology. 2002;86(7):748-54.
83. Gilmour DF, Manners TD, Devonport H, Varga Z, Solebo AL, Miles J. Viscocanalostomy versus trabeculectomy for primary open angle glaucoma: 4-year prospective randomized clinical trial. Eye (London, England). 2009;23(9):1802-7.
84. Jonescu-Cuypers C, Jacobi P, Konen W, Krieglstein G. Primary viscocanalostomy versus trabeculectomy in white patients with open-angle glaucoma: A randomized clinical trial. Ophthalmology. 2001;108(2):254-8.
85. Samuelson TW, Sarkisian SR, Jr., Lubeck DM, Stiles MC, Duh YJ, Romo EA, et al. Prospective, Randomized, Controlled Pivotal Trial of an Ab Interno Implanted Trabecular Micro-Bypass in Primary Open-Angle Glaucoma and Cataract: Two-Year Results. Ophthalmology. 2019;126(6):811-21.
86. Samuelson TW, Chang DF, Marquis R, Flowers B, Lim KS, Ahmed IIK, et al. A Schlemm Canal Microstent for Intraocular Pressure Reduction in Primary Open-Angle Glaucoma and Cataract: The HORIZON Study. Ophthalmology. 2019;126(1):29-37.
87. Vold S, Ahmed, II, Craven ER, Mattox C, Stamper R, Packer M, et al. Two-Year COMPASS Trial Results: Supraciliary Microstenting with Phacoemulsification in Patients with Open-Angle Glaucoma and Cataracts. Ophthalmology. 2016;123(10):2103-12.
88. Chatzara A, Chronopoulou I, Theodossiadis G, Theodossiadis P, Chatziralli I. XEN Implant for Glaucoma Treatment: A Review of the Literature. Seminars in ophthalmology. 2019;34(2):93-7.
89. Zhang ML, Hirunyachote P, Jampel H. Combined surgery versus cataract surgery alone for eyes with cataract and glaucoma. The Cochrane database of systematic reviews. 2015(7):Cd008671.
90. Hu K, Shah A, Virgili G, Bunce C, Gazzard G. Ab interno trabecular bypass surgery with Trabectome for open-angle glaucoma. The Cochrane database of systematic reviews. 2021;2(2):Cd011693.
91. Sandhu A, Jayaram H, Hu K, Bunce C, Gazzard G. Ab interno supraciliary microstent surgery for open-angle glaucoma. The Cochrane database of systematic reviews. 2021;5(5):Cd012802.
92. Otarola F, Virgili G, Shah A, Hu K, Bunce C, Gazzard G. Ab interno trabecular bypass surgery with Schlemm´s canal microstent (Hydrus) for open angle glaucoma. The Cochrane database of systematic reviews. 2020;3(3):Cd012740.
93. Le JT, Bicket AK, Wang L, Li T. Ab interno trabecular bypass surgery with iStent for open-angle glaucoma. The Cochrane database of systematic reviews. 2019;3(3):Cd012743.
94. King AJ, Shah A, Nikita E, Hu K, Mulvaney CA, Stead R, et al. Subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma. The Cochrane database of systematic reviews. 2018;12(12):Cd012742.
95. Brandao LM, Grieshaber MC. Update on Minimally Invasive Glaucoma Surgery (MIGS) and New Implants. Journal of ophthalmology. 2013;2013:705915.
96. Almasieh M, Levin LA. Neuroprotection in Glaucoma: Animal Models and Clinical Trials. Annual review of vision science. 2017;3:91-120.
97. Levin LA, Danesh-Meyer HV. Lost in translation: bumps in the road between bench and bedside. Jama. 2010;303(15):1533-4.
98. Krasnov MM. Q-switched laser goniopuncture. Archives of ophthalmology (Chicago, Ill : 1960). 1974;92(1):37-41.
99. Worthen DM, Wickham MG. Argon laser trabeculotomy. Transactions - American Academy of Ophthalmology and Otolaryngology American Academy of Ophthalmology and Otolaryngology. 1974;78(2):Op371-5.
100. Wise JB, Witter SL. Argon laser therapy for open-angle glaucoma. A pilot study. Archives of ophthalmology (Chicago, Ill : 1960). 1979;97(2):319-22.
101. Thomas JV, Simmons RJ, Belcher CD, 3rd. Argon laser trabeculoplasty in the presurgical glaucoma patient. Ophthalmology. 1982;89(3):187-97.
102. Brubaker RF, Liesegang TJ. Effect of trabecular photocoagulation on the aqueous humor dynamics of the human eye. American journal of ophthalmology. 1983;96(2):139-47.
103. Rodrigues MM, Spaeth GL, Donohoo P. Electron microscopy of argon laser therapy in phakic open-angle glaucoma. Ophthalmology. 1982;89(3):198-210.
104. Melamed S, Pei J, Epstein DL. Short-term effect of argon laser trabeculoplasty in monkeys. Archives of ophthalmology (Chicago, Ill : 1960). 1985;103(10):1546-52.
105. Alexander RA, Grierson I. Morphological effects of argon laser trabeculoplasty upon the glaucomatous human meshwork. Eye (London, England). 1989;3 (Pt 6):719-26.
106. Alexander RA, Grierson I, Church WH. The effect of argon laser trabeculoplasty upon the normal human trabecular meshwork. Graefes archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 1989;227(1):72-7.
107. Van Buskirk EM. Pathophysiology of laser trabeculoplasty. Survey of ophthalmology. 1989;33(4):264-72.
108. Kagan DB, Gorfinkel NS, Hutnik CM. Mechanisms of selective laser trabeculoplasty: a review. Clinical & experimental ophthalmology. 2014;42(7):675-81.
109. Coakes R. Laser trabeculoplasty. The British journal of ophthalmology. 1992;76(10):624-6.
110. The Glaucoma Laser Trial (GLT). 2. Results of argon laser trabeculoplasty versus topical medicines. The Glaucoma Laser Trial Research Group. Ophthalmology. 1990;97(11):1403-13.
111. Greenidge KC, Spaeth GL, Fiol-Silva Z. Effect of argon laser trabeculoplasty on the glaucomatous diurnal curve. Ophthalmology. 1983;90(7):800-4.
112. Elsas T, Junk H, Johnsen H. Diurnal intraocular pressure after successful primary laser trabeculoplasty. American journal of ophthalmology. 1991;112(1):67-9.
113. Schwartz AL, Love DC, Schwartz MA. Long-term follow-up of argon laser trabeculoplasty for uncontrolled open-angle glaucoma. Archives of ophthalmology (Chicago, Ill : 1960). 1985;103(10):1482-4.
114. Baez KA, Spaeth GL. Argon laser trabeculoplasty controls one third of patients with progressive, uncontrolled open-angle glaucoma for five years. Transactions of the American Ophthalmological Society. 1991;89:47-56; discussion -8.
115. Grinich NP, Van Buskirk EM, Samples JR. Three-year efficacy of argon laser trabeculoplasty. Ophthalmology. 1987;94(7):858-61.
116. Richter CU, Shingleton BJ, Bellows AR, Hutchinson BT, Jacobson LP. Retreatment with argon laser trabeculoplasty. Ophthalmology. 1987;94(9):1085-9.
117. The Advanced Glaucoma Intervention Study (AGIS): 11. Risk factors for failure of trabeculectomy and argon laser trabeculoplasty. American journal of ophthalmology. 2002;134(4):481-98.
118. Higginbotham EJ, Richardson TM. Response of exfoliation glaucoma to laser trabeculoplasty. The British journal of ophthalmology. 1986;70(11):837-9.
119. The Glaucoma Laser Trial. I. Acute effects of argon laser trabeculoplasty on intraocular pressure. Glaucoma Laser Trial Research Group. Archives of ophthalmology (Chicago, Ill : 1960). 1989;107(8):1135-42.
120. Keightley SJ, Khaw PT, Elkington AR. The prediction of intraocular pressure rise following argon laser trabeculoplasty. Eye (London, England). 1987;1 (Pt 5):577-80.
121. Traverso CE, Greenidge KC, Spaeth GL. Formation of peripheral anterior synechiae following argon laser trabeculoplasty. A prospective study to determine relationship to position of laser burns. Archives of ophthalmology (Chicago, Ill : 1960). 1984;102(6):861-3.
122. Rouhiainen HJ, Terasvirta ME, Tuovinen EJ. Peripheral anterior synechiae formation after trabeculoplasty. Archives of ophthalmology (Chicago, Ill : 1960). 1988;106(2):189-91.
123. Richter CU, Shingleton BJ, Bellows AR, Hutchinson BT, OConnor T, Brill I. The development of encapsulated filtering blebs. Ophthalmology. 1988;95(9):1163-8.
124. Schwartz AL, Van Veldhuisen PC, Gaasterland DE, Ederer F, Sullivan EK, Cyrlin MN. The Advanced Glaucoma Intervention Study (AGIS): 5. Encapsulated bleb after initial trabeculectomy. American journal of ophthalmology. 1999;127(1):8-19.
125. Rolim de Moura C, Paranhos A, Jr., Wormald R. Laser trabeculoplasty for open angle glaucoma. The Cochrane database of systematic reviews. 2007(4):Cd003919.
126. Watson PG, Allen ED, Graham CM, Porter GP, Pickering MS. Argon laser trabeculoplasty or trabeculectomy a prospective randomised block study. Transactions of the ophthalmological societies of the United Kingdom. 1985;104 (Pt 1):55-61.
127. Migdal C, Hitchings R. Control of chronic simple glaucoma with primary medical, surgical and laser treatment. Transactions of the ophthalmological societies of the United Kingdom. 1986;105 (Pt 6):653-6.
128. Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science (New York, NY). 1983;220(4596):524-7.
129. Latina MA, Park C. Selective targeting of trabecular meshwork cells: in vitro studies of pulsed and CW laser interactions. Experimental eye research. 1995;60(4):359-71.
130. Arons I. SLT: New treatment for Glaucoma becomes available. Ocular Surgery News 2001.
131. Arora KS, Robin AL, Corcoran KJ, Corcoran SL, Ramulu PY. Use of Various Glaucoma Surgeries and Procedures in Medicare Beneficiaries from 1994 to 2012. Ophthalmology. 2015;122(8):1615-24.
132. Beltran-Agullo L, Alaghband P, Obi A, Husain R, Lim KS. The effect of selective laser trabeculoplasty on aqueous humor dynamics in patients with ocular hypertension and primary open-angle glaucoma. Journal of glaucoma. 2013;22(9):746-9.
133. Goyal S, Beltran-Agullo L, Rashid S, Shah SP, Nath R, Obi A, et al. Effect of primary selective laser trabeculoplasty on tonographic outflow facility: a randomised clinical trial. The British journal of ophthalmology. 2010;94(11):1443-7.
134. Gulati V, Fan S, Gardner BJ, Havens SJ, Schaaf MT, Neely DG, et al. Mechanism of Action of Selective Laser Trabeculoplasty and Predictors of Response. Investigative ophthalmology & visual science. 2017;58(3):1462-8.
135. Skaat A, Rosman MS, Chien JL, Ghassibi MP, Liebmann JM, Ritch R, et al. Microarchitecture of Schlemm Canal Before and After Selective Laser Trabeculoplasty in Enhanced Depth Imaging Optical Coherence Tomography. Journal of glaucoma. 2017;26(4):361-6.
136. Kramer TR, Noecker RJ. Comparison of the morphologic changes after selective laser trabeculoplasty and argon laser trabeculoplasty in human eye bank eyes. Ophthalmology. 2001;108(4):773-9.
137. SooHoo JR, Seibold LK, Ammar DA, Kahook MY. Ultrastructural Changes in Human Trabecular Meshwork Tissue after Laser Trabeculoplasty. Journal of ophthalmology. 2015;2015:476138.
138. Izzotti A, Longobardi M, Cartiglia C, Rathschuler F, Sacca SC. Trabecular meshwork gene expression after selective laser trabeculoplasty. PloS one. 2011;6(7):e20110.
139. Bradley JM, Anderssohn AM, Colvis CM, Parshley DE, Zhu XH, Ruddat MS, et al. Mediation of laser trabeculoplasty-induced matrix metalloproteinase expression by IL-1beta and TNFalpha. Investigative ophthalmology & visual science. 2000;41(2):422-30.
140. Lee JY, Kagan DB, Roumeliotis G, Liu H, Hutnik CM. Secretion of matrix metalloproteinase-3 by co-cultured pigmented and non-pigmented human trabecular meshwork cells following selective laser trabeculoplasty. Clinical & experimental ophthalmology. 2016;44(1):33-42.
141. Alvarado JA, Katz LJ, Trivedi S, Shifera AS. Monocyte modulation of aqueous outflow and recruitment to the trabecular meshwork following selective laser trabeculoplasty. Archives of ophthalmology (Chicago, Ill : 1960). 2010;128(6):731-7.
142. Guzey M, Vural H, Satici A. Endothelin-1 increase in aqueous humour caused by frequency-doubled Nd:YAG laser trabeculoplasty in rabbits. Eye (London, England). 2001;15(Pt 6):781-5.
143. Guzey M, Vural H, Satici A, Karadede S, Dogan Z. Increase of free oxygen radicals in aqueous humour induced by selective Nd:YAG laser trabeculoplasty in the rabbit. European journal of ophthalmology. 2001;11(1):47-52.
144. Alvarado JA, Iguchi R, Martinez J, Trivedi S, Shifera AS. Similar effects of selective laser trabeculoplasty and prostaglandin analogs on the permeability of cultured Schlemm canal cells. American journal of ophthalmology. 2010;150(2):254-64.
145. Leahy KE, White AJ. Selective laser trabeculoplasty: current perspectives. Clinical ophthalmology (Auckland, NZ). 2015;9:833-41.
146. Latina MA, Sibayan SA, Shin DH, Noecker RJ, Marcellino G. Q-switched 532-nm Nd:YAG laser trabeculoplasty (selective laser trabeculoplasty): a multicenter, pilot, clinical study. Ophthalmology. 1998;105(11):2082-8; discussion 9-90.
147. Chen E, Golchin S, Blomdahl S. A comparison between 90 degrees and 180 degrees selective laser trabeculoplasty. Journal of glaucoma. 2004;13(1):62-5.
148. Tawfique K, Khademi P, Querat L, Khadamy J, Chen E. Comparison between 90-degree and 360-degree selective laser trabeculoplasty (SLT): A 2-year follow-up. Acta ophthalmologica. 2019;97(4):427-9.
149. Nagar M, Ogunyomade A, OBrart DP, Howes F, Marshall J. A randomised, prospective study comparing selective laser trabeculoplasty with latanoprost for the control of intraocular pressure in ocular hypertension and open angle glaucoma. The British journal of ophthalmology. 2005;89(11):1413-7.
150. George MK, Emerson JW, Cheema SA, McGlynn R, Ford BA, Martone JF, et al. Evaluation of a modified protocol for selective laser trabeculoplasty. Journal of glaucoma. 2008;17(3):197-202.
151. Wong C, Tao LW, Skalicky SE. A Retrospective Review Comparing the Safety and Efficacy of 120 Versus 160 Applications of Selective Laser Trabeculoplasty. Journal of glaucoma. 2018;27(1):94-9.
152. Tang M, Fu Y, Fu MS, Fan Y, Zou HD, Sun XD, et al. The efficacy of low-energy selective laser trabeculoplasty. Ophthalmic surgery, lasers & imaging : the official journal of the International Society for Imaging in the Eye. 2011;42(1):59-63.
153. Lee JW, Wong MO, Liu CC, Lai JS. Optimal selective laser trabeculoplasty energy for maximal intraocular pressure reduction in open-angle glaucoma. Journal of glaucoma. 2015;24(5):e128-31.
154. Habib L, Lin J, Berezina T, Holland B, Fechtner RD, Khouri AS. Selective laser trabeculoplasty: Does energy dosage predict response? Oman journal of ophthalmology. 2013;6(2):92-5.
155. Stunf Pukl S, Drnovsek-Olup B. Impact of laser pulse duration on the reduction of intraocular pressure during selective laser trabeculoplasty. International ophthalmology. 2016.
156. Latina MA, de Leon JM. Selective laser trabeculoplasty. Ophthalmology clinics of North America. 2005;18(3):409-19, vi.
157. Zhang L, Weizer JS, Musch DC. Perioperative medications for preventing temporarily increased intraocular pressure after laser trabeculoplasty. The Cochrane database of systematic reviews. 2017;2:Cd010746.
158. Liu Y, Birt CM. Argon versus selective laser trabeculoplasty in younger patients: 2-year results. Journal of glaucoma. 2012;21(2):112-5.
159. Kent SS, Hutnik CM, Birt CM, Damji KF, Harasymowycz P, Si F, et al. A randomized clinical trial of selective laser trabeculoplasty versus argon laser trabeculoplasty in patients with pseudoexfoliation. Journal of glaucoma. 2015;24(5):344-7.
160. Martinez-de-la-Casa JM, Garcia-Feijoo J, Castillo A, Matilla M, Macias JM, Benitez-del-Castillo JM, et al. Selective vs argon laser trabeculoplasty: hypotensive efficacy, anterior chamber inflammation, and postoperative pain. Eye (London, England). 2004;18(5):498-502.
161. Shibata M, Sugiyama T, Ishida O, Ueki M, Kojima S, Okuda T, et al. Clinical results of selective laser trabeculoplasty in open-angle glaucoma in Japanese eyes: comparison of 180 degree with 360 degree SLT. Journal of glaucoma. 2012;21(1):17-21.
162. Rosenfeld E, Shemesh G, Kurtz S. The efficacy of selective laser trabeculoplasty versus argon laser trabeculoplasty in pseudophakic glaucoma patients. Clinical ophthalmology (Auckland, NZ). 2012;6:1935-40.
163. Bovell AM, Damji KF, Hodge WG, Rock WJ, Buhrmann RR, Pan YI. Long term effects on the lowering of intraocular pressure: selective laser or argon laser trabeculoplasty? Canadian journal of ophthalmology Journal canadien dophtalmologie. 2011;46(5):408-13.
164. Shazly TA, Latina MA. Intraocular pressure response to selective laser trabeculoplasty in the first treated eye vs the fellow eye. Archives of ophthalmology (Chicago, Ill : 1960). 2011;129(6):699-702.
165. De Keyser M, De Belder M, De Groot V. Randomized Prospective Study of the Use of Anti-Inflammatory Drops After Selective Laser Trabeculoplasty. Journal of glaucoma. 2017;26(2):e22-e9.
166. Realini T, Charlton J, Hettlinger M. The impact of anti-inflammatory therapy on intraocular pressure reduction following selective laser trabeculoplasty. Ophthalmic surgery, lasers & imaging : the official journal of the International Society for Imaging in the Eye. 2010;41(1):100-3.
167. Jinapriya D, DSouza M, Hollands H, El-Defrawy SR, Irrcher I, Smallman D, et al. Anti-inflammatory therapy after selective laser trabeculoplasty: a randomized, double-masked, placebo-controlled clinical trial. Ophthalmology. 2014;121(12):2356-61.
168. Groth SL, Albeiruti E, Nunez M, Fajardo R, Sharpsten L, Loewen N, et al. SALT Trial: Steroids after Laser Trabeculoplasty: Impact of Short-Term Anti-inflammatory Treatment on Selective Laser Trabeculoplasty Efficacy. Ophthalmology. 2019;126(11):1511-6.
169. Gracner T. Intraocular pressure response of capsular glaucoma and primary open-angle glaucoma to selective Nd:YAG laser trabeculoplasty: a prospective, comparative clinical trial. European journal of ophthalmology. 2002;12(4):287-92.
170. Shazly TA, Latina MA, Dagianis JJ, Chitturi S. Effect of prior cataract surgery on the long-term outcome of selective laser trabeculoplasty. Clinical ophthalmology (Auckland, NZ). 2011;5:377-80.
171. Gracner T, Falez M, Gracner B, Pahor D. [Long-term follow-up of selective laser trabeculoplasty in primary open-angle glaucoma]. Klinische Monatsblatter fur Augenheilkunde. 2006;223(9):743-7.
172. Melamed S, Ben Simon GJ, Levkovitch-Verbin H. Selective laser trabeculoplasty as primary treatment for open-angle glaucoma: a prospective, nonrandomized pilot study. Archives of ophthalmology (Chicago, Ill : 1960). 2003;121(7):957-60.
173. Koucheki B, Hashemi H. Selective laser trabeculoplasty in the treatment of open-angle glaucoma. Journal of glaucoma. 2012;21(1):65-70.
174. Lai JS, Chua JK, Tham CC, Lam DS. Five-year follow up of selective laser trabeculoplasty in Chinese eyes. Clinical & experimental ophthalmology. 2004;32(4):368-72.
175. Khawaja AP, Campbell JH, Kirby N, Chandwani HS, Keyzor I, Parekh M, et al. Real-World Outcomes of Selective Laser Trabeculoplasty in the United Kingdom. Ophthalmology. 2019.
176. McAlinden C. Selective laser trabeculoplasty (SLT) vs other treatment modalities for glaucoma: systematic review. Eye (London, England). 2014;28(3):249-58.
177. Wong MO, Lee JW, Choy BN, Chan JC, Lai JS. Systematic review and meta-analysis on the efficacy of selective laser trabeculoplasty in open-angle glaucoma. Survey of ophthalmology. 2015;60(1):36-50.
178. Wang W, He M, Zhou M, Zhang X. Selective laser trabeculoplasty versus argon laser trabeculoplasty in patients with open-angle glaucoma: a systematic review and meta-analysis. PloS one. 2013;8(12):e84270.
179. Wang H, Cheng JW, Wei RL, Cai JP, Li Y, Ma XY. Meta-analysis of selective laser trabeculoplasty with argon laser trabeculoplasty in the treatment of open-angle glaucoma. Canadian journal of ophthalmology Journal canadien dophtalmologie. 2013;48(3):186-92.
180. Nagar M, Luhishi E, Shah N. Intraocular pressure control and fluctuation: the effect of treatment with selective laser trabeculoplasty. The British journal of ophthalmology. 2009;93(4):497-501.
181. Li X, Wang W, Zhang X. Meta-analysis of selective laser trabeculoplasty versus topical medication in the treatment of open-angle glaucoma. BMC ophthalmology. 2015;15:107.
182. McIlraith I, Strasfeld M, Colev G, Hutnik CM. Selective laser trabeculoplasty as initial and adjunctive treatment for open-angle glaucoma. Journal of glaucoma. 2006;15(2):124-30.
183. Fea AM, Ahmed, II, Lavia C, Mittica P, Consolandi G, Motolese I, et al. Hydrus microstent compared to selective laser trabeculoplasty in primary open angle glaucoma: one year results. Clinical & experimental ophthalmology. 2017;45(2):120-7.
184. Weinand FS, Althen F. Long-term clinical results of selective laser trabeculoplasty in the treatment of primary open angle glaucoma. European journal of ophthalmology. 2006;16(1):100-4.
185. Juzych MS, Chopra V, Banitt MR, Hughes BA, Kim C, Goulas MT, et al. Comparison of long-term outcomes of selective laser trabeculoplasty versus argon laser trabeculoplasty in open-angle glaucoma. Ophthalmology. 2004;111(10):1853-9.
186. Lee JW, Chan CW, Wong MO, Chan J, Li Q, Lai JS. A randomized control trial to evaluate the effect of adjuvant selective laser trabeculoplasty versus medication alone in primary open-angle glaucoma: preliminary results. Clinical ophthalmology (Auckland, NZ). 2014;8:1987-92.
187. Cvenkel B. One-year follow-up of selective laser trabeculoplasty in open-angle glaucoma. Ophthalmologica Journal international dophtalmologie International journal of ophthalmology Zeitschrift fur Augenheilkunde. 2004;218(1):20-5.
188. Gracner T. Intraocular pressure response to selective laser trabeculoplasty in the treatment of primary open-angle glaucoma. Ophthalmologica Journal international dophtalmologie International journal of ophthalmology Zeitschrift fur Augenheilkunde. 2001;215(4):267-70.
189. Patel V, El Hawy E, Waisbourd M, Zangalli C, Shapiro DM, Gupta L, et al. Long-term outcomes in patients initially responsive to selective laser trabeculoplasty. International journal of ophthalmology. 2015;8(5):960-4.
190. Francis BA, Ianchulev T, Schofield JK, Minckler DS. Selective laser trabeculoplasty as a replacement for medical therapy in open-angle glaucoma. American journal of ophthalmology. 2005;140(3):524-5.
191. Klamann MK, Maier AK, Gonnermann J, Ruokonen PC. Adverse effects and short-term results after selective laser trabeculoplasty. Journal of glaucoma. 2014;23(2):105-8.
192. Woo DM, Healey PR, Graham SL, Goldberg I. Intraocular pressure-lowering medications and long-term outcomes of selective laser trabeculoplasty. Clinical & experimental ophthalmology. 2015;43(4):320-7.
193. Birt CM. Selective laser trabeculoplasty retreatment after prior argon laser trabeculoplasty: 1-year results. Canadian journal of ophthalmology Journal canadien dophtalmologie. 2007;42(5):715-9.
194. Zhang H, Yang Y, Xu J, Yu M. Selective laser trabeculoplasty in treating post-trabeculectomy advanced primary open-angle glaucoma. Experimental and therapeutic medicine. 2016;11(3):1090-4.
195. Sluch IM, Khaimi MA, Ding K, Sarkisian SR. Efficacy of selective laser trabeculoplasty after canaloplasty. Clinical & experimental ophthalmology. 2016;44(6):522-3.
196. Asrani S, Zeimer R, Wilensky J, Gieser D, Vitale S, Lindenmuth K. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. Journal of glaucoma. 2000;9(2):134-42.
197. Kiddee W, Atthavuttisilp S. The effects of selective laser trabeculoplasty and travoprost on circadian intraocular pressure fluctuations: A randomized clinical trial. Medicine. 2017;96(6):e6047.
198. Prasad N, Murthy S, Dagianis JJ, Latina MA. A comparison of the intervisit intraocular pressure fluctuation after 180 and 360 degrees of selective laser trabeculoplasty (SLT) as a primary therapy in primary open angle glaucoma and ocular hypertension. Journal of glaucoma. 2009;18(2):157-60.
199. Lee JW, Fu L, Chan JC, Lai JS. Twenty-four-hour intraocular pressure related changes following adjuvant selective laser trabeculoplasty for normal tension glaucoma. Medicine. 2014;93(27):e238.
200. Tojo N, Oka M, Miyakoshi A, Ozaki H, Hayashi A. Comparison of fluctuations of intraocular pressure before and after selective laser trabeculoplasty in normal-tension glaucoma patients. Journal of glaucoma. 2014;23(8):e138-43.
201. Leonardi M, Pitchon EM, Bertsch A, Renaud P, Mermoud A. Wireless contact lens sensor for intraocular pressure monitoring: assessment on enucleated pig eyes. Acta ophthalmologica. 2009;87(4):433-7.
202. Mansouri K, Medeiros FA, Tafreshi A, Weinreb RN. Continuous 24-hour monitoring of intraocular pressure patterns with a contact lens sensor: safety, tolerability, and reproducibility in patients with glaucoma. Archives of ophthalmology (Chicago, Ill : 1960). 2012;130(12):1534-9.
203. Ayala M. Intraocular pressure reduction after initial failure of selective laser trabeculoplasty (SLT). Graefes archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2014;252(2):315-20.
204. Francis BA, Loewen N, Hong B, Dustin L, Kaplowitz K, Kinast R, et al. Repeatability of selective laser trabeculoplasty for open-angle glaucoma. BMC ophthalmology. 2016;16:128.
205. Hong BK, Winer JC, Martone JF, Wand M, Altman B, Shields B. Repeat selective laser trabeculoplasty. Journal of glaucoma. 2009;18(3):180-3.
206. Polat J, Grantham L, Mitchell K, Realini T. Repeatability of selective laser trabeculoplasty. The British journal of ophthalmology. 2016;100(10):1437-41.
207. Avery N, Ang GS, Nicholas S, Wells A. Repeatability of primary selective laser trabeculoplasty in patients with primary open-angle glaucoma. International ophthalmology. 2013;33(5):501-6.
208. Khouri AS, Lin J, Berezina TL, Maltzman B, Fechtner RD. Repeat selective laser trabeculoplasty can be effective in eyes with initial modest response. Middle East African journal of ophthalmology. 2014;21(3):205-9.
209. Khouri AS, Lari HB, Berezina TL, Maltzman B, Fechtner RD. Long term efficacy of repeat selective laser trabeculoplasty. Journal of ophthalmic & vision research. 2014;9(4):444-8.
210. Narayanaswamy A, Leung CK, Istiantoro DV, Perera SA, Ho CL, Nongpiur ME, et al. Efficacy of selective laser trabeculoplasty in primary angle-closure glaucoma: a randomized clinical trial. JAMA ophthalmology. 2015;133(2):206-12.
211. Ali Aljasim L, Owaidhah O, Edward DP. Selective Laser Trabeculoplasty in Primary Angle-closure Glaucoma After Laser Peripheral Iridotomy: A Case-Control Study. Journal of glaucoma. 2016;25(3):e253-8.
212. Lee JW, Ho WL, Chan JC, Lai JS. Efficacy of selective laser trabeculoplasty for normal tension glaucoma: 1 year results. BMC ophthalmology. 2015;15:1.
213. Lee JW, Shum JJ, Chan JC, Lai JS. Two-Year Clinical Results After Selective Laser Trabeculoplasty for Normal Tension Glaucoma. Medicine. 2015;94(24):e984.
214. Goldenfeld M, Geyer O, Segev E, Kaplan-Messas A, Melamed S. Selective laser trabeculoplasty in uncontrolled pseudoexfoliation glaucoma. Ophthalmic surgery, lasers & imaging : the official journal of the International Society for Imaging in the Eye. 2011;42(5):390-3.
215. Shazly TA, Smith J, Latina MA. Long-term safety and efficacy of selective laser trabeculoplasty as primary therapy for the treatment of pseudoexfoliation glaucoma compared with primary open-angle glaucoma. Clinical ophthalmology (Auckland, NZ). 2010;5:5-10.
216. Ayala M, Chen E. Comparison of selective laser trabeculoplasty (SLT) in primary open angle glaucoma and pseudoexfoliation glaucoma. Clinical ophthalmology (Auckland, NZ). 2011;5:1469-73.
217. Miraftabi A, Nilforushan N, Nassiri N, Nouri-Mahdavi K. Selective laser trabeculoplasty in patients with pseudoexfoliative glaucoma vs primary open angle glaucoma: a one-year comparative study. International journal of ophthalmology. 2016;9(3):406-10.
218. Kennedy JB, SooHoo JR, Kahook MY, Seibold LK. Selective Laser Trabeculoplasty: An Update. Asia-Pacific journal of ophthalmology (Philadelphia, Pa). 2016;5(1):63-9.
219. Harasymowycz PJ, Papamatheakis DG, Latina M, De Leon M, Lesk MR, Damji KF. Selective laser trabeculoplasty (SLT) complicated by intraocular pressure elevation in eyes with heavily pigmented trabecular meshworks. American journal of ophthalmology. 2005;139(6):1110-3.
220. Ayala M. Long-term outcomes of selective laser trabeculoplasty (SLT) treatment in pigmentary glaucoma patients. Journal of glaucoma. 2014;23(9):616-9.
221. Rubin B, Taglienti A, Rothman RF, Marcus CH, Serle JB. The effect of selective laser trabeculoplasty on intraocular pressure in patients with intravitreal steroid-induced elevated intraocular pressure. Journal of glaucoma. 2008;17(4):287-92.
222. Bozkurt E, Kara N, Yazici AT, Yuksel K, Demirok A, Yilmaz OF, et al. Prophylactic selective laser trabeculoplasty in the prevention of intraocular pressure elevation after intravitreal triamcinolone acetonide injection. American journal of ophthalmology. 2011;152(6):976-81.e2.
223. Maleki A, Swan RT, Lasave AF, Ma L, Foster CS. Selective Laser Trabeculoplasty in Controlled Uveitis with Steroid-Induced Glaucoma. Ophthalmology. 2016;123(12):2630-2.
224. Zhang M, Li B, Wang J, Liu W, Sun Y, Wu X. Clinical results of selective laser trabeculoplasty in silicone oil-induced secondary glaucoma. Graefes archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2014;252(6):983-7.
225. Hodge WG, Damji KF, Rock W, Buhrmann R, Bovell AM, Pan Y. Baseline IOP predicts selective laser trabeculoplasty success at 1 year post-treatment: results from a randomised clinical trial. The British journal of ophthalmology. 2005;89(9):1157-60.
226. Martow E, Hutnik CM, Mao A. SLT and adjunctive medical therapy: a prediction rule analysis. Journal of glaucoma. 2011;20(4):266-70.
227. Tzimis V, Tze L, Ganesh J, Muhsen S, Kiss A, Kranemann C, et al. Laser trabeculoplasty: an investigation into factors that might influence outcomes. Canadian journal of ophthalmology Journal canadien dophtalmologie. 2011;46(4):305-9.
228. Bruen R, Lesk MR, Harasymowycz P. Baseline Factors Predictive of SLT Response: A Prospective Study. Journal of ophthalmology. 2012;2012:642869.
229. Chun M, Gracitelli CP, Lopes FS, Biteli LG, Ushida M, Prata TS. Selective laser trabeculoplasty for early glaucoma: analysis of success predictors and adjusted laser outcomes based on the untreated fellow eye. BMC ophthalmology. 2016;16(1):206.
230. Lee JW, Liu CC, Chan J, Wong RL, Wong IY, Lai JS. Predictors of success in selective laser trabeculoplasty for primary open angle glaucoma in Chinese. Clinical ophthalmology (Auckland, NZ). 2014;8:1787-91.
231. Pillunat KR, Spoerl E, Elfes G, Pillunat LE. Preoperative intraocular pressure as a predictor of selective laser trabeculoplasty efficacy. Acta ophthalmologica. 2016;94(7):692-6.
232. Katz LJ, Steinmann WC, Kabir A, Molineaux J, Wizov SS, Marcellino G. Selective laser trabeculoplasty versus medical therapy as initial treatment of glaucoma: a prospective, randomized trial. Journal of glaucoma. 2012;21(7):460-8.
233. Miki A, Kawashima R, Usui S, Matsushita K, Nishida K. Treatment Outcomes and Prognostic Factors of Selective Laser Trabeculoplasty for Open-angle Glaucoma Receiving Maximal-tolerable Medical Therapy. Journal of glaucoma. 2016;25(10):785-9.
234. Hirneiss C, Sekura K, Brandlhuber U, Kampik A, Kernt M. Corneal biomechanics predict the outcome of selective laser trabeculoplasty in medically uncontrolled glaucoma. Graefes archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2013;251(10):2383-8.
235. Song J. Complications of selective laser trabeculoplasty: a review. Clinical ophthalmology (Auckland, NZ). 2016;10:137-43.
236. Kim DY, Singh A. Severe iritis and choroidal effusion following selective laser trabeculoplasty. Ophthalmic surgery, lasers & imaging : the official journal of the International Society for Imaging in the Eye. 2008;39(5):409-11.
237. Hernandez Pardines F, Molina Martin JC, Fernandez Montalvo L, Aguirre Balsalobre F. Bilateral choroidal effusion after selective laser trabeculoplasty. Archivos de la Sociedad Espanola de Oftalmologia. 2017;92(6):295-8.
238. Koktekir BE, Gedik S, Bakbak B. Bilateral severe anterior uveitis after unilateral selective laser trabeculoplasty. Clinical & experimental ophthalmology. 2013;41(3):305-7.
239. Baser EF, Akbulut D. Significant peripheral anterior synechiae after repeat selective laser trabeculoplasty. Canadian journal of ophthalmology Journal canadien dophtalmologie. 2015;50(3):e36-8.

240. Ha JH, Bowling B, Chen SD. Cystoid macular oedema following selective laser trabeculoplasty in a diabetic patient. Clinical & experimental ophthalmology. 2014;42(2):200–1.
241. Wechsler DZ, Wechsler IB. Cystoid macular oedema after selective laser trabeculoplasty. Eye (London, England). 2010;24(6):1113.
242. Wu ZQ, Huang J, Sadda S. Selective laser trabeculoplasty complicated by cystoid macular edema: report of two cases. Eye science. 2012;27(4):193–7.
243. Phillis CA, Bourke RD. Bilateral Subretinal Fluid Mimicking Subretinal Neovascularization Within 24 Hours After Selective Laser Trabeculoplasty. Journal of glaucoma. 2016;25(2):e110–4.
244. White AJ, Mukherjee A, Hanspal I, Sarkies NJ, Martin KR, Shah P. Acute transient corneal endothelial changes following selective laser trabeculoplasty. Clinical & experimental ophthalmology. 2013;41(5):435–41.
245. Ong K, Ong L, Ong LB. Corneal endothelial abnormalities after selective laser trabeculoplasty (SLT). Journal of glaucoma. 2015;24(4):286–90.
246. Lee JW, Chan JC, Chang RT, Singh K, Liu CC, Gangwani R, et al. Corneal changes after a single session of selective laser trabeculoplasty for open–angle glaucoma. Eye (London, England). 2014;28(1):47–52.
247. Moubayed SP, Hamid M, Choremis J, Li G. An unusual finding of corneal edema complicating selective laser trabeculoplasty. Canadian journal of ophthalmology Journal canadien dophtalmologie. 2009;44(3):337–8.
248. Regina M, Bunya VY, Orlin SE, Ansari H. Corneal edema and haze after selective laser trabeculoplasty. Journal of glaucoma. 2011;20(5):327–9.
249. Knickelbein JE, Singh A, Flowers BE, Nair UK, Eisenberg M, Davis R, et al. Acute corneal edema with subsequent thinning and hyperopic shift following selective laser trabeculoplasty. Journal of cataract and refractive surgery. 2014;40(10):1731–5.
250. Dirani M, Crowston JG, Taylor PS, Moore PT, Rogers S, Pezzullo ML, et al. Economic impact of primary open–angle glaucoma in Australia. Clinical & experimental ophthalmology. 2011;39(7):623–32.
251. Lee PP, Walt JG, Doyle JJ, Kotak SV, Evans SJ, Budenz DL, et al. A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. Archives of ophthalmology (Chicago, Ill : 1960). 2006;124(1):12–9.
252. Kobelt G, Jonsson L. Modeling cost of treatment with new topical treatments for glaucoma. Results from France and the United Kingdom. International journal of technology assessment in health care. 1999;15(1):207–19.
253. Cantor LB, Katz LJ, Cheng JW, Chen E, Tong KB, Peabody JW. Economic evaluation of medication, laser trabeculoplasty and filtering surgeries in treating patients with glaucoma in the US. Current medical research and opinion. 2008;24(10):2905–18.
254. Taylor HR. Glaucoma: where to now? Ophthalmology. 2009;116(5):821–2.
255. Seider MI, Keenan JD, Han Y. Cost of selective laser trabeculoplasty vs topical medications for glaucoma. Archives of ophthalmology (Chicago, Ill : 1960). 2012;130(4):529–30.
256. Lee R, Hutnik CM. Projected cost comparison of selective laser trabeculoplasty versus glaucoma medication in the Ontario Health Insurance Plan. Canadian journal of ophthalmology Journal canadien dophtalmologie. 2006;41(4):449–56.
257. Guedes RA, Guedes VM, Gomes CE, Chaoubah A. Maximizing cost–effectiveness by adjusting treatment strategy according to glaucoma severity. Medicine. 2016;95(52):e5745.
258. Berdahl JP, Khatana AK, Katz LJ, Herndon L, Layton AJ, Yu TM, et al. Cost–comparison of two trabecular micro–bypass stents versus selective laser trabeculoplasty or medications only for intraocular pressure control for patients with open–angle glaucoma. Journal of medical economics. 2017;20(7):760–6.
259. Jones L, Garway–Heath DF, Azuara–Blanco A, Crabb DP. Are patient self–reported outcome measures (PROMs) sensitive enough to be used as endpoints in clinical trials? Evidence from the United Kingdom Glaucoma Treatment Study. Ophthalmology. 2018.
260. Azuara–Blanco A, Burr J, Ramsay C, Cooper D, Foster PJ, Friedman DS, et al. Effectiveness of early lens extraction for the treatment of primary angle–closure glaucoma (EAGLE): a randomised controlled trial. Lancet (London, England). 2016;388(10052):1389–97.
261. De Keyser M, De Belder M, De Groot V. Quality of life in glaucoma patients after selective laser trabeculoplasty. International journal of ophthalmology. 2017;10(5):742–8.
262. Jones L, Garway–Heath DF, Azuara–Blanco A, Crabb DP. Are Patient Self–Reported Outcome Measures Sensitive Enough to Be Used as End Points in Clinical Trials?: Evidence from the United Kingdom Glaucoma Treatment Study. Ophthalmology. 2018.
263. McHugh D, Marshall J, Ffytche TJ, Hamilton PA, Raven A. Diode laser trabeculoplasty (DLT) for primary open–angle glaucoma and ocular hypertension. The British journal of ophthalmology. 1990;74(12):743–7.
264. McHugh D, Marshall J, Ffytche TJ, Hamilton PA, Raven A. Ultrastructural changes of human trabecular meshwork after photocoagulation with a diode laser. Investigative ophthalmology & visual science. 1992;33(9):2664–71.
265. Ingvoldstad DD, Krishna R, Willoughby L. MicroPulse Diode Laser Trabeculoplasty versus Argon Laser Trabeculoplasty in the Treatment of Open Angle Glaucoma. Investigative ophthalmology & visual science. 2005;46(13):123–.
266. Ekici F, Waisbourd M, Katz LJ. Current and Future of Laser Therapy in the Management of Glaucoma. The open ophthalmology journal. 2016;10:56–67.
267. Rantala E, Valimaki J. Micropulse diode laser trabeculoplasty –– 180–degree treatment. Acta ophthalmologica. 2012;90(5):441–4.
268. Fea AM, Bosone A, Rolle T, Brogliatti B, Grignolo FM. Micropulse diode laser trabeculoplasty (MDLT): A phase II clinical study with 12 months follow–up. Clinical ophthalmology (Auckland, NZ). 2008;2(2):247–52.
269. Lee JW, Yau GS, Yick DW, Yuen CY. MicroPulse Laser Trabeculoplasty for the Treatment of Open–Angle Glaucoma. Medicine. 2015;94(49):e2075.
270. Abramowitz B, Chadha N, Kouchouk A, Alhabshan R, Belyea DA, Lamba T. Selective laser trabeculoplasty vs micropulse laser trabeculoplasty in open–angle glaucoma. Clinical ophthalmology (Auckland, NZ). 2018;12:1599–604.
271. Ma A, Yu SWY, Wong JKW. Micropulse laser for the treatment of glaucoma: A literature review. Survey of ophthalmology. 2019;64(4):486–97.
272. Goldenfeld M, Melamed S, Simon G, Ben Simon GJ. Titanium:sapphire laser trabeculoplasty versus argon laser trabeculoplasty in patients with open–angle glaucoma. Ophthalmic surgery, lasers & imaging : the official journal of the International Society for Imaging in the Eye. 2009;40(3):264–9.
273. Kaplowitz K, Wang S, Bilonick R, Oatts JT, Grippo T, Loewen NA. Randomized Controlled Comparison of Titanium–Sapphire Versus Standard Q–Switched Nd: YAG Laser Trabeculoplasty. Journal of glaucoma. 2016;25(7):e663–7.
274. Blumenkranz MS, Yellachich D, Andersen DE, Wiltberger MW, Mordaunt D, Marcellino GR, et al. Semiautomated patterned scanning laser for retinal photocoagulation. Retina (Philadelphia, Pa). 2006;26(3):370–6.
275. Mansouri K, Shaarawy T. Comparing pattern scanning laser trabeculoplasty to selective laser trabeculoplasty: A randomized controlled trial. Acta ophthalmologica. 2017;95(5):e361–e5.
276. Belkin M, Geffen N, Ofir S, Kaplan Messas A, Barkana Y, Belkin A, et al. Direct Trans–Scleral Selective Laser Trabeculoplasty (SLT) Without a Gonioscopy Lens. Investigative ophthalmology & visual science. 2014;55(13):819–.
277. Geffen N, Ofir S, Belkin A, Segev F, Barkana Y, Kaplan Messas A, et al. Transscleral Selective Laser Trabeculoplasty Without a Gonioscopy Lens. Journal of glaucoma. 2017;26(3):201–7.
278. Gazzard G, Konstantakopoulou E, Garway–Heath D, Garg A, Vickerstaff V, Hunter R, et al. Selective laser trabeculoplasty vs drops for the treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial
. The Lancet. 2019;In press.
279. Hee OK, Thng ZX, Zhu HY, Lamoureux EL. Usage of glaucoma–specific patient–reported outcome measures (PROMs) in the Singapore context: a qualitative scoping exercise. BMC ophthalmology. 2018;18(1):197.
280. Vickerstaff V, Ambler G, Bunce C, Xing W, Gazzard G. Statistical analysis plan for the Laser–1st versus Drops–1st for Glaucoma and Ocular Hypertension Trial (LiGHT): a multi–centre randomised controlled trial. Trials. 2015;16:517.
281. Gazzard G, Konstantakopoulou E, Garway–Heath D, Barton K, Wormald R, Morris S, et al. Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial. A multicentre, randomised controlled trial: design and methodology. The British journal of ophthalmology. 2017.
282. NICE. National Institute for Health and Clinical Excellence. NICE: Guidance on Glaucoma: Diagnosis and management of chronic open angle glaucoma and ocular hypertension: DoH; 2010 [Available from: www.nice.org.uk/CG85fullguideline. 2010.
283. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five–level version of EQ–5D (EQ–5D–5L). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20(10):1727–36.
284. Burr JM, Kilonzo M, Vale L, Ryan M. Developing a preference–based Glaucoma Utility Index using a discrete choice experiment. Optometry and vision science : official publication of the American Academy of Optometry. 2007;84(8):797–808.
285. Lee BL, Gutierrez P, Gordon M, Wilson MR, Cioffi GA, Ritch R, et al. The Glaucoma Symptom Scale. A brief index of glaucoma–specific symptoms. Arch Ophthalmol. 1998;116(7):861–6.
286. Nelson P, Aspinall P, Papasouliotis O, Worton B, OBrien C. Quality of life in glaucoma and its relationship with visual function. J Glaucoma. 2003;12(2):139–50.
287. Patel A, Rendu A, Moran P, Leese M, Mann A, Knapp M. A comparison of two methods of collecting economic data in primary care. Fam Pract. 2005;22(3):323–7.
288. Damji KF, Behki R, Wang L, Target IOPWP. Canadian perspectives in glaucoma management: setting target intraocular pressure range. Can J Ophthalmol. 2003;38(3):189–97.
289. Mills RP, Budenz DL, Lee PP, Noecker RJ, Walt JG, Siegartel LR, et al. Categorizing the stage of glaucoma from pre–diagnosis to end–stage disease. Am J Ophthalmol. 2006;141(1):24–30.
290. Kotecha A, Crabb DP, Spratt A, Garway–Heath DF. The relationship between diurnal variations in intraocular pressure measurements and central corneal thickness and corneal hysteresis. Invest Ophthalmol Vis Sci. 2009;50(9):4229–36.
291. Canadian Glaucoma Study Group. Canadian Glaucoma Study: 1. Study design, baseline characteristics, and preliminary analyses. Can J Ophthalmol. 2006;41(5):566–75.
292. European Glaucoma S. Terminology and Guidelines for Glaucoma 3rd Ed. EGS. 2008;http://www.eugs.org/eng/EGS_guidelines.asp.
293. American Academy of Ophthalmology. Primary Open–Angle Glaucoma: Preferred Practice Pattern. 2005.
294. SEAGIG. South East Asia Gluacoma Interest Group: Asia Pacific Glaucoma Guidelines. SEAGIG. 2003.
295. Strouthidis NG, Scott A, Peter NM, Garway–Heath DF. Optic disc and visual field progression in ocular hypertensive subjects: detection rates, specificity, and agreement. Investigative ophthalmology & visual science. 2006;47(7):2904–10.
296. National Institute for Health and Clinical Excellence. NICE: Guidance on Glaucoma: Diagnosis and management of chronic open angle glaucoma and ocular hypertension: DoH; 2010 [Available from: www.nice.org.uk/CG85fullguideline.
297. Patel A, Rendu A, Moran P, Leese M, Mann A, Knapp M. A comparison of two methods of collecting economic data in primary care. Family Practice. 2005;22(3):323–7.
298. Caprioli J, Coleman AL. Intraocular Pressure Fluctuation: A Risk Factor for Visual Field Progression at Low Intraocular Pressures in the Advanced Glaucoma Intervention Study. Ophthalmology. 2008;115(7):1123–9.e3.
299. Garg A, Gazzard G. Selective laser trabeculoplasty: past, present, and future. Eye (London, England). 2018.
300. Aspinall PA, Johnson ZK, Azuara–Blanco A, Montarzino A, Brice R, Vickers A. Evaluation of Quality of Life and Priorities of Patients with Glaucoma. Investigative Ophthalmology Visual Science. 2008;49(5):1907–15.
301. Gazzard G, Konstantakopoulou E, Garway–Heath D, Garg A, Vickerstaff V, Hunter R, et al. Selective laser trabeculoplasty versus eye drops for first–line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial. Lancet (London, England). 2019.
302. Garg A, Vickerstaff V, Nathwani N, Garway–Heath D, Konstantakopoulou E, Ambler G, et al. Primary Selective Laser Trabeculoplasty for Open Angle Glaucoma and Ocular Hypertension: Clinical Outcomes, Predictors of Success and Safety from the Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial. Ophthalmology. 2019.
303. Wallace DK, Melia M. Post hoc power calculations. Ophthalmology. 2008;115(11):2098; author reply –9.
304. Smith SD. Statistical tools in the quest for truth: hypothesis testing, confidence intervals, and the power of clinical studies. Ophthalmology. 2008;115(3):423–4.
305. Wang F, Javitt JC, Tielsch JM. Racial variations in treatment for glaucoma and cataract among Medicare recipients. Ophthalmic epidemiology. 1997;4(2):89–100.
306. Stein JD, Talwar N, Laverne AM, Nan B, Lichter PR. Racial disparities in the use of ancillary testing to evaluate individuals with open–angle glaucoma. Archives of ophthalmology (Chicago, Ill : 1960). 2012;130(12):1579–88.
307. King AJ, Fernie G, Azuara–Blanco A, Burr JM, Garway–Heath T, Sparrow JM, et al. Treatment of Advanced Glaucoma Study: a multicentre randomised controlled trial comparing primary medical treatment with primary trabeculectomy for people with newly diagnosed advanced glaucoma–study protocol. The British journal of ophthalmology. 2018;102(7):922–8.
308. Lindén C, Heijl A, Jóhannesson G, Aspberg J, Andersson Geimer S, Bengtsson B. Initial intraocular pressure reduction by mono– versus multi–therapy in patients with open–angle glaucoma: results from the Glaucoma Intensive Treatment Study. Acta ophthalmologica. 2018;96(6):567–72.
309. Heijl A, Leske MC, Hyman L, Yang Z, Bengtsson B. Intraocular pressure reduction with a fixed treatment protocol in the Early Manifest Glaucoma Trial. Acta ophthalmologica. 2011;89(8):749–54.
310. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. Journal of clinical epidemiology. 1996;49(12):1373–9.
311. Realini T, Shillingford–Ricketts H, Burt D, Balasubramani GK. West Indies Glaucoma Laser Study (WIGLS): 2. Predictors of Selective Laser Trabeculoplasty Efficacy in Afro–Caribbeans with Glaucoma. Journal of glaucoma. 2018.
312. Realini T, Shillingford–Ricketts H, Burt D, Balasubramani GK. West Indies Glaucoma Laser Study (WIGLS): 1. 12–Month Efficacy of Selective Laser Trabeculoplasty in Afro–Caribbeans With Glaucoma. American journal of ophthalmology. 2017;184:28–33.
313. Cvenkel B, Hvala A, Drnovsek–Olup B, Gale N. Acute ultrastructural changes of the trabecular meshwork after selective laser trabeculoplasty and low power argon laser trabeculoplasty. Lasers in surgery and medicine. 2003;33(3):204–8.
314. Hutnik Cindy C, Crichton A, Ford B, Nicolela M, Shuba L, Birt C, et al. SLT Versus ALT in Glaucoma Patients Treated Previously with 360–degree SLT: A Randomized, Single–Blind, Equivalence Clinical Trial. Ophthalmology. 2018.
315. Goldberg I, Clement CI, Chiang TH, Walt JG, Lee LJ, Graham S, et al. Assessing quality of life in patients with glaucoma using the Glaucoma Quality of Life–15 (GQL–15) questionnaire. Journal of glaucoma. 2009;18(1):6–12.

APPENDIX:

Appendix 1

EQ5D Questionnaire

1 EuroQol questionnaire

We are asking you the following questions to see how you rate your own health. For each of the following questions please place a tick in the box that closest describes your state of health **TODAY**.

1 Please indicate your level of mobility *(please tick **one** box)*

- ☐ I have no problems in walking about
- ☐ I have slight problems in walking about
- ☐ I have moderate problems in walking about
- ☐ I have severe problems in walking about
- ☐ I am unable to walk about

2 Please indicate your level of self-care (*please tick **one** box)*

- ☐ I have no problems washing or dressing myself
- ☐ I have slight problems washing or dressing myself
- ☐ I have moderate problems washing or dressing myself
- ☐ I have severe problems washing or dressing myself
- ☐ I am unable to wash or dress myself

3 Please indicate your ability to perform your usual activities e.g. work, study, housework, family or leisure activities (*please tick **one** box)*

- ☐ I have no problems doing my usual activities
- ☐ I have slight problems doing my usual activities
- ☐ I have moderate problems doing my usual activities
- ☐ I have severe problems doing my usual activities
- ☐ I am unable to do my usual activities

4 Please indicate your level of pain (*please tick **one** box)*

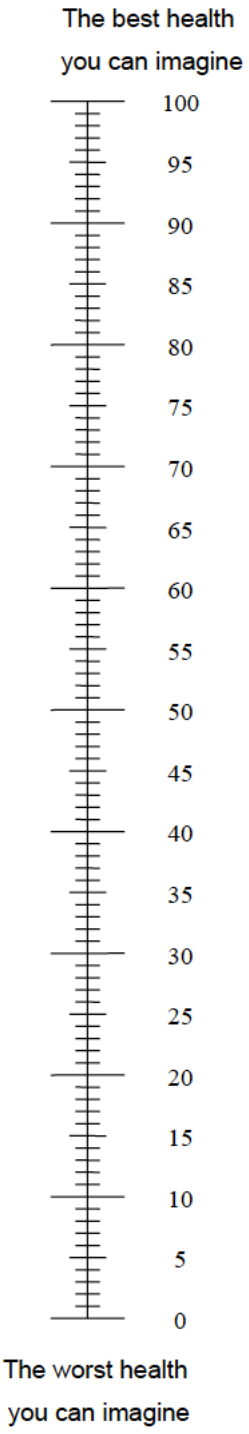
- ☐ I have no pain or discomfort
- ☐ I have slight pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have severe pain or discomfort
- ☐ I have extreme pain or discomfort

5 Please indicate your level of anxiety or depression (*please tick **one** box)*

- ☐ I am not anxious or depressed
- ☐ I am slightly anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am severely anxious or depressed
- ☐ I am extremely anxious or depressed

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



2 Glaucoma Utility Index

"*Tick one* box, for each of the categories 1-6, which best describes any difficulties you have had **in the last month** with your eyes or vision, wearing your usual glasses or contact lenses. Under each category there is an example, to help you answer these questions."

Domains	Level of difficulty			
	No difficulty	Some difficulty	Quite a lot of difficulty	Severe difficulty
1. Central and Near Vision For example difficulties with reading, writing, watching TV, reading dials on clocks?	☐	☐	☐	☐
2.Lighting and glare For example difficulties with adjusting from light to dark and vice-versa, bright lights may dazzle, difficulties seeing in dim light?	☐	☐	☐	☐
3. Mobility For example difficulties with crossing roads, walking along busy pavements, tripping into low objects e.g. pushchairs?	☐	☐	☐	☐
4. Activities of daily living For example difficulties in seeing adequately to do domestic, DIY or self-care tasks around the home?	☐	☐	☐	☐
5. Eye discomfort For example difficulties with gritty, sore, tired eyes?	☐	☐	☐	☐
6. Other effects For example fatigue, shortness of breath, dry mouth, bitter taste etc?	☐	☐	☐	☐

3. Glaucoma Symptom Scale

Have you experienced any of the following problems with your eyes **in the last 4 weeks**? (Please *tick* a box below for each symptom). If your answer is '*yes*' please tick how bothersome it is.

1 Burning, Smarting, Stinging

No ☐, Go to next question **Yes** ☐, How bothersome is it?

Very ☐

Somewhat ☐

A little ☐

Not at all ☐

2 Tearing ("Watering Eyes")

No ☐, Go to next question **Yes** ☐, How bothersome is it?

Very ☐

Somewhat ☐

A little ☐

Not at all ☐

3 Dryness

No ☐, Go to next question **Yes** ☐, How bothersome is it?

Very ☐

Somewhat ☐

A little ☐

Not at all ☐

Glaucoma Symptom Scale continued …..

4 Itching

No ☐, Go to next question **Yes** ☐, How bothersome is it?

Very ☐

Somewhat ☐

A little ☐

Not at all ☐

5 Soreness, Tiredness

No ☐, Go to next question **Yes** ☐, How bothersome is it?

Very ☐

Somewhat ☐

A little ☐

Not at all ☐

6 Blurry/dim vision

No ☐, Go to next question **Yes** ☐, How bothersome is it?

Very ☐

Somewhat ☐

A little ☐

Not at all ☐

7 Feeling of something in your eye

No ☐, Go to next question **Yes** ☐, How bothersome is it?

Very ☐

Somewhat ☐

A little ☐

Not at all ☐

8 Hard to see in daylight

No ☐, Go to next question **Yes** ☐, How bothersome is it?

Very ☐

Somewhat ☐

A little ☐

Not at all ☐

9 Hard to see in dark places

No ☐, Go to next question **Yes** ☐, How bothersome is it?

Very ☐

Somewhat ☐

A little ☐

Not at all ☐

Glaucoma Symptom Scale continued …..

10 Halos around lights

No ☐ **Yes** ☐, How bothersome is it?

Very ☐

Somewhat ☐

A little ☐

Not at all ☐

4. The Glaucoma Quality of Life-15 Questionnaire

Please *Tick one* box, for each of the categories 1-15, which best describes any difficulties you have had in **the last month**, even with your usual glasses or contact lenses.

Activities	None	A little bit of difficulty	Some difficulty	Quite a lot difficulty	Severe difficulty	Do not perform for non visual reasons
1. Reading newspapers	☐	☐	☐	☐	☐	☐
2. Walking after dark	☐	☐	☐	☐	☐	☐
3. Seeing at night	☐	☐	☐	☐	☐	☐
4. Walking on uneven ground	☐	☐	☐	☐	☐	☐
5. Adjusting to bright lights	☐	☐	☐	☐	☐	☐
6. Adjusting to dim lights	☐	☐	☐	☐	☐	☐
7. Going from light to dark room or vice versa	☐	☐	☐	☐	☐	☐
8. Tripping over objects	☐	☐	☐	☐	☐	☐
9. Seeing objects coming from the side	☐	☐	☐	☐	☐	☐
10. Crossing the road	☐	☐	☐	☐	☐	☐
11. Walking up steps/stairs	☐	☐	☐	☐	☐	☐
12. Bumping into objects	☐	☐	☐	☐	☐	☐
13. Judging distance of foot to step/curb	☐	☐	☐	☐	☐	☐
14. Finding dropped objects	☐	☐	☐	☐	☐	☐
15.Recognizing faces	☐	☐	☐	☐	☐	☐

Appendix 2

Statistical Analysis Plan (SAP) Template

LiGHT Trial – Clinical outcomes of Primary SLT

1. Summary

The analyses detailed in this document are in addition to the primary outcome analyses detailed elsewhere by Vickerstaff et al. 2015.

These analyses are 'exploratory' and are aimed at exploring the clinical efficacy of primary SLT in those treatment naïve, newly diagnosed POAG/OHT patients that were randomly allocated to receive primary SLT at the start of the LiGHT trial.

With the above considered, there is no 'null' hypothesis to be tested in this analysis – we are aiming to report clinical outcomes in our treated patients up to a period of the 36 months and compare our findings to current literature.

We have a total of 355 patients (271 POAG, 84 OHT) who have undergone primary SLT treatment. This is also represented as a total of 611 eyes (416 POAG, 195 OHT).

The unit of analysis will be eyes.

2. Outcome measures

Outcome measures will include

- IOP lowering
- Regression analysis to look for predictors of IOP lowering
- Number of treatments required to maintain target IOP
- Regression analysis to look for predictors of success of SLT treatment at 36 months
- Complications
- Repeatability of SLT

3. CRFs, data collection, data verification and data management

The data for the analyses described has already been gathered via CRFs – this data has also been inputted into the Sealed Envelope Data management system.

Data verification

Before analysis, basic checks will be performed to check the quality of the data. Incomplete or inconsistent data include:

- Missing data
- Data outside expected range
- Other inconsistencies between variables e.g. in the dates the questionnaires were completed

If any inconsistencies are found, the corresponding values will be double checked with the researchers and corrected if necessary. All changes will be documented by the statistical team.

Some loss to follow-up is expected over 36 months.

Potential bias due to missing data will be investigated initially by comparing the baseline characteristics of the trial participants with complete follow-up measurements compared to those who have incomplete follow-up or no outcome data, using descriptive comparisons and t-/chi-square tests.

4. Sample size calculation

The sample size in the LiGHT Trial is calculated based on the primary outcome measure - health-related quality of life (HRQL) powered to detect superiority of a treatment pathway at 36 months. A study with 311 participants in each group would have 90% power to detect at 5% significance level a difference in means of 0.05, assuming that the common standard deviation is 0.19 and using a two-sample t-test (we may gain precision using ANCOVA). Allowing for 15% loss to follow-up at 36 months, the total number required for the study is 718 (359 in each group) which we have recruited.

As the analyses detailed in this SAP are exploratory and largely descriptive of a subset of patients receiving primary SLT – there is no power calculation for this SAP.

5. Data Analysis Plan

Unit of Analysis

The Unit of analysis will be eyes.

During the study, some patients will have had only one eye treated with SLT and others will have had both eyes treated. As we are choosing to use data on both eyes, we will need to account for the non-independence and will perform adjustment for 2 eyes to avoid bias using a mixed model analysis.

Analysis of Primary outcomes

We will present data of:

- Mean IOP at baseline (OHT; mild POAG; moderate POAG; severe POAG)
- Mean IOP at 2 months (OHT; mild POAG; moderate POAG; severe POAG)
- Mean decrease in IOP from baseline (mmHg) at 2 months
- Mean % decrease in IOP from baseline at 2 months

Analysis of Secondary outcomes

IOP Success

In the literature, success in IOP reduction has been measured in different ways and thus for this outcome measure. We will categorise success by % eyes achieving target IOP at 36 months as per our IOP treatment protocol.

'Setting of the treatment IOP' protocol is set such that:

- OHT patients must achieve >20% reduction + IOP <25mmHg
- Mild POAG patients must achieve >20% reduction + IOP <21mmHg
- Moderate POAG patients must achieve >30% reduction + IOP <18mmHg
- Severe POAG patients must achieve >30% reduction <15mmHg

Number of treatments required to maintain target IOP

We will also report the number of SLT treatments required (1, 2, 3, 4 etc.) to maintain target IOP till 36 months per group (OHT, mild POAG, moderate POAG, severe POAG)

Regression Analysis

We will investigate factors that predict IOP lowering at 2 months using linear regression. We will also investigate predictors of successful SLT at 36-months using logistic regression. We will compare potential factors (these will be sorted according to whether they are categorical variables or continuous variables) – and compare these between 'success' and 'non-success' groups using logistic regression.

We will adopt a backwards elimination approach to develop the multivariable regression model, keeping covariates that achieve P<0.1 for the univariate analysis that will then be included in the final multivariable logistic regression model.

Complications

We will describe complications of SLT in our patient cohort at 36 months. We will report incidence and rates of:

- Post laser IOP spike
- Corneal oedema
- Acute anterior uveitis
- Hyphaema
- Macular oedema
- Pain
- Change in visual acuity
- Conjunctival erythema

Repeatability

- We will investigate the efficacy of repeat SLT in those requiring retreatment
- Specifically, we will evaluate IOP lowering and duration of effect allowing for equivalent duration of follow up
- We will investigate whether timing of initial SLT failure influences efficacy of repeat laser treatment

- Specifically, we will evaluate IOP lowering and duration of effect allowing for equivalent duration of follow up
- We will investigate whether timing of initial SLT failure influences efficacy of repeat laser treatment

Additional HRQL analyses

- We will explore whether any difference in HRQL at 36 months between patients that are 'drop free' vs those 'on drops' within SLT arm
- We will explore whether any difference in HRQL at 36 months between patients with evidence of disease progression vs. those with no evidence of disease progression in SLT arm

Appendix 3

AT BASELINE	Clinical data at 36 months (536 eyes) Mean (SD)	No clinical data at 36 months (77 eyes) Mean (SD)	Mean Difference	P value
IOP** (mmHg)	24.5 (5.2)	24.3 (5.4)	0.2mmHg (95% CI, -1.1 to 1.4)	0.80
VA*** (LogMAR)	0.07 (0.2)	0.13 +/- 0.2	-0.06 (95% CI, -0.1 to -0.01)	**0.02**
MD*** (dB)	-3.1 (3.4)	-2.9 (3.1)	-0.2 dB (95% CI, -1.0 to 0.6)	0.68
Sex – M:F	182:132	18:24		0.06
Age*** (years)	63.4 (12.1)	64.3 (12.4)		0.94
Ethnicity (patients)	White European 217 (69.11%) Black 62 (19.75%) Asian 22 (7.01%) Other 13 (4.14%)	White European 26 (61.90%) Black 15 (35.71%) Asian 1 (2.38%) Other 0		0.11
Severity (eyes)	OHT 164 eyes (30.60%) Mild 275 eyes (51.31%) Moderate 58 eyes (10.82%) Severe 39 eyes (7.28%)	OHT 31 eyes (40.26%) Mild 34 eyes (44.16%) Moderate 9 eyes (11.67%) Severe 1 eye (1.30%)		0.10

Table 40 :Comparison between eyes available vs. unavailable for analysis* at 36 months in Primary SLT arm

*2 eyes of 1 patient withdrew at Baseline visit – prior to disease severity assessment, IOP measurement, visual field, disc imaging or receiving SLT treatment

**IOP assumed to have normal distribution – tested by visualising data using histogram.
***Differences in VA, MD and age tested using t-test with results presented. Using alternative assumption of non-parametric distribution for following variables – Wilcoxon Rank Sum Test performed with no change in results (Baseline VA, p=0.03) (Baseline MD, p= 0.85) (Age, p=0.93)

Appendix 4

Characteristics	Value
Age (years), mean (SD)	62.7 (11.6)
Gender (patients), (%)	
Male	197 (54.4%)
Female	165 (45.6%)
Ethnicity (patients), (%)	
White European	258 (71.3%)
Black	69 (19.1%)
Asian	28 (7.7%)
Other	7 (1.9%)
Laterality (patients), (%)	
Bilateral Eyes	260 (71.8%)
Right Eye	47 (13.0%)
Left Eye	55 (15.2%)
Hypertension (patients), (%)	
Yes	119 (32.9%)
No	243 (67.1%)
Diabetes Mellitus (patients), (%)	
Yes	40 (11.1%)
No	322 (88.9%)
Disease Severity (eyes), (%)	
OHT	185 (29.7%)
'Mild' POAG	325 (52.3%)
'Moderate' POAG	77 (12.4%)
'Severe' POAG	35 (5.6%)
Mean Deviation (dB), mean (SD)	-3.0 (3.6)
Pattern Standard Deviation (dB), mean (SD)	3.8 (3.1)
Mean HRT area (mm2), mean (SD)	1.1 (0.4)
Baseline IOP (mmHg), mean (SD)	
Overall	24.4 (5.1)
OHT	26.8 (3.5)
POAG	23.9 (5.5)
Average Trabecular Pigmentation Grade (eyes), (%)	
0 -None	240 (38.6%)
1- Mild	253 (40.7%)
2-Moderate	121(19.5%)
3-Dense	2(0.3%)
Unknown	6 (1.0%)
Habitual VA (Logmar), mean (SD)	0.10 (0.1)
CCT (microns), mean (SD)	551.6 (36.2)
PXF (eyes), (%)	
Yes	12 (1.9%)
No	610 (98.1%)
Target IOP (mmHg)	
OHT	21.3 (2.3)
'Mild' POAG	17.9 (3.0)
'Moderate' POAG	15.3 (2.6)
'Severe' POAG	14.6 (1.0)

Table 41: Baseline characteristics of Medication 1st Arm. Baseline patient characteristics. POAG: Primary Open Angle Glaucoma, OHT: Ocular Hypertension. Self-defined ethnicity; 'Asian' ethnicity refers to Indian, Pakistani, Bangladeshi and any other Asian background, 'Black' ethnicity refers to Caribbean, African and any other black background, 'Other' ethnicity refers to Chinese and any other ethnic groups.

Appendix 5

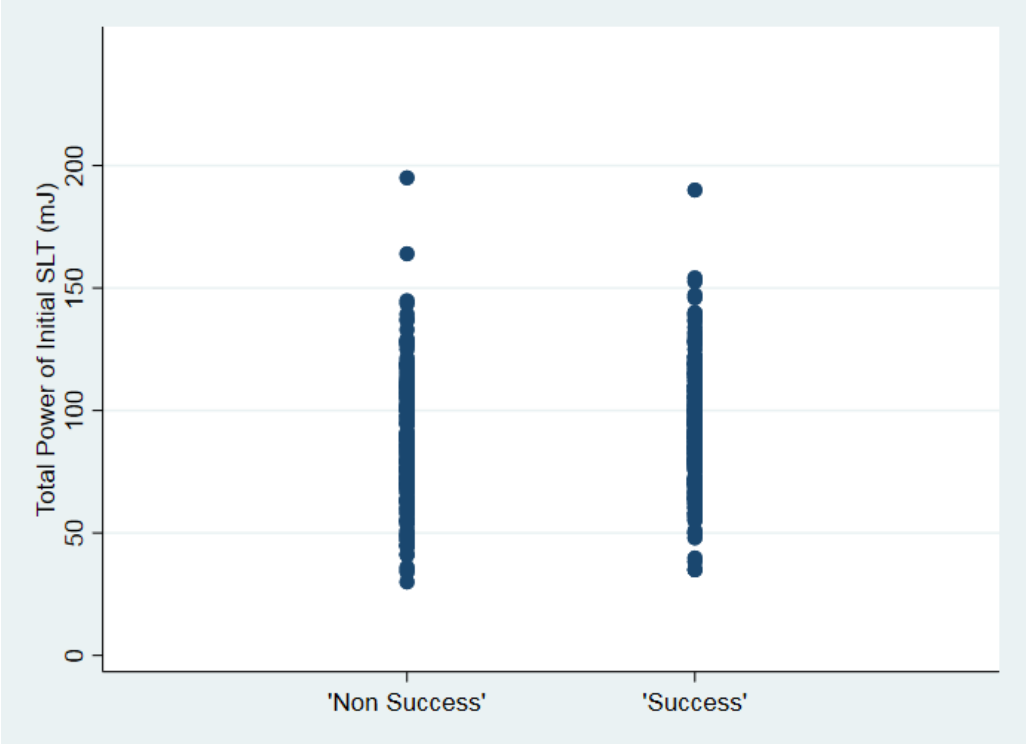


Figure 14: Scatter plot of total power of initial SLT vs achievement of "disease-control" at 36-months following initial single SLT at baseline

Appendix 6

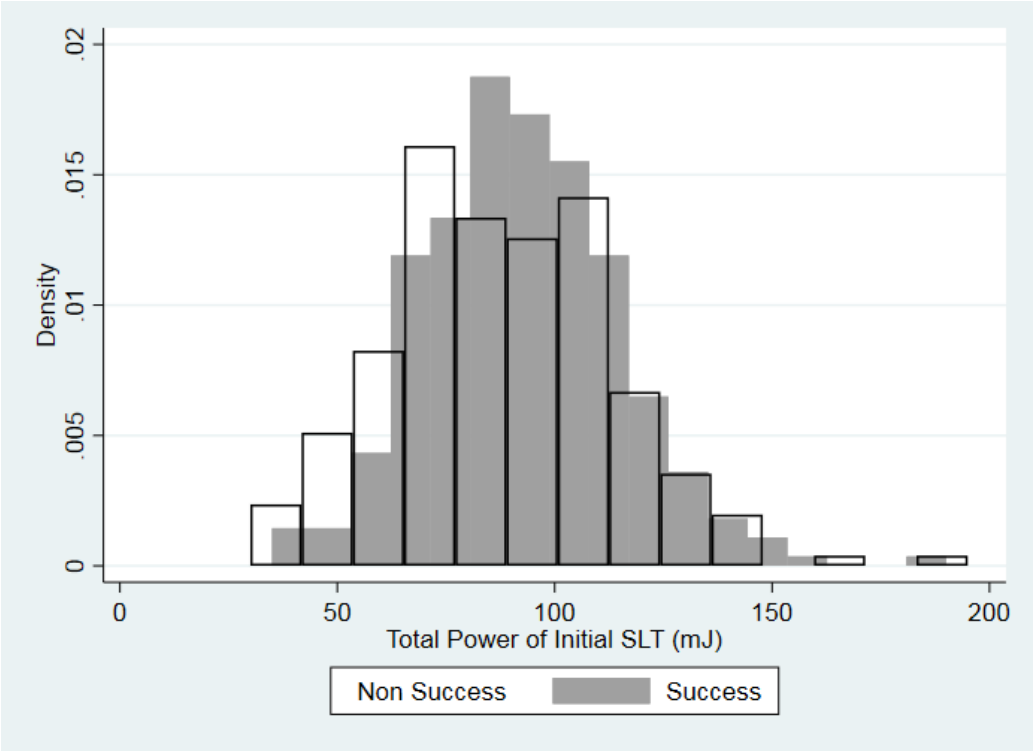


Figure 15: Histogram of total power of initial SLT vs achievement of "disease-control" at 36-months following initial single SLT at baseline

Appendix 7

SENSITIVITY ANALYSIS – Repeat SLT

ONE EYE PER PERSON – RANDOMLY SELECTED

	Number of eyes (n)	Initial SLT Mean IOP (SD) (mmHg)	Initial SLT Mean absolute IOP reduction from pre-treatment IOP (mmHg; 95% CI)	Initial SLT Mean % IOP reduction from pre-treatment IOP (SD)	Number of eyes (n)	Repeat SLT Mean IOP (SD) (mmHg)	Repeat SLT Mean absolute IOP reduction from pre-retreatment IOP (mmHg; 95% CI)	Repeat SLT Mean % IOP reduction from pre-retreatment IOP (SD)	Initial vs. Repeat SLT Mean difference in absolute IOP reduction from pre-treatment IOP (mmHg; 95% CI)	Initial vs. Repeat SLT *Adjusted* mean difference in absolute IOP reduction from pre-treatment IOP (mmHg; 95% CI)
Pre-treatment	**90**	**24.9** ** **(6.6)**			**90**	**21.1** ** **(4.1)**				
2 months	**78**[a,b]	**19.2 (3.9)**	**5.4* (4.5 to 6.4)**	**20.0 (13.5)**	**80**[c,d]	**16.5 (3.3)**	**4.3* (3.6 to 5.0)**	**19.8 (12.8)**	**1.5 (0.4 to 2.6)**	**-0.9 (-1.7 to -0.2)**
6 months	46[a,b]	19.0 (3.9)	4.9* (3.7 to 6.2)	19.0 (14.0)	68[c,d]	17.1 (3.3)	4.3 (3.4 to 5.1)	18.9 (13.6)	0.7 (-0.8 to 2.2)	-0.8 (-1.8 to 0.2)
12 months	21[a,b]	20.8 (4.6)	3.6* (1.8 to 5.4)	13.5 (13.6)	58[c,d]	17.5 (3.6)	3.9 (2.9 to 4.8)	16.8 (16.0)	-1.1 (-4.0 to 1.7)	-1.7 (-3.3 to -0.1)
18 months	0[b]	-	-	-	47[c,d]	16.8 (3.7)	3.9 (2.9 to 4.9)	17.7 (15.2)	-	-

Table 42: Summary of Mean IOP for Initial SLT and Repeat SLT.

a: IOP data missing: 9 eyes at 2 months, 2 eyes at 6 months, 1 eye at 12 months for Initial SLT.
b: IOP data censored (no longer at target, treatment escalated): 3 eyes at 2 months, 42 eyes at 6 months, 68 eyes at 12 months, 90 eyes for Initial SLT.

c: IOP data missing: 9 eyes at 2 months, 5 eyes at 6 months, 6 eyes at 12 months, 12 eyes at 18 months for Repeat SLT.
d: IOP data censored (no longer at target, treatment escalated): 1 eye at 2 months, 17 eyes at 6 months, 26 eyes at 12 months, 31 eyes at 18 months for Repeat SLT.

**Significant reduction in mean absolute IOP reduction from pre-treatment IOP at 2 months for Initial and Repeat SLT (p<0.001) calculated using t-test*

*** Significant difference in pre-treatment IOP between Initial and Repeat SLT (mean difference: 3.9, 95% CI 2.8 to 4.9; p<0.001) using t-test*

	Number of eyes (n)	'Early Failure' Repeat SLT Mean IOP (SD) (mmHg)	'Early Failure' Repeat SLT Mean (SD) absolute IOP reduction (mmHg)	'Early Failure' Repeat SLT % IOP reduction (SD)	Number of eyes (n)	'Later Failure' Repeat SLT Mean IOP (SD) (mmHg)	'Later Failure' Repeat SLT Mean (SD) absolute IOP reduction (mmHg)	'Later Failure' Repeat SLT % IOP reduction (SD)	'Early Failure' vs. 'Later Failure' Mean difference in absolute IOP reduction (mmHg; 95% CI)
Pre-treatment	**29**	**21.8 (3.6)**			**61**	**20.7 (4.2)**			
2 months	**25**	**17.5 (3.0)**	**4.1 (3.7)**	**17.7 (13.9)**	**55**	**16.0 (3.3)**	**4.4 (3.1)**	**20.7 (12.3)**	**-0.4 (-1.9 to 1.2)**

Table 43: Summary of Repeat SLT IOP reduction at 2 months for 'Early Failures' vs 'Late Failures'

No significant difference in pre-treatment IOP between 'Early Failures' vs 'Late Failures' for Repeat SLT (p=0.223) – (mixed model analysis)
**No significant reduction in mean absolute IOP reduction at 2 months (p=0.645) – (mixed model anaylsis)*

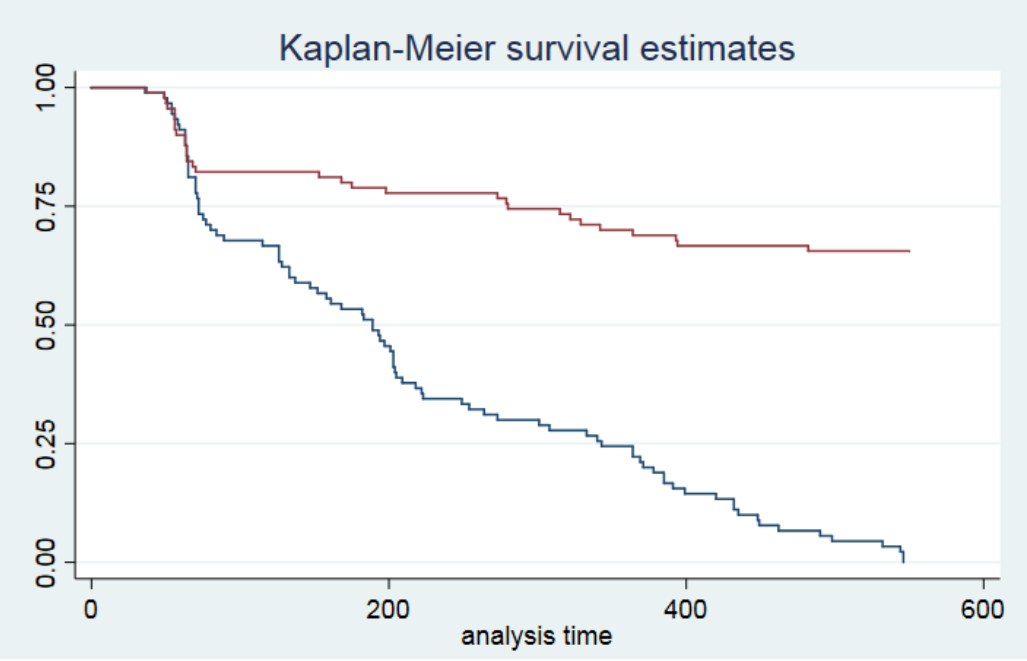


Figure 16: Kaplan Meier Plot for 90 eyes: Initial SLT (blue line) vs. Repeat SLT (red line)