

## **The Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial. A multicentre randomised controlled trial: Baseline patient characteristics.**

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**Abbreviations:** Laser in Glaucoma and Ocular-Hypertension: LiGHT, Selective laser trabeculoplasty: SLT, Primary Open Angle Glaucoma: POAG, Ocular Hypertension: OHT, Treatment in Pursuit of Control: TPC, Quality of Life: QoL, Central Corneal Thickness: CCT, The National Institute of Care Excellence: NICE, Intra-ocular pressure: IOP, Randomised clinical trials: RCT, Health-related quality of Life: HRQL, Early Manifest Glaucoma Trial: EMGT, United States of America: USA, Advanced Glaucoma Intervention Study: AGIS, Collaborative Initial Glaucoma Treatment Study, Ocular Hypertension Treatment Study: OHTS, United Kingdom Glaucoma Treatment Study: UKGTS, European Glaucoma Prevention Study: EGPS, Effectiveness in Angle-closure Glaucoma of Lens Extraction: EAGLE, Glaucoma Utility Index: GUI, Glaucoma Symptom Scale: GSS, Glaucoma Quality of Life-15: GQL-15, Client Service Receipt Inventory: CSRI, Glaucoma Progression Analysis: GPA, European Glaucoma Society: EGS, Maximum medical therapy: MMT, Humphrey Visual Field: HVF, Glaucoma Progression Analysis: GPA, Heidelberg Retinal Tomograph: HRT, Visual field: VF, Standard operating procedures: SOP, Quality-Adjusted Life Years: QALYs, National Health Service: NHS.

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**SYNOPSIS**

The Laser in Glaucoma and Ocular Hypertension trial is a multicentre randomised controlled trial comparing the health-related quality of life, clinical and cost-effectiveness of drops vs. selective laser trabeculoplasty as a first line treatment.

## ABSTRACT

**Purpose:** The Laser in Glaucoma and Ocular-Hypertension (LiGHT) Trial aims to establish whether initial treatment with selective laser trabeculoplasty (SLT) is superior to initial treatment with topical medication for Primary Open Angle Glaucoma (POAG) or Ocular Hypertension (OHT).

**Design:** LiGHT is a prospective unmasked, multi-centre, pragmatic, randomised controlled trial (RCT).

**Participants:** 718 previously untreated patients with POAG or OHT were recruited at 6 UK centres between 2012 and 2014.

**Methods:** Patients were randomised to initial SLT followed by medical therapy or medical therapy without laser. Participants will be monitored for 3 years, according to routine clinical practice. The primary outcome is EQ-5D-5L. Secondary outcomes are treatment pathway cost and cost-effectiveness, Glaucoma Utility Index, Glaucoma Symptom Scale, Glaucoma Quality of Life, pathway effectiveness, visual function, safety and concordance.

**Results:** A total of 555 patients had POAG and 163 OHT; 518 patients had both eyes eligible. The mean age for POAG patients was 64 years and for OHT 58 years. 70% of all participants were white. Median IOP for OHT eyes was 26mmHg and 23mmHg for POAG eyes. Median baseline VF MD was -0.81dB for OHT eyes and -2.82dB for POAG eyes. There was no difference between POAG and OHT patients on the EQ-5D-5DL; the difference between OHT and POAG on the GUI was -0.02 and on the GQL 1.23.

**Conclusions:** The LiGHT Trial is the first RCT to compare the two treatment options in a real-world setting. The baseline characteristics of the LiGHT cohort compare well with other landmark glaucoma studies.

## INTRODUCTION

Glaucoma is recognised as the leading cause of irreversible blindness worldwide.<sup>1</sup> Intra-ocular pressure (IOP) is the only modifiable risk factor; laser and topical medication both effectively reduce IOP.<sup>2-4</sup> Topical medical treatment is associated with questionable long-term acceptability and impaired Health Related Quality of Life (HRQL) due to considerable cost, side effects and numerous hospital visits.<sup>5</sup>

The Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial compares HRQL in patients who started treatment using topical IOP lowering medication to that in patients who were treated with SLT first. LiGHT also compares the clinical and cost-effectiveness of the two pathways. The design of LiGHT has been described elsewhere.<sup>6</sup> Briefly, LiGHT is a multicentre, randomised clinical trial, unmasked to treatment allocation. Eligible patients with POAG or OHT were randomised to either SLT or medical therapy (drops) as first line treatment. Patients with one or both eyes eligible were treated identically. All measurements influencing treatment escalation decisions were made by observers masked to treatment status. Target IOP, follow-up intervals and treatment escalation decisions were guided by custom written decision-support software using visual field, IOP and disc imaging information to avoid bias in clinical decision-making. Patients were followed up for 3 years.

## METHODS

Eligible patients were identified at the National Health Service (NHS) clinics of six participating centres in the UK from October 2012 through to October 2014 (Appendix 1). Patients had newly diagnosed, untreated POAG in one or both eyes (including normal tension glaucoma and pseudoexfoliative glaucoma) or OHT qualifying for treatment according to NICE guidelines,<sup>7</sup> open angles, and for POAG visual field loss with mean deviation (VF MD) not worse than -12 dB in the better eye or -15 dB in the worse eye and corresponding damage to the optic nerve head. Patients were 18 years or older and able to understand English, had a visual acuity of 6/36 or better in the treated eye(s), no history of treatment for POAG or OHT and no previous intra-ocular surgery, except uncomplicated phaco-emulsification at least one year before entering the trial. Patients were excluded if there were contra-indications to SLT, they were unable to use topical medical therapy, they had visually significant cataract, or were having treatment for another ophthalmic condition. A glaucoma sub-specialist fellowship-trained consultant ophthalmologist's decision to initiate treatment was required for inclusion in the Trial.

The IOP was measured with Goldman applanation tonometry, by experienced clinicians masked to treatment allocation. The VF tests were performed with the Humphrey Field Analyser Mark II (SITA standard 24-2) (Carl Zeiss Meditec, Dublin, CA). Optic nerve head scans were obtained with the Heidelberg retina tomograph (HRT) (Heidelberg Engineering, Heidelberg, Germany). The refractive error was calculated as the spherical diopters measured with an autorefractor. General health information and medication was recorded based on the patients' reporting.

The study adheres to the tenets of the Declaration of Helsinki and had been granted ethical approval.

### Disease classification

The NICE recommended thresholds were used for disease classification and for initiating treatment.<sup>7</sup> For the purposes of disease classification 'per patient', participants were classified as having POAG in at least one eye, as this represents the pragmatic treatment in a clinical setting. Patients were classified as having OHT if at least one eye had OHT (but no POAG).

## Outcome Measures

The primary outcome measure is HRQL measured using EQ-5D-5L<sup>8</sup> with utility scores calculated using the English Time Trade Off (TTO) value set.<sup>9</sup> Secondary outcome measures are treatment pathway health care resource use, cost and cost-effectiveness [Client Service Receipt Inventory' (CSRI)] questionnaire,<sup>10</sup> glaucoma specific treatment-related quality of life [(Glaucoma Utility Index (GUI))]<sup>11</sup> patient reported disease and treatment related symptoms [Glaucoma Symptom Scale (GSS)],<sup>12</sup> and visual function [Glaucoma Quality of Life – 15 (GQL-15)]<sup>13</sup>, objective measurements of pathway effectiveness for IOP lowering and visual function preservation, objective safety measures for each treatment pathway and concordance. Questionnaires are sent to patients at six-monthly intervals.

## Statistical analysis

Summary measures for the baseline characteristics of the participating patients and eyes are presented as mean and standard deviation for continuous variables with a symmetric distribution, medians and inter-quartile ranges for continuous, skewed variables and frequencies and percentages for categorical variables. Means and standard deviations are also reported in some cases and for EQ-5D-5L and GUI to allow for comparisons with values reported in other studies. The difference in means and corresponding 95% confidence intervals between OHT and POAG in EQ-5D-5L utility scores, GUI, GSS and GQL are generated using linear regression and bootstrapping with 1,000 replications. These summaries are based on observed data only and the number of missing observations will be reported. Stata 13.0 (StataCorp LP, Texas, USA) was used for the data analysis.

## RESULTS

### Baseline Patient Characteristics

718 patients were recruited: 301 patients (41.9%) had bilateral POAG; 161 (22.4%) had unilateral POAG (fellow eye healthy); 93 patients (13.0%) had POAG in one eye and OHT in the other eye; 124 patients (17.3%) had bilateral OHT and 39 patients (5.4%) had unilateral OHT. A total of 555 patients (77.2%) were classified as POAG and 163 patients (22.7%) were classified as OHT: 518 patients (72.1%) had both eyes eligible for the trial; 96 patients (13.4%) had only the right eye eligible and 104 patients (14.5%) had only the left eye eligible; 55% of the better eyes were right eyes. Table 1 summarises the baseline patient characteristics.

		All	Diagnosis	
		N (%)n=718	OHT n=163	POAG n=555
<b>Centres</b>	<b>Queen's University Belfast</b>	30 (4)	5 (3)	25 (5)
	<b>Guy's and St Thomas' Hospital</b>	106 (15)	55 (34)	51 (9)
	<b>Huntingdon Hospital</b>	82 (11)	14 (9)	68 (12)
	<b>Moorfields Eye Hospital</b>	374 (52)	73 (45)	301 (54)
	<b>Norfolk and Norwich University Hospital</b>	89 (12)	13 (8)	76 (14)
	<b>York Hospital</b>	37 (5)	3 (2)	34 (6)
<b>Gender</b>	<b>Female</b>	321 (45)	69 (42)	252 (45)
	<b>Male</b>	397 (55)	94 (58)	303 (55)
<b>Age</b>	<b>Mean (SD)</b>	63 (12)	58 (11)	64 (12)
<b>Ethnicity<sup>a</sup></b>	<b>Asian</b>	51 (7)	8 (5)	43 (8)
	<b>Black</b>	146 (20)	45 (28)	101 (18)
	<b>Whites</b>	501 (70)	104 (64)	397 (71)
	<b>Other</b>	20 (3)	6 (4)	14 (3)

<b>General health</b>	<b>Asthma</b>	93 (13)	17 (10)	76 (14)
	<b>Hypertension</b>	251 (35)	60 (37)	191 (34)
	<b>Diabetes</b>	82 (11)	24 (15)	58 (10)
	<b>Angina</b>	21 (3)	4 (2)	17 (3)
	<b>Cardiac Arrhythmia</b>	37 (5)	4 (2)	33 (6)
	<b>Ischaemic Heart Disease</b>	20 (3)	3 (2)	17 (3)
	<b>CVA/Stroke</b>	14 (2)	2 (1)	12 (2)
	<b>Migraines</b>	94 (13)	16 (10)	78 (14)
	<b>Peripheral vasospastic symptoms</b>	63 (9)	7 (4)	56 (10)
	<b>Blood Loss/Transfusion</b>	76 (11)	14 (9)	62 (11)
<b>Family Ocular History of Glaucoma<sup>b</sup> (1st degree relative)</b>		214 (30)	46 (28)	168 (30)

**Table 1** Baseline patient characteristics. IQR - Interquartile range; a: '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: n = 717

In both diagnostic groups, more male than female patients were recruited (POAG 55% males; OHT 58% males). The mean age for POAG patients was 64 years (SD=12 years) (median (IQR) = 65 (56 to 73)) and for OHT 58 years (SD=11 years) (median (IQR) = 57 (50 to 65)). A total of 70% of all participants were white; black was the second largest ethnic group (20%). 30% of POAG patients reported a family history of glaucoma, compared to 28% of OHT patients. Systemic hypertension was noted in 34% of the POAG patients and 37% of the OHT patients. Use of systemic antihypertensive medication was noted in 35% of all patients, 27% were on statins and 11% were smokers.

### Baseline Characteristics for Eligible Eyes

A total of 854 eyes (69%) were classified as POAG and 380 eyes (31%) were classified as OHT. The median baseline VF MD was -0.81dB for OHT eyes (mean (SD) = -1.25 (2.05) dB) and -2.82dB for POAG eyes (mean (SD) = 3.81 (3.68) dB). The median IOP for OHT eyes was 26mmHg (mean (SD) = 26.7 (3.5) mmHg) and 23mmHg for POAG eyes (mean (SD) = 23.5 (5.4) mmHg). A total of 24% of the POAG eyes had a baseline IOP of 19mmHg or below. Median neuro-retinal rim area was 1.25mm<sup>2</sup> for OHT eyes and 1.04mm<sup>2</sup> for POAG eyes. Median CCT for OHT eyes was 557µm (mean CCT (SD) = 557 (39) µm) and for POAG eyes 549 µm (mean CCT (SD) = 549 (36) µm). Glaucomatous eyes were more myopic and had worse VA than OHT eyes (Table 2).

	<b>All eyes (N = 1234)</b>	<b>OHT (n= 380 )</b>	<b>POAG (n= 854)</b>
	<b>Median (IQR)</b>		
<b>Refractive Error<sup>a</sup> (Spherical D)</b>	0.25 (-1.25 to 1.5)	0.44 (-0.75 to 1.5)	0.25 (-1.5 to 1.5)
<b>Visual acuity</b>	0.04 (-0.04 to 0.14)	0.02 (-0.08 to 0.12)	0.06 (-0.02 to 0.16)
<b>VF MD (dB)</b>	-2.15 (-4.46 to -0.57)	-0.81 (-2.4 to 0.28)	-2.82 (-5.53 to -1.16)
<b>VF PSD (dB)</b>	2.42 (1.71 to 4.73)	1.74 (1.465 to 2.295)	3.08 (1.99 to 6.21)
<b>HRT Rim Area</b>	1.13 (0.91 to 1.37)	1.25 (1.09 to 1.53)	1.04 (0.83 to 1.29)
<b>IOP</b>	24 (21 to 28)	26 (24 to 29)	23 (20 to 27)
<b>CCT (µm)<sup>b</sup></b>	551 (527 to 576)	557 (531 to 580)	549 (524 to 573)
<b>PXF, n (%)</b>	17 (1)	9 (2)	8 (1)
<b>Phacoemulsification in the past, n (%)</b>	72 (6)	7 (2)	65 (8)

**Table 2** 1234 eyes of 718 patients were treated in the study. a: data available for 713 patients; b: data available for 715 patients. 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; IQR- Inter-quartile range.

### Baseline Data of Questionnaire Survey

POAG patients scored a median of 0.94 on the EQ-5D-5DL (mean (SD) = 0.92 (0.13)) and 0.90 on GUI (mean (SD) = 0.89 (0.12)). On GSS POAG patients scored a median of 85 (mean (SD) = 82.4 (16.7)) and on GQL-15 17 (mean (SD) = 19.1 (6.3)). OHT patients scored a median of 0.94 on the EQ-5D-5DL (mean (SD) = 0.91 (0.14)) and 0.93 on GUI (mean (SD) = 0.91 (0.1)). On GSS OHT patients scored a median of 85 (mean (SD) = 82.3 (17.6)) and on GQL-15 16 (mean (SD) = 17.9 (5.4)) (Table 3). There was no difference between POAG and OHT patients on the EQ-5D-5L (difference 0.00, 95% confidence interval (CI) -0.02 to 0.03) and on the GSS (difference 0.08, 95% CI -2.91 to 3.07); the difference between OHT and POAG on the GUI was -0.02 (95% CI -0.04 to 0.001) and on the GQL difference 1.23 (95% CI 0.15 to 2.31)).

	OHT (n=163)	POAG (n=554)
	Median (IQR)	
EQ-5D-5L Index	0.94 (0.89, 1.00)	0.94 (0.88, 1.00)
Glaucoma Utility Index <sup>a</sup>	0.93 (0.87, 1.00)	0.90 (0.81, 1.00)
Glaucoma Symptom Scale <sup>b</sup>	85 (75, 95)	85 (73, 95)
Symptom	83 (71, 100)	83 (71, 96)
Function	88 (75, 100)	88 (75, 100)
Glaucoma Quality of Life-15 <sup>c</sup>	16 (15, 19)	17 (15, 21)
Central	2 (2, 3)	2 (2, 3)
Peripheral	7 (7, 8)	7 (7, 9)
Dark	6 (6, 8)	7 (6, 9)
Outdoor	1 (1, 1)	1 (1, 1)

**Table 3:** Baseline values for EQ5D-5L, Glaucoma Utility Index, Glaucoma Utility Scale, Glaucoma Quality of Life-15; a: n = 716, b: n=710, c: n=712.

## DISCUSSION

The LiGHT Trial is a multi-centre RCT, comparing HRQL, clinical- and cost-effectiveness and safety of SLT versus topical IOP lowering medication in treatment-naïve patients with newly diagnosed POAG or OHT. LiGHT has an eye specific Target IOP and follows routine clinical practice, permitting any medication (apart from pilocarpine) and any treatment escalations, providing a realistic analysis of glaucoma and OHT management.

The higher black population in LiGHT (20%) compared to the United Kingdom Glaucoma Treatment Study (UKGTS) (5.2%)<sup>14</sup> is attributable to the high proportion recruited in ethnically diverse London (66.8%), similar to studies conducted in the USA, such as the Advanced Glaucoma Intervention Study (AGIS),<sup>15</sup> Collaborative Glaucoma Initial Glaucoma Treatment Study (CIGTS)<sup>16</sup> and Ocular Hypertension Treatment Study (OHTS),<sup>17</sup> with higher proportions of black participants (56.2%, 38.1%, 25%, respectively).

A total of 42% of the patients had bilateral POAG, a proportion lower than UKGTS (51.8%), but higher than the Early Manifest Glaucoma Trial (EMGT) (24% overall).<sup>18</sup>

### Clinical characteristics

LiGHT POAG patients were slightly younger than the UKGTS cohort (mean 64.1 and 66 years, respectively). The EMGT recruited older newly-diagnosed patients (median 65 years for LiGHT POAG and 68 years for EMGT), whereas CIGTS recruited younger patients (median 56 and 61 years for black and white patients, respectively). Age differences might reflect the differing proportion of black patients, in whom POAG is seen at a younger age. There were more male patients in the LiGHT POAG cohort (55%), as in the UKGTS (52.9%) and CIGTS (55%).

The LiGHT POAG cohort had overall higher IOPs than UKGTS (mean IOP 23.5 vs 19.5mmHg, respectively) and EMGT (median LiGHT 23 mmHg vs EMGT 20.5mmHg); CIGTS reported distinctly higher IOPs (mean 27.6mmHg medicine group, 27.4mmHg surgery group). Nearly a quarter of POAG LiGHT eyes had a baseline IOP  $\leq$ 19mmHg, fewer than in the EMGT (56.1%) and UKGTS (43%). Differences in mean presenting IOP between studies may reflect differences between referral patterns, with a more frequent rate of normal tension glaucoma (NTG) diagnosis in some areas.

LiGHT POAG patients appeared to have early stage disease similar to UKGTS (median VF MD -2.8dB for LiGHT, UKGTS -2.9dB), and less severe than EMGT (median VF MD -4.7dB) and CIGTS (-5.5dB), possibly reflecting different referral thresholds or access to screening. Similarly to UKGTS and CIGTS, 30% of LiGHT POAG patients reported having a family history of POAG.

Systemic hypertension was noted in 34% of the LiGHT POAG patients, similar to EMGT (38%) and CIGTS (37% overall), but lower than UKGTS (57.8%) and AGIS (overall 46.78%). Diabetes was recorded for 11% of the LiGHT patients, similar to the UKGTS (10.5%), but different to studies conducted in other countries (AGIS 20.3%, EMGT 4%). A total of 3% of LiGHT POAG patients reported ischemic heart disease (UKGTS 5.4%, EMGT 6%). Almost a quarter of the POAG patients reported symptoms suggestive of vasospastic conditions, (LiGHT POAG 10%, EMGT 9%) or migraines (LiGHT POAG 14%, EMGT 10%), compared to almost half of the UKGTS patients (overall 47.4%).

The LiGHT OHT cohort was on average slightly older than the OHTS cohort (mean LiGHT 57.7, OHTS 55.4 years), but similar to the European Glaucoma Prevention Study (EGPS) cohort.<sup>19</sup> The LiGHT OHT cohort also had more males (58%) than females, unlike OHTS and EGPS.

OHT eyes of the LiGHT cohort had a mean IOP of 26.7mmHg, higher than that reported by OHTS (24.9mmHg) and EGPS (23.6mmHg). LiGHT OHT eyes had worse VF MD (mean -1.25dB) than the OHTS cohort (0.24dB) and the EGPS cohort (0.18dB). CCT in the LiGHT OHT cohort was lower than the OHTS cohort (mean 557 vs 573 $\mu$ m, respectively). These differences could arise from differences between NICE treatment thresholds and OHTS entry criteria.

Of the LiGHT OHT patients 28% reported a family history of glaucoma, in contrast to 44% of the OHTS cohort. The prevalence of systemic hypertension and diabetes in the LiGHT OHT cohort were similar to OHTS.

The mean IOP was lower in POAG eyes compared to OHT eyes (23.5 vs 26.7mmHg, respectively). OHT eyes had overall thicker corneas compared to POAG eyes (557 vs 549 $\mu$ m, respectively). More POAG patients reported symptoms suggestive of vasospastic conditions compared to OHT patients.

## HRQL

The EQ-5D-5L was developed to overcome some of the ceiling effects commonly seen in the EQ-5D-3L, having more discriminatory power and less of a ceiling effect.<sup>20</sup> This is the

only study, after EAGLE, to report the results of the EQ-5D-5L in a UK population with OHT or POAG.

The mean EQ-5D-5L score of 0.92 for the LiGHT POAG cohort is higher than the UK average EQ-5D-3L score of 0.799 to 0.779.<sup>21</sup> LiGHT patients diagnosed with POAG had lower scores than newly diagnosed EAGLE patients, despite the previous exposure of the latter cohort to IOP lowering treatment.<sup>22</sup> The utility scores of the LiGHT POAG cohort are higher than other cohorts of POAG patients, although these are for older patients with more advanced disease or under various treatment modalities.<sup>23</sup>

Mean GUI scores of the POAG LiGHT cohort (0.89) were not substantially different from the EAGLE study (lens extraction 0.897, peripheral iridotomy 0.921).<sup>22</sup> LiGHT POAG patients scored higher in the GSS than patients in other studies.<sup>12</sup> LiGHT POAG patients showed better QoL compared to other POAG cohorts as measured with the GQL-15 and scored similarly to patients with normal VF.<sup>24</sup>

HRQL has not been studied extensively in OHT patients. In OHTS, the recruited patients showed better HRQL at baseline than age- and gender-matched population based norms, which was attributed to the cohort's high educational and/or socioeconomic status. The LiGHT OHT cohort shows higher utility scores, measured with the EQ-5D-5DL and GQL-15, when compared to a different cohort of untreated OHT.<sup>25</sup>

There was no difference between POAG and OHT patients on EQ-5D-5L and the GSS, but GUI, a preference based tool to measure disutility directly related to glaucoma used by the EAGLE trial, and GQL were both better at discriminating between OHT and POAG, even at an early disease stage, suggesting greater sensitivity in this setting.

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## Competing interests

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The full protocol can be accessed at:

<https://njl-admin.nihr.ac.uk/document/download/2010005>.

Further information is available at:

<https://www.journalslibrary.nihr.ac.uk/programmes/hta/0910440/#/>

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