Title: The Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial. A multicentre randomised controlled trial: Design and methodology

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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, Hospital Eye Service: HES, 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 investigating 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

The LiGHT Trial is a prospective unmasked, multi-centre, pragmatic, randomised controlled trial. 718 previously untreated patients with POAG or OHT were recruited at 6 collaborating centres in the United Kingdom between 2012 and 2014. The trial comprises two treatment arms: initial SLT followed by conventional medical therapy as required and medical therapy without laser therapy. Randomisation was provided online by a web-based randomisation service. Participants will be monitored for 3 years, according to routine clinical practice. The target intraocular pressure (IOP) was set at baseline according to an algorithm, based on disease severity and lifetime risk of loss of vision at recruitment and subsequently adjusted on the basis of IOP control, optic disc and visual field. The primary outcome measure is Health Related Quality of Life (EQ-5D-5L). Secondary outcomes are treatment pathway cost and cost-effectiveness, Glaucoma Utility Index, Glaucoma Symptom Scale, Glaucoma Quality of Life, objective measures of pathway effectiveness, visual function and safety profiles and concordance. A single main analysis will be performed at the end of the trial on an intention-to-treat basis.

Conclusions

The LiGHT Trial is a multicentre, pragmatic, randomised clinical trial that will provide valuable data on the relative HRQL, clinical and cost effectiveness of SLT and topical IOP lowering medication.

INTRODUCTION

Primary open-angle glaucoma (POAG) is an irreversible optic neuropathy, affecting up to 4% of white and 15% of black populations by the age of 80[1] and a leading cause of blind registrations, falls and loss of independence,[2] significantly affecting Quality of Life (QoL).[3] IOP is the only modifiable risk factor, the reduction of which is proven to slow down the progression of the disease.[4] Although the effectiveness of hypotensive drops is irrefutable, they come with a number of potential aesthetic, sight threatening and serious systemic side effects,[5, 6] and may have a negative impact on the success of subsequent surgical intervention.[7] Medical management of POAG and OHT requires regular monitoring, as well as multiple hospital visits.

Selective laser trabeculoplasty (SLT) involves a painless outpatient application of laser to the trabecular meshwork. Economic modelling has predicted that using SLT as a first line treatment compared to topical medication will significantly reduce healthcare costs,[8] although this has been refuted by others.[9] Research recommendations by NICE and Cochrane have identified the need for robust randomised clinical trials (RCT) investigating the efficacy and cost-effectiveness of SLT as a first line treatment.[10, 11]

This paper describes the design of the Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial that compares health-related quality of life (HRQL), cost effectiveness and clinical outcomes for patients who start treatment with topical IOP lowering medication ("Medicine-1st" pathway) to that for patients who are first treated with SLT ("Laser-1st" pathway).

METHODS

Study design

LiGHT is a multicentre RCT unmasked to treatment allocation. The study adheres to the tenets of the Declaration of Helsinki and is registered at www.controlled-trials.com (registration number ISRCTN32038223). Ethical approval was granted by the City Road and Hampstead Research and Ethics Committee. The trial is monitored by a Trial Management Group, a Trial Steering Committee and a Data and Safety Monitoring Committee.

Eligible patients are randomised on a 1:1 ratio to receive either medical therapy or SLT as first line treatment for POAG or OHT. All measurements influencing treatment escalation decisions, i.e. IOP, HRT, VF, are made by masked observers (optometrists and/or technicians). Patients are monitored for 3 years. Monitoring intervals and treatment escalation decisions are guided by clinical decision support software (DSS) implementing a defined protocol based on published evidence-based guidelines, while also attempting to capture the complexities of clinical practice. Inclusion and exclusion criteria are shown in Table 1.

Inclusion criteria	Exclusion criteria
Newly diagnosed and untreated POAG or OHT[a] with a decision to treat[b] made by a consultant ophthalmologist[c]	Advanced POAG[d]
18 years or older	Visual acuity worse than 6/36 in a study eye[e]
Able to provide informed consent	Secondary glaucoma[f]
Able to understand English	Angle closure
	Congenital/early childhood glaucoma

	Previous treatment for POAG/OHT
	Contra-indication to SLT
	Inability to use topical medical therapy
	Visually significant cataract
	Active treatment for another ophthalmic condition in either eye
	History of retinal ischaemia, macular oedema or diabetic retinopathy
	Age-related macular degeneration with neovascularisation or geographic atrophy
	Previous intra-ocular surgery[g]
	Pregnancy or intention to become pregnant
	Medically unfit for completion of the trial
	Involvement in another interventional research study

Table 1 Inclusion and exclusion criteria to the LiGHT Trial; a: in one or both eyes (including pseudoexfoliation glaucoma) b: under NICE guidelines[11] c: fellowship-trained glaucoma sub-specialist consultant ophthalmologist, , d: VF loss mean deviation worse than -12 dB in the better or -15 dB in the worse eye, e: uni-ocular patients were eligible, f: pigment dispersion syndrome, trauma, g: except uncomplicated phaco-emulsification at least one year before entering the trial.

Recruitment

Consecutive eligible patients were identified at six participating centres from October 2012 until October 2014 (Appendix 1). Patients who decided to participate were given a baseline assessment on a different day and those who declined were asked for a reason for their refusal.

Baseline assessment

At the baseline assessment, participants underwent visual acuity testing (ETDRS logMAR), slit-lamp examination, automated visual field (VF) testing (Humphrey Field Analyser (HFA) Mark II SITA standard 24-2), Heidelberg Retina Tomography (HRT) optic disc imaging, IOP measurement, gonioscopy, central corneal thickness (CCT) measurement, assessment of the optic discs, maculae and fundi. The schedule of examinations is given in Appendix 2. The patients also filled in the following questionnaires: EQ-5D 5 level (EQ-5D-5L),[12] Glaucoma Utility Index (GUI),[13] Glaucoma Symptom Scale (GSS),[14] Glaucoma Quality of Life – 15 (GQL-15; a visual function, rather than quality of life, measure)[14] and a modified version of the 'Client Service Receipt Inventory' (CSRI) questionnaire to collect health-related cost data.[15]

Standardisation of disease stratification and individual patient treatment IOP targets using a web-based real-time decision support algorithm

The NICE recommended thresholds were used for defining disease (POAG or OHT) for entry into the study, as well as initiating treatment.[11] A real-time web-based clinical DSS, based on the analysis of HRT, VF and IOP measurements, avoids bias from unmasked clinicians. A disease category and stage were defined, using preset objective severity criteria

from the Canadian Target IOP Workshop[16] with additional central VF loss criteria according to Mills et al. 2006.[17] Severity stratification (mild, moderate or severe) then determined the follow-up intervals and an eye specific 'Treatment Target IOP'. Target IOP was objectively defined based on both percentage reduction from untreated IOP and an absolute value and then adjusted during the study according to presence or absence of disease progression (Figure 1). The lowest permitted Target was 8 mmHg for POAG and 18 mmHg for OHT[†]. Not all permutations of clinical behaviour could be captured within the DSS, thereforedeviation by the treating consultant from DSS advice was permitted; the reason was recorded for comparison between treatment arms, e.g. if poor concordance contributed to a failure to meet Target IOP rather than drug effectiveness.

Randomisation and allocation of participants to treatment groups

Randomisation was undertaken online using a web-based randomisation service, achieving full allocation concealment (www.sealedenvelope.co.uk). 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 and treatment centre. Patients with one or both eyes eligible were treated identically.

Trial arm 1 – Laser-1st pathway

Standardisation of SLT delivery was achieved by protocol-defined settings and clinical endpoint of fine bubble formation at the trabecular meshwork at least 50% of the time (Appendix 3). One SLT re-treatment was allowed, provided there was an initial response to the treatment. After two SLT treatments the next escalation was medical treatment. Significant complications of laser treatment (e.g. severe uveitis, IOP spike greater than 15 mmHg) or other new medical conditions prevented repetition of SLT.

Trial arm 2 – Medicine-1st pathway

Patients on the Medicine-1st pathway or patients that remained uncontrolled on Laser-1st pathway were started on single drugs at initiation and with each treatment switch or escalation. Drug classes for 1st, 2nd, or 3rd line treatment were defined as per NICE[11] and European Glaucoma Society (EGS) guidance[18] (1st line: prostaglandin analogues, 2nd line: beta blockers, 3rd or 4th line: topical carbonic anhydrase inhibitors or alpha-agonists). Fixed combination drops were allowed. Systemic carbonic anhydrase inhibitors were only permitted as a temporary measure while awaiting surgery and did not influence treatment escalation. Maximum medical therapy (MMT) is defined as the most intensive combination of drops an individual can reasonably, reliably and safely use and varied between patients. MMT is defined as a maximum of 3 drugs and 5 dosages per day for triggering the offer of surgery, although MMT may be less for certain patients; more agents could be used for patients who decline trabeculectomy. Criteria for failure to meet and to reassess Target IOP are shown in Appendix 4.

Treatment escalation

To minimise bias for escalating treatment, standardised criteria were used according to a protocol following international guidelines by the EGS, American Academy of Ophthalmology Preferred Practice Pattern and the South-East Asia Glaucoma Interest Group. Treatment was escalated under the following circumstances:

1. 'Strong Evidence' of progression irrespective of IOP

[†] 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 is, therefore, not used in the algorithm for setting Target IOP. Myopia and family history are also not included in this algorithm, as data on the effect size of these risk factors on progression rates are weak.

2. IOP above Target by more than 4mmHg at a single visit
3. IOP above Target by less than 4mmHg and 'Less Strong Evidence' for progression. If the IOP is above Target by less 4mmHg with no evidence for progression, then the 'Treatment Target IOP' is re-evaluated

The process for escalating treatment is shown in Figure 2.

Defining disease progression by HRT and Visual Field

A minimum of 2 reliable baseline VF measurements (based on reliability indices and clinician judgement) and 3 follow-up VF were required. 'Likely VF Progression' is determined as ≥3 locations on the HFA GPA were at <0.05 probability for deterioration on 3 consecutive occasions. 'Possible VF Progression' was determined as ≥3 locations were at <0.05 probability for deterioration on 2 consecutive occasions. Any treatment escalation triggered by worsening visual field loss required senior clinician verification.

Progression of optic disc damage was defined as a statistically significant rate of neuro-retinal rim loss exceeding 1% of baseline rim area/year on a minimum of 5 repeat HRT images.

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).

Follow-up procedure and timing

Follow-up intervals were initially set at entry to the study according to NICE guidance[11] and subsequently adjusted on the basis of IOP control, glaucoma progression or adverse reactions. The routine schedule of appointments and assessments for patients are shown in Appendices 2 and 5, respectively.

Adverse events

Adverse events were reported according to standard operating procedures to achieve standardisation across sites and between treatment allocation, with an annual safety report to the Research and Ethics Committee.

Outcome measures

The primary outcome measure is Health Related Quality of Life (HRQL) using EQ-5D-5L utility scores at 3 years, calculated using the EQ-5D-5L descriptive system and value set for England (Office of Health Economics).[19] Quality-Adjusted Life Years (QALYs) will also be calculated over the 36 month period, using the baseline and 6-monthly follow up questionnaires and calculating the area under the curve.

The secondary outcomes are:

- Treatment pathway health care resource use, cost and cost-effectiveness. Health care resource use will be ascertained from the record of treatment episodes and additional healthcare contacts from a modified CSRI.[15] The cost components will include the cost of SLT, number of visits, number and type of medications and glaucoma surgeries and clinical tests
- Glaucoma specific treatment-related quality of life will be measured using the GUI
- Patient reported disease and treatment related symptoms using the GSS
- Patient reported visual function using the GQL-15
- Objective measurements of pathway effectiveness for IOP lowering and visual function preservation (e.g. treatment intensity and time taken to achieve Target IOP,

the number of Target IOP revisions, proportion of patients achieving Target after each year of treatment, number of patients with confirmed disease deterioration and rates of ocular surgery)
- Objective safety measures for each pathway
- Concordance, was assessed by two questions shown to predict the probability of non-concordance [20]

Sample size calculation

A difference in EQ-5D-5L utility scores of 0.05 has been considered to be clinically meaningful in an MRC-funded trial of glaucoma surgery[21], less than the difference between mild (0.84±0.17) and moderate (0.68±0.26) visual field loss.[22] A study with 305 participants in each group would have 90% power to detect, at 5% significance level, a difference in means of 0.05, assuming that a common standard deviation of 0.19 and using a two-sided-test. Allowing for 15% loss to follow-up at 36 months, the total number required for the study is 718 (359 in each group). The sample size was calculated using Stata 12 (StataCorp LP, Texas, USA).

Statistical analysis plan

The statistical analysis has been published elsewhere.[23] The analysis will be based on all participants as randomised, irrespective of subsequent concordance with allocated treatment. The primary outcome will be compared between treatment arms using regression methods that adjust for baseline EQ-5D-5L score, IOP and disease laterality. Statistical significance will be at 5%. Mixed models will be used to investigate how primary and secondary outcomes change over time.

Discussion

LiGHT is a multi-centre RCT, unmasked to treatment allocation, designed to compare HRQL, clinical- and cost-effectiveness and clinical safety of SLT versus topical IOP lowering medication in treatment-naïve patients with newly diagnosed POAG or OHT. This study addresses well one of the James Lind Alliance glaucoma research priorities.[24]

In the LiGHT Trial concern about possible confounding effects of placebo treatment and altered compliance from sham laser require patients to be aware of their treatment allocation. Patients' knowledge of prior medical treatment and/or initial treatment with laser may influence subsequent medication-taking behaviour and compliance. Although the patients and clinicians are unmasked to the treatment arm, all clinical measures (IOP, VF, HRT) are made by masked observers. Moreover, treatment decisions are masked by the use of a computerised evidence-based DSS. The potential for bias arising from lack of masking patients to treatment allocation will be investigated by comparison of EQ5D and GUI in patients who use eye-drops after laser alone with those patients who never received laser and with the prior period when laser alone was sufficient.

Very few controlled trials have compared medical to laser treatment in patients with POAG or OHT. The LiGHT Trial compares the two treatment pathways in previously untreated patients, unlike previously conducted trials.[25, 26] The non-randomised trial by Katz et al is the only trial to have set a personalised IOP target.[26] The Target IOP for LiGHT is eye specific, objectively defined and adjusted by the DSS, to avoid bias from unmasked clinicians.

The LiGHT Trial will provide valuable data on the HRQL, clinical and cost effectiveness of SLT and topical IOP lowering medication, with the potential to define the choice of 1st line treatment.

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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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Figure Legends

Figure 1 Process for target IOP setting. *Disease stratification according to Mills et al. 2006 [31]. IOP: Intra-ocular pressure, OHT: Ocular Hypertension, POAG: Primary Open Angle Glaucoma, GON: Glaucoma Optic Neuropathy, VF: Visual Field

Figure 2 Process for escalating treatment in POAG. *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