HEALTH TECHNOLOGY ASSESSMENT

VOLUME 23 ISSUE 31 JUNE 2019
ISSN 1366-5278

Selective laser trabeculoplasty versus drops for newly diagnosed ocular hypertension and glaucoma: the LiGHT RCT

Gus Gazzard, Evgenia Konstantakopoulou, David Garway-Heath, Anurag Garg, Victoria Vickerstaff, Rachael Hunter, Gareth Ambler, Catey Bunce, Richard Wormald, Neil Nathwani, Keith Barton, Gary Rubin, Stephen Morris and Marta Buszewicz on behalf of the LiGHT Trial Study Group

National Institute for Health Research

DOI 10.3310/hta23310

Selective laser trabeculoplasty versus drops for newly diagnosed ocular hypertension and glaucoma: the LiGHT RCT

Gus Gazzard,[1,2]* Evgenia Konstantakopoulou,[1,2] David Garway-Heath,[1,2] Anurag Garg,[1,2] Victoria Vickerstaff,[3,4] Rachael Hunter,[4] Gareth Ambler,[5] Catey Bunce,[1,6] Richard Wormald,[1,2,7] Neil Nathwani,[1] Keith Barton,[1,2] Gary Rubin,[2] Stephen Morris[8] and Marta Buszewicz[4] on behalf of the LiGHT Trial Study Group

[1]National Institute for Health Research Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust, London, UK
[2]Institute of Ophthalmology, University College London, London, UK
[3]Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, UK
[4]Research Department of Primary Care and Population Health, University College London, London, UK
[5]Department of Statistical Science, University College London, London, UK
[6]School of Population Health and Environmental Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK
[7]London School of Hygiene & Tropical Medicine, London, UK
[8]Department of Applied Health Research, Institute of Epidemiology and Health Care, University College London, London, UK

*Corresponding author

Declared competing interests of authors: Gus Gazzard, David Garway-Heath, Rachael Hunter, Gareth Ambler, Catey Bunce, Richard Wormald, Keith Barton, Gary Rubin and Marta Buszewicz have received a grant from the National Institute for Health Research (NIHR) for the submitted work. Gus Gazzard reports grants from Lumenis (Borehamwood, UK) during the conduct of the study; grants from Ellex Medical Lasers (Adelaide, SA, Australia), Ivantis, Inc. (Irvine, CA, USA) and Thea Pharmaceuticals (Keele, UK) outside the submitted work; and personal fees from Allergan (Dublin, Ireland), Alcon (Fort Worth, TX, USA), Glaukos Corporation (San Clemente, CA, USA), Santen Pharmaceutical Co., Ltd (Osaka, Japan) and Thea Pharmaceuticals outside the submitted work. David Garway-Heath reports personal fees from Aerie Pharmaceuticals, Inc. (Durham, NC, USA), Alcon, Allergan, Bausch + Lomb (Rochester, NY, USA), Quark Pharmaceuticals, Inc. (Ness Ziona, Israel), Quethera Limited and Roche (Basel, Switzerland); grants from the Alcon Research Institute; and grants and personal fees from Pfizer (New York, NY, USA) and Santen Pharmaceutical Co., Ltd, outside the submitted work. In addition, David Garway-Heath was a member of the Health Technology Assessment (HTA) Clinical Trials Board from 2014 to 2017. Keith Barton received a grant from NIHR for the Treatment of Advanced Glaucoma Study during the conduct of the study. In addition, Keith Barton reports grants from Johnson & Johnson Vision (Santa Ana, CA, USA), New World

Medical (Rancho Cucamonga, CA, USA), Alcon, Merck & Co. (Kenilworth, NJ, USA), Allergan and Refocus Group (Dallas, TX, USA); that he has had other financial relationships with Alcon, Merck & Co., Allergan, Refocus, AqueSys Inc. (Taipei, Taiwan), Ivantis, Carl Zeiss Meditec AG (Jena, Germany), Kowa Europe GmbH (Düsseldorf, Germany), Santen Pharmaceutical Co., Ltd, Transcend Medical (Scottsboro, AL, USA), Glaukos (San Clemente, CA, USA), Amakem NV (Diepenbeek, Belgium), Thea Pharmaceuticals, Alimera Sciences (Alpharette, GA, USA), Pfizer, Advanced Ophthalmic Implants Pte Ltd (Singapore), Vision Futures (UK) Ltd (London, UK), London Claremont Clinic Ltd (London, UK) and Vision Medical Events Ltd (London, UK), outside the submitted work; and that he has a patent with Ophthalmic Implants (PTE) Ltd. Stephen Morris was a member of NIHR Health Services and Delivery Research (HSDR) Research Funding Board (2014–19), the NIHR HSDR Commissioned Board (2014–16), the NIHR HSDR Evidence Synthesis Sub Board (2016), the NIHR HTA Clinical Evaluation and Trials Board (2007–10), the NIHR HTA Commissioning Board (2009–13), the NIHR Public Health Research Funding Board (2011–17) and the NIHR Programme Grants for Applied Research expert subpanel (2017–present). Marta Buszewicz was a member of the HTA Mental Health Panel from January to May 2018. In September 2018 this panel was amalgamated into the HTA Prioritisation Committee C (mental health, women and children's health), of which Marta Buszewicz was also a member. Marta Buszewicz has also been a member of the NIHR Research for Patient Benefit, London, funding panel since May 2017.

Published June 2019
DOI: 10.3310/hta23310

This report should be referenced as follows:

Gazzard G, Konstantakopoulou E, Garway-Heath D, Garg A, Vickerstaff V, Hunter R, *et al*. Selective laser trabeculoplasty versus drops for newly diagnosed ocular hypertension and glaucoma: the LiGHT RCT. *Health Technol Assess* 2019;**23**(31).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.513

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 09/104/40. The contractual start date was in September 2012. The draft report began editorial review in September 2018 and was accepted for publication in December 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

Selective laser trabeculoplasty versus drops for newly diagnosed ocular hypertension and glaucoma: the LiGHT RCT

Gus Gazzard,[1,2]* Evgenia Konstantakopoulou,[1,2] David Garway-Heath,[1,2] Anurag Garg,[1,2] Victoria Vickerstaff,[3,4] Rachael Hunter,[4] Gareth Ambler,[5] Catey Bunce,[1,6] Richard Wormald,[1,2,7] Neil Nathwani,[1] Keith Barton,[1,2] Gary Rubin,[2] Stephen Morris[8] and Marta Buszewicz[4] on behalf of the LiGHT Trial Study Group

[1]National Institute for Health Research Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust, London, UK
[2]Institute of Ophthalmology, University College London, London, UK
[3]Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, UK
[4]Research Department of Primary Care and Population Health, University College London, London, UK
[5]Department of Statistical Science, University College London, London, UK
[6]School of Population Health and Environmental Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK
[7]London School of Hygiene & Tropical Medicine, London, UK
[8]Department of Applied Health Research, Institute of Epidemiology and Health Care, University College London, London, UK

*Corresponding author g.gazzard@nhs.net

Background: Newly diagnosed open-angle glaucoma (OAG) and ocular hypertension (OHT) are habitually treated with intraocular pressure (IOP)-lowering eyedrops. Selective laser trabeculoplasty (SLT) is a safe alternative to drops and is rarely used as first-line treatment.

Objectives: To compare health-related quality of life (HRQoL) in newly diagnosed, treatment-naive patients with OAG or OHT, treated with two treatment pathways: topical IOP-lowering medication from the outset (Medicine-1st) or primary SLT followed by topical medications as required (Laser-1st). We also compared the clinical effectiveness and cost-effectiveness of the two pathways.

Design: A 36-month pragmatic, unmasked, multicentre randomised controlled trial.

Settings: Six collaborating specialist glaucoma clinics across the UK.

Participants: Newly diagnosed patients with OAG or OHT in one or both eyes who were aged ≥ 18 years and able to provide informed consent and read and understand English. Patients needed to qualify for treatment, be able to perform a reliable visual field (VF) test and have visual acuity of at least 6 out of 36 in the study eye. Patients with VF loss mean deviation worse than –12 dB in the better eye or –15 dB in the worse eye were excluded. Patients were also excluded if they had congenital, early childhood or secondary glaucoma or ocular comorbidities; if they had any previous ocular surgery except phacoemulsification,

at least 1 year prior to recruitment or any active treatment for ophthalmic conditions; if they were pregnant; or if they were unable to use topical medical therapy or had contraindications to SLT.

Interventions: SLT according to a predefined protocol compared with IOP-lowering eyedrops, as per national guidelines.

Main outcome measures: The primary outcome was HRQoL at 3 years [as measured using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) questionnaire]. Secondary outcomes were cost and cost-effectiveness, disease-specific HRQoL, clinical effectiveness and safety.

Results: Of the 718 patients enrolled, 356 were randomised to Laser-1st (initial SLT followed by routine medical treatment) and 362 to Medicine-1st (routine medical treatment only). A total of 652 (91%) patients returned the primary outcome questionnaire at 36 months. The EQ-5D-5L score was not significantly different between the two arms [adjusted mean difference (Laser-1st – Medicine-1st) 0.01, 95% confidence interval (CI) –0.01 to 0.03; $p = 0.23$] at 36 months. Over 36 months, the proportion of visits at which IOP was within the target range was higher in the Laser-1st arm (93.0%, 95% CI 91.9% to 94.0%) than in the Medicine-1st arm (91.3%, 95% CI 89.9% to 92.5%), with IOP-lowering glaucoma surgery required in 0 and 11 patients, respectively. There was a 97% probability of Laser-1st being more cost-effective than Medicine-1st for the NHS, at a willingness to pay for a quality-adjusted life-year of £20,000, with a reduction in ophthalmology costs of £458 per patient (95% of bootstrap iterations between –£585 and –£345).

Limitation: An unmasked design, although a limitation, was essential to capture any treatment effects on patients' perception. The EQ-5D-5L questionnaire is a generic tool used in multiple settings and may not have been the most sensitive tool to investigate HRQoL.

Conclusions: Compared with medication, SLT provided a stable, drop-free IOP control to 74.2% of patients for at least 3 years, with a reduced need for surgery, lower cost and comparable HRQoL. Based on the evidence, SLT seems to be the most cost-effective first-line treatment option for OAG and OHT, also providing better clinical outcomes.

Future work: Longitudinal research into the clinical efficacy of SLT as a first-line treatment will specify the long-term differences of disease progression, treatment intensity and ocular surgery rates between the two pathways.

Trial registration: Current Controlled Trials ISRCTN32038223.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 23, No. 31. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

List of abbreviations

AE	adverse event
CCT	central corneal thickness
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CRF	case report form
CRO	central research optometrist
CSRI	Client Service Receipt Inventory
CTM	central trial manager
CTO	central trial optometrist
DMC	Data Management Committee
DSS	decision support software
EMGT I	Early Manifest Glaucoma Trial
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GCP	good clinical practice
GON	glaucomatous optic neuropathy
GPA	glaucoma progression analysis
GQL-15	Glaucoma Quality of Life-15
GSS	Glaucoma Symptom Scale
GUI	Glaucoma Utility Index
HRQoL	health-related quality of life
HRT	Heidelberg retinal tomography
ICER	incremental cost-effectiveness ratio
IOP	intraocular pressure
IQR	interquartile range
IT	information technology
ITT	intention to treat
LAG	lay advisory group
Laser-1st	initial selective laser trabeculoplasty followed by routine medical treatment
LiGHT	Laser in Glaucoma and Ocular Hypertension
logMAR	log of the minimum angle of resolution
MD	mean deviation
Medicine-1st	routine medical treatment only
MEH	Moorfields Eye Hospital
MMT	maximum medical treatment
NICE	National Institute For Health and Care Excellence
NIHR	National Institute for Health Research
OAG	open-angle glaucoma
OHT	ocular hypertension
PI	principal investigator
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Resource Unit
QALY	quality-adjusted life-year
QoL	quality of life
SAE	serious adverse event
SD	standard deviation
SE	standard error
SLT	selective laser trabeculoplasty
SOP	standard operating procedure
TSC	Trial Steering Committee
VA	visual acuity
VF	visual field

Plain English summary

Glaucoma is an eye condition in which the optic nerve becomes damaged and, if left untreated, will lead to loss of vision. Ocular hypertension (OHT) is the medical name for high pressure in the eye that increases the risk of getting glaucoma. Lowering the eye pressure is the only known way to prevent glaucoma from getting worse. Before this trial, the standard initial treatment of these conditions was the prescription of eyedrops to lower the pressure in the eye. An alternative is a laser therapy that is known to reduce the eye pressure. This study investigated if starting treatment of glaucoma or OHT with laser therapy (using eyedrops later, if needed) affected the patients' quality of life (QoL) more or less than starting treatment with eyedrops alone. The study also investigated if initial treatment with laser and initial treatment with eyedrops are equally good at controlling eye pressure and are equally safe and how much they cost the NHS. Patients were randomly assigned to starting treatment with either laser or eyedrops and the two groups were then compared.

The study found that for the first 3 years QoL was similar regardless of treatment. However, three-quarters of patients initially treated with laser did not need any eyedrops to control their eye pressure for 3 years. Patients initially treated with laser were less likely to require cataract surgery, and none needed any glaucoma surgery in the first 3 years. In contrast, among those patients treated with eyedrops, glaucoma surgery was required in 11 eyes (out of 622 eyes). Initial treatment with laser was cheaper than initial treatment with eyedrops.

The results of this study suggest that laser is an efficient, safe and cheaper alternative to eyedrops, and that three-quarters of the patients initially treated with laser do not need any eyedrops for the first 3 years of treatment.

Scientific summary

Background

Glaucoma is a group of conditions characterised by the progressive damage of the optic nerve head and loss of visual field (VF). It is a leading cause of visual morbidity in the UK, causing falls, road traffic accidents, loss of independence in the elderly and a reduction in quality of life (QoL). Ocular hypertension (OHT), a state of raised intraocular pressure (IOP) in otherwise healthy eyes, is a risk factor for developing glaucoma and often requires treatment. The only known treatment for glaucoma and OHT is lowering the IOP; this has traditionally been done with IOP-lowering eyedrops when patients are treated for the first time.

Glaucoma monitoring and treatment take up a major proportion of hospital eye service outpatient appointments, with > 1 million glaucoma-related hospital eye service visits annually. Glaucoma treatment incurs significant costs to both the NHS and the patients; in 2012 alone, > 8 million glaucoma treatment-related items were dispensed in the community, costing > £105M. In addition, annual increases in the items prescribed and their cost have been reported for more than a decade.

The traditional first-line treatment for glaucoma and OHT, IOP-lowering eyedrops, has numerous side effects both topical and systemic. These range from mild to severe, take up a significant proportion of outpatient visits and may affect the success of further glaucoma surgery. Glaucoma and its treatment have been shown to have a significant negative impact on patients' QoL as a result of impairments in visual function, as well as the side effects of treatment.

An alternative to reducing IOP is selective laser trabeculoplasty (SLT), a quick and painless outpatient procedure. Until now this has principally been used not as a first-line treatment but as a last resort before intraocular surgery. However, this is because earlier forms of laser trabeculoplasty had a relatively low safety margin and repeatability; SLT is better than earlier types of laser trabeculoplasty in both respects.

Selective laser trabeculoplasty has the potential of providing IOP control for glaucoma and OHT patients without the need for topical medical treatment (eyedrops) and this has implications for both NHS expenditure and the patients' QoL. Additionally, the use of SLT from the outset of patients' treatment may offer clinical benefits in the later management of the disease.

Objective

To investigate if lowering IOP with SLT as a first-line treatment for patients with newly diagnosed OHT or open-angle glaucoma (OAG) (Laser-1st) leads to a better health-related quality of life (HRQoL) than first-line treatment with IOP-lowering eyedrops (Medicine-1st), and whether or not this is associated with reduced costs, better clinical outcomes and improved tolerability of treatment.

Objectives

Primary objective

To determine if, in a pragmatic study that mirrors the realities of clinical decision-making, a Laser-1st (initial SLT followed by routine medical treatment) pathway delivers a better HRQoL at 3 years than a Medicine-1st (routine medical treatment only) pathway, in the management of patients with OAG or OHT.

Secondary objectives

To determine whether or not a Laser-1st treatment pathway:

- costs less than the conventional treatment pathway of Medicine-1st
- achieves the desired level of IOP with less intensive treatment over the course of the study
- leads to equivalent levels of visual function after 3 years
- is better tolerated by patients.

Methods

We designed a pragmatic randomised control trial, with participants unmasked to treatment allocation, across six UK NHS sites, to compare initial SLT followed by routine medical treatment (Laser-1st) with routine medical treatment only (Medicine-1st).

Patients were adults, newly diagnosed with OAG or OHT, with no other ocular pathology and were randomised in a 1 : 1 ratio to receive either SLT (Laser-1st) or medical therapy (Medicine-1st). Patients were monitored for 3 years and received care in accordance with standard clinical practice.

Eyes were stratified into predefined categories of disease severity and were treated to achieve an eye-specific target IOP generated by a decision support software (DSS), based on published research and internationally recognised guidelines. SLT was performed in accordance with a strict protocol to standardise energy levels and the number of shots. Medical treatment was conducted and escalated in accordance with guidelines from the National Institute for Health and Care Excellence. Patient care, as well as monitoring intervals and treatment escalations, was guided by the DSS. All DSS suggestions could be overruled by the treating specialist consultant ophthalmologist if this was deemed to be to the patients' benefit. In such cases the consultant was required to record a detailed explanation for the decision. All measurements influencing treatment escalation decisions (VF, Heidelberg retinal tomography and IOP) were made by masked observers.

Patients were sent a series of questionnaires investigating HRQoL, health-care resource use and concordance at 6-month intervals [EuroQol-5 Dimensions, five-level version (EQ-5D-5L), Glaucoma Utility Index (GUI), Glaucoma Symptom Scale (GSS), Glaucoma Quality of Life-15 (GQL-15), a modified Client Service Receipt Inventory and two questions regarding concordance].

Statistical analysis

The primary outcome was analysed using linear regression with terms for randomisation arm, baseline EQ-5D-5L, stratification factors (diagnosis and centre), baseline IOP and number of eyes affected at baseline. The unit of analysis was the patient. If both of a patient's eyes were included, baseline severity and IOP were based on the worse eye, defined using VF mean deviation (MD) at baseline. EQ-5D-5L values missing at 36 months were imputed using values at 30 months, if available. Sensitivity analyses were performed to verify the results of the primary analysis. Mixed-effects models were used to analyse the EQ-5D-5L measurements recorded at all time points to investigate possible changes in treatment effect over the 36 months (using interaction terms between randomisation arm and time) and to estimate the average treatment effect over the 36-month follow-up period. The secondary outcomes were analysed using similar regression methods. All analyses were performed on an intention-to-treat basis with participants analysed according to the arm to which they were randomised.

Economic evaluation

Quality-adjusted life-years (QALYs) were calculated over the course of the trial using the baseline and 6-monthly follow-up EQ-5D-5L questionnaires and calculating the area under the curve. Health-care resource use cost was calculated using published sources. Eyedrops for OAG and OHT were costed based on prescribed medications using the *British National Formulary* [Joint Formulary Committee. *British National Formulary* (online). London: BMJ Group and Pharmaceutical Press. URL: www.medicinescomplete.com (accessed 15 July 2018)]. Cost-effectiveness acceptability curves were generated and the probability that the intervention is cost-effective was investigated for a range of values of willingness to pay.

Results

Between October 2012 and October 2014 a total of 16,379 patients were assessed for eligibility (15,483 were excluded as a result of ineligibility). Of the 896 patients who were eligible, 718 (1235 eyes) were recruited (80.1% participation rate), of whom 356 (613 eyes) were allocated to SLT (Laser-1st pathway) and 362 (622 eyes) to medical treatment (Medicine-1st pathway).

The average age of the patients was 63.1 years (± 11.8 years) and more male patients than females were recruited (55.3% males vs. 44.7% females). In total, 70% of all participants were white (black was the second largest ethnic group; 20%). Thirty per cent of the patients reported a family history of glaucoma affecting at least one first-degree relative.

A total of 301 patients (41.9%) had bilateral OAG, 161 patients (22.4%) had unilateral OAG (fellow eye healthy), 93 patients (13.0%) had OAG in one eye and OHT in the other eye, 124 patients (17.3%) had bilateral OHT and 39 patients (5.4%) had unilateral OHT (fellow eye healthy). A total of 555 patients (77.2%) were classified as having OAG (if at least one eye had OAG) and 163 patients (22.7%) were classified as having OHT; in 517 patients (72.0%) both eyes were eligible for the trial.

At baseline, the average EQ-5D-5L score was similar in the two treatment arms (Medicine-1st 0.92 ± 0.13; Laser-1st 0.91 ± 0.13), as was the GUI score (Medicine-1st 0.89 ± 0.11; Laser-1st 0.89 ± 0.12) and the GQL-15 score (Medicine-1st 18.7 ± 5.6; Laser-1st 18.9 ± 6.6). The average baseline GSS score was slightly higher in the Medicine-1st arm than in the Laser-1st arm (Medicine-1st 83.3 ± 16.6; Laser-1st 81.4 ± 17.2).

Sixteen patients in the Laser-1st arm and nine patients in the Medicine-1st arm withdrew from the trial. A total of 652 patients returned the primary outcome at 36 months, yielding a 91% return rate. At 36 months the Laser-1st arm had an average EQ-5D-5L score of 0.90 [standard deviation (SD) 0.16], compared with 0.89 (SD 0.18) in the Medicine-1st arm [adjusted mean difference (Laser-1st – Medicine-1st) 0.01, 95% confidence interval (CI) –0.01 to 0.03; $p = 0.23$]. Taking into account the outcome data from all time points across 36 months, the two treatment arms had similar EQ-5D-5L scores at 36 months (adjusted mean difference 0.02, 95% CI –0.00 to 0.03).

The Laser-1st arm scored an average of 0.89 (SD 0.13) on the GUI, compared with 0.89 (SD 0.13) for the Medicine-1st arm (adjusted mean difference 0.007, 95% CI –0.010 to 0.025). The Laser-1st arm had a mean GSS score of 83.3 (SD 17.3) at 36 months, compared with 83.1 (SD 17.7) for the Medicine-1st arm (adjusted mean difference 1.595, 95% CI –0.797 to 3.988). The mean GQL-15 scores at 36 months were similar in the two arms (19.8 for Laser-1st and 19.8 Medicine-1st, adjusted mean difference –0.368, 95% CI –0.605 to 1.341).

At 36 months, 536 eyes (87.7%) of 314 patients in the Laser-1st arm and 536 eyes (86.2%) of 306 patients in the Medicine-1st arm were available for analysis of clinical outcomes. The two treatment arms had comparable end-point visual acuity [0.08 (SD 0.17) vs. 0.07 (SD 0.18) log of the minimum angle of resolution,

Medicine-1st and Laser-1st, respectively)], IOP [16.3 (SD 3.9) vs. 16.6 (SD 3.6) mmHg, Medicine-1st and Laser-1st, respectively] and VF MD [–3.2 dB for both arms (SD 3.8 dB Medicine-1st; SD 3.9 dB Laser-1st)].

Overall, 95% of the eyes treated with Laser-1st ($n = 509$) were at target IOP at 36 months, which was achieved without medication for 78.2% of the eyes ($n = 419$), corresponding to 74.2% ($n = 233$, 95% CI 69.3% to 78.6%) of the patients. Of the eyes that received Medicine-1st, 93.1% ($n = 499$) were at target IOP at 36 months; 64.6% ($n = 346$) were using a single medication. During the 36 months of the trial, target IOP was achieved at 93% of visits in the Laser-1st arm, compared with 91.3% of visits in the Medicine-1st arm. The number of treatment escalations was higher in the Medicine-1st arm than in in the Laser-1st arm (348 vs. 299), as was the number of eyes showing disease deterioration (36 vs. 23); 11 eyes in the Medicine-1st arm (1.8%) required IOP-lowering surgery (trabeculectomy), compared with none in the Laser-1st arm. Twenty-five cataract extractions were carried out in the Medicine-1st arm and 13 in the Laser-1st arm.

There were no sight-threatening complications of SLT. The IOP rose > 5 mmHg compared with baseline IOP in six eyes of six patients who received SLT, but only one eye required treatment. Patients in the Medicine-1st arm reported more ophthalmic eyedrop-related adverse events (AEs) (150 aesthetic side effects and ocular allergic reactions were reported by 73 patients) than those in the Laser-1st arm (30 equivalent events were reported by 20 patients). Transient AEs were reported by 34.4% ($n = 122$) of the patients in the Laser-1st arm as a result of the SLT application. AEs during the SLT procedure were reported for 14 patients. Systemic AEs were similar in the two treatment arms. Eyedrop-related systemic AEs were reported more often and by more patients in the Medicine-1st arm than in the Laser-1st arm [148 events reported by 52 patients (14.4%) vs. 87 events reported by 23 patients (6.5%)]. Serious AEs were overall similar in both arms: 95 in the Medicine-1st arm, affecting 68 patients, and 107 in the Laser-1st arm, affecting 64 patients.

Laser-1st dominated Medicine-1st in that it resulted in a greater QALY gain at a lower cost (although the difference was not significant; $p = 0.286$). Laser-1st treatment cost £458 less than Medicine-1st, with 95% of bootstrap iterations falling between –£585 and –£345 (for specialist eye-related costs), and had a mean incremental QALY gain of 0.011, with 95% bootstrap iterations falling between –0.024 and 0.050. Over 36 months, discounted and adjusted, at willingness to pay for a QALY of £20,000 and £30,000, the probability that Laser-1st is more cost-effective than Medicine-1st when only ophthalmology costs are included is 97% and 93%, respectively. When community- and non-eye-related costs are added, there is a 68% chance that Laser-1st is more cost-effective, at willingness-to-pay levels of both £20,000 and £30,000.

Conclusions

This study shows that patients newly diagnosed with glaucoma or OHT can be safely treated with SLT and achieve predominantly eyedrop-free IOP control over at least 3 years, with less intense treatment, fewer AEs and a reduced need for glaucoma and cataract surgery, than patients treated with IOP-lowering eyedrops. This can be achieved at a lower cost per QALY than standard medical therapy alone and with a similar effect on generic HRQoL as assessed by the EQ-5D-5L. Primary SLT is a cost-effective alternative to eyedrops that can be offered to patients with OAG or OHT who need IOP-lowering treatment.

Implications for health care

The findings of this trial have the potential to change glaucoma and OHT treatment worldwide. An eyedrop-free IOP control may be a desired form of treatment for many patients and clinicians, while also providing a cost-effective alternative to eyedrops. The results of this study may also have important implications for resource-poor health-care settings where access to medication is a major barrier to glaucoma treatment and/or where glaucoma prevalence is high.

Despite the promising results with regard to the safety of the SLT procedure and the eyedrop-free IOP control that SLT offers, clinicians need to consider the perceived necessity of monitoring visits by the patient (patients may not always comprehend the necessity of frequent monitoring) in the absence of daily medication. Patients need to understand the importance of attending follow-up visits and the lifelong need for monitoring. SLT should not be perceived as a one-off glaucoma or OHT treatment and this needs to be communicated clearly to patients.

Recommendations for research

- Longitudinal research into the clinical efficacy of SLT as a first-line treatment, with particular focus on disease progression and ocular surgery rates.
- Longitudinal research into the effect of SLT on subsequent medicine-taking behaviour.
- Longitudinal HRQoL in OAG and OHT in particular (where data are lacking) to understand the impact of medical treatment on patients over a longer period of time, when more intense medical treatment might become necessary.

Longer follow-up already under way (the Laser in Glaucoma And Ocular Hypertension extension trial) will help us answer the majority of the above questions.

Trial registration

The trial is registered as ISRCTN32038223.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Background

Primary open-angle glaucoma and ocular hypertension

Primary open-angle glaucoma (OAG) is a common, irreversible optic neuropathy affecting the vision of predominantly older adults. It is strongly associated with elevated intraocular pressure (IOP), but may also occur with IOP in the normal range. Glaucoma results in progressive visual field (VF) loss and is a leading cause of blindness worldwide. In the UK, glaucoma affects over half a million individuals, with over one-quarter of a million aged > 65 years.[1] It is a leading cause of visual morbidity, accounting for 12% of blind registrations.[2] Glaucoma is a significant cause of falls, road traffic accidents[3] and loss of independence in the elderly (even in the case of mild asymptomatic disease),[3,4] and can significantly reduce the quality of life (QoL) of these patients.[5–8]

Ocular hypertension (OHT) is a state of raised IOP without optic nerve damage, which can progress to OAG in some patients.[9,10] Those with a higher IOP, lower central corneal thickness (CCT) and a family history of OAG are more at risk of developing glaucoma.[11] IOP is the only modifiable risk factor for the development of OAG, the reduction of which is proven to slow down the progression of OAG or the conversion of OHT to OAG.[10,12–14] National Institute for Health and Care Excellence (NICE) guidelines recommend that patients with OHT at high risk of developing OAG should be offered treatment.[15]

Current first-line treatment options

Medical therapy (eyedrops) is widely used and is currently the most commonly used first-line treatment for mild to moderate disease,[16] leading to approximately 1.2 million prescriptions per month in the UK.[17] Medical treatment is usually lifelong; patients may need to instil multiple eyedrops, which can become expensive, while also experiencing side effects that limit the acceptability of the treatment and impair their QoL.[18–21]

Although the effectiveness of IOP-lowering eyedrops is irrefutable, they come with a number of aesthetic, sight- and potentially life-threatening side effects: pain on instillation, conjunctival hyperaemia, elongation and darkening of eyelashes, iris colour changes, periocular skin pigmentation, allergic reactions, accelerated cataract formation, cystoid macular oedema, anterior uveitis and reactivation of herpes simplex keratitis,[19,20] in addition to serious respiratory (e.g. airway obstruction) and cardiovascular side effects in some, falls and increased mortality.[22,23] These adverse effects influence the acceptability of eyedrops to patients, as well as patients' concordance with medical treatment plans and their QoL. Indeed, reported non-compliance rates for medical treatment range from 24% to 80%, depending on definition.[24–26] Approximately 22% of initial treatment regimens need adjustment[27] and up to 50% of patients discontinue their medication within 6 months of the initial consultation.[24] Although patients with diagnosed glaucoma are more likely than those with suspected glaucoma to adhere to therapy,[24] side effects are likely to have a direct adverse effect on patients diagnosed with OHT, in whom proper IOP control can reduce the incidence of OAG.[28] Medical management of OAG and OHT requires regular monitoring and modification of therapy by ophthalmologists, as well as multiple hospital visits for patients.[29]

Long-term use of topical IOP-lowering medication induces significant subclinical conjunctival inflammation and conjunctival fibroblast activation by medications or preservatives,[30–32] and has been shown to have a negative impact on the success rates of subsequent surgical intervention[33] (long-term eyedrop use is a known powerful risk factor for later surgical failure).[31,34]

Laser trabeculoplasty (an alternative treatment method) has been inconsistently performed in the UK; NICE has identified a lack of evidence governing its use.[17] The procedure involves a single, painless outpatient application of laser to the trabecular meshwork using a contact lens. It is easy to deliver by clinicians competent in gonioscopy and has a wide safety margin. Selective laser trabeculoplasty (SLT) uses bursts of nanosecond pulses with a larger spot (400 microns) and lowers IOP by increasing the aqueous humour outflow through the trabecular meshwork by causing increased macrophage activity and trabecular tissue remodelling.[35,36]

The IOP-lowering effect of SLT is comparable with that of prostaglandin analogues,[37,38] the current first-line medical treatment recommended by NICE. SLT can delay and, in some cases, prevent the need for eyedrops.[38] The effects are not permanent; however, SLT does not prejudice the effectiveness of later medical or surgical treatments. Because minimal trabecular meshwork damage is caused, SLT has also been shown to have good efficacy on repeat treatment.[39–41]

The use of SLT for lowering IOP has been inconsistent and has in the past often been reserved as a last resort before surgery, possibly because of concerns arising from older forms of laser trabeculoplasty. Use of SLT as a first-line treatment has the potential to offer patients an eyedrop-free window of several years, remove the concerns about concordance with medication and reduce both hospital visits and side effects compared with medical therapy.

Glaucoma filtration surgery is usually reserved for those who continue to lose vision despite other treatments. It has a significant failure rate and may cause permanent ocular discomfort and, rarely, chronic pain.[42,43] A study comparing medical management (eyedrops) with surgery (trabeculectomy) as a first-line treatment for advanced OAG is currently under way.[44]

Economic burden of treatment to the NHS

The treatment of OAG and OHT can incur significant costs to both the patient and the NHS. Direct treatment costs in the UK were estimated at an equivalent of US$1337 per patient per year in 1999;[45] up to 61% of these costs were for IOP-lowering medication.[46] In 2012, > 8 million glaucoma treatment-related items were dispensed in the community alone, costing > £105M, with increases in the number of items dispensed and their cost reported annually.[47] Both direct costs and indirect costs are higher for more severe disease,[48] suggesting that effective IOP control early in the course of the disease is likely to reduce later costs, as well as improve vision-dependent health-related quality of life (HRQoL).

Extensive economic modelling of SLT has taken place in various health-care systems worldwide. In the USA, the 5-year cumulative costs per patient were lower for SLT than for eyedrops and surgery, whereas an Australian study found that every AU$1 spent on laser treatment resulted in a saving of AU$2.50 compared with initial medical therapy, with projections of increasing cost savings over time.[49,50] The time threshold at which bilateral SLT would become less costly than bilateral use of topical medication has also been modelled.[51] It was found that SLT became less costly than most brand-name medications within 1 year and less costly than generic latanoprost and generic timolol eyedrops after 13 and 40 months, respectively. This is supported by a projected 6-year cost comparison of primary SLT with primary medical therapy in OAG treatment in a Canadian health-care model;[46] if primary SLT had to be repeated between 2 and 3 years, use of primary SLT over mono-, bi-, and tri-drug therapy produced a 6-year cumulative cost saving of CA$580.52, CA$2042.54 and CA$3366.65 per patient, respectively. Similar findings have also been published for the management of both mild and moderate glaucoma.[52]

Although the limited existing data are very difficult to apply to the UK population, the above data would suggest annual savings to the NHS of £2.4M in direct treatment costs for new OAG patients alone from a Laser-1st (initial SLT followed by routine medical treatment) paradigm. This rises to £16.8M per year if a conservative 20% of new OHT/OAG referrals require treatment. Australian data give far higher predictions: were SLT to be extended to previously diagnosed patients, as is common practice in the USA, cost savings would be up to 20 times higher. Indirect cost savings (e.g. reduced visual loss) are, of course, greater still.

Use of selective laser trabeculoplasty as a first-line treatment for open-angle glaucoma/ocular hypertension

Initial treatment with SLT potentially offers an 'eyedrop-free window' of several years, removes concerns about concordance and possibly reduces the need for multiple eyedrops, even years later. Even when insufficient as a sole therapy, SLT may reduce the intensity of subsequent medical treatment and possibly the need for later surgery. A single outpatient treatment is likely to be more acceptable to patients than daily self-administration of eyedrops, securing 100% concordance from those attending for treatment and resulting in fewer hospital visits and fewer side effects than eyedrop therapy alone.

Although SLT is an existing technology, proven to lower IOP, neither HRQoL nor cost-effectiveness has been compared with outcomes in patients who received eyedrops as a first-line treatment. A Laser-1st pathway allows an eyedrop-free period and, possibly, lower intensity of treatment. This is likely to be associated with greater HRQoL, improved patient acceptability and better treatment compliance, with fewer patient visits resulting from treatment changes and fewer adverse events (AEs), at a much lower cost than treatment with eyedrops.[46,50,53]

Uptake of SLT by surgeons in the UK has so far been limited because of past experiences with older laser technology. SLT is delivered in an outpatient setting using topical anaesthesia and is quick and pain free. It is simple and safe to deliver and has a wide safety margin and good repeatability. Widespread uptake of SLT has the potential to substantially improve HRQoL for many patients and produce substantial cost savings to the NHS (lower medication costs, reduced side effects, fewer hospital visits, lower surgery rates and indirect savings from care costs for fewer visually impaired patients).

Rationale for research

Research recommendations by NICE[17] and a Cochrane systematic review[54] have identified the need for robust randomised controlled trials investigating the efficacy and cost-effectiveness of SLT as a first-line treatment for OAG and OHT.

Aims and objectives

Hypothesis

Our hypothesis is that, in patients with newly diagnosed OHT or OAG, primary treatment with SLT (Laser-1st) leads to a better HRQoL than primary treatment with IOP-lowering eyedrops (Medicine-1st), and that this is associated with reduced costs, better clinical outcomes and an improved tolerability of treatment.

Primary objective

To determine if, in a pragmatic study that mirrors the realities of clinical decision-making, a Laser-1st pathway delivers a better HRQoL at 3 years than a Medicine-1st (routine medical treatment only) pathway, in the management of patients with OAG and OHT.

Secondary objectives

To determine whether or not a Laser-1st treatment pathway:

- costs less than the conventional treatment pathway of Medicine-1st
- achieves the desired level of IOP with less intensive treatment over the course of the study
- leads to equivalent levels of visual function after 3 years
- is better tolerated by patients.

Chapter 2 Methods

Trial design

The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial was designed to evaluate the difference in HRQoL, cost and clinical efficacy between two first-line treatment arms for OAG and OHT. The LiGHT trial is a multicentre, randomised clinical trial, unmasked to treatment allocation, with two treatment arms: initial SLT followed by routine medical treatment (Laser-1st) and routine medical treatment only (Medicine-1st).[55,56]

Eligible patients were randomised in a 1 : 1 ratio to receive either SLT (Laser-1st) or medical therapy (Medicine-1st) as the first-line treatment for OAG or OHT. All measurements influencing treatment escalation decisions [VF, Heidelberg retinal tomography (HRT) and IOP] were made by masked observers. Patients were monitored for 3 years and monitoring intervals were guided by a defined protocol to avoid bias in clinical decision-making. A clinical decision algorithm, attempting to capture the complexities of clinical practice, defined triggers for escalation. This was a pragmatic trial aiming to mirror the 'real-world' patient experience of treatment as closely as possible and seeking to capture the full effects of laser treatment.

Ethics approval and research governance

The study adhered to the tenets of the Declaration of Helsinki. Ethics approval was granted by the City Road and Hampstead Research and Ethics Committee (former Moorfields and Whittington Research Ethics Committee then East London and The City Research Ethics Committee 1, reference 12/LO/0940) on 20 June 2012. The LiGHT trial is registered as ISRCTN32038223 [the full protocol can be accessed at URL: www.moorfields.nhs.uk/sites/default/files/LiGHT%20Trial%20Protocol%203.0%20-%2020-5-2015_3.pdf (accessed 3 May 2019)].

Patient population

The LiGHT trial aimed to recruit patients with newly diagnosed OAG or OHT in one or both eyes from six collaborating specialist glaucoma clinics at large ophthalmic centres in the UK (see *Appendix 1*).

Inclusion criteria

Patients were required to have newly diagnosed OAG or OHT in one or both eyes, which needed treatment. Definitions of OAG and OHT, as well as criteria for initiating treatment, are shown in *Appendix 2*. The following criteria were also specified:[56]

- A decision to treat had been made by a glaucoma specialist consultant ophthalmologist.
- Patients were aged > 18 years and were able to provide informed consent.
- Patients were able to complete QoL, disease-specific symptom and cost questionnaires in English (physical help with completion and assistance with reading was permitted, as long as an interpreter was not required).
- It was possible to perform a VF test in the study eye(s) with < 15% false positives.

Exclusion criteria

Patients were not considered for the study if there was:[56]

- advanced glaucoma in the potentially eligible eye as determined by Early Manifest Glaucoma Trial (EMGT I)[59] criteria (77 VF loss mean deviation (MD) worse than –12 dB in the better eye or –15 dB in the worse eye)
- secondary glaucoma (e.g. pigment dispersion syndrome, rubeosis, trauma, etc.) or any angle closure
- any contraindication to SLT (e.g. unable to sit at the laser-mounted slit-lamp, past history of or active uveitis, neovascular glaucoma, inadequate visualisation of trabecular meshwork)
- an inability to use topical medical therapy because of, for example, physical infirmity and a lack of carers able to administer daily eyedrops
- a previous treatment for OAG or OHT
- congenital or early childhood glaucoma
- a visually significant cataract in symptomatic patients who want to undergo cataract surgery
- any current, active treatment for another ophthalmic condition in the hospital eye service (this applied to both eyes, even if one was not in the trial, as the fellow eye might affect the patient's visit frequency)
- any history of retinal ischaemia, macular oedema or diabetic retinopathy
- age-related macular degeneration with neovascularisation in either eye or geographic atrophy
- visual acuity (VA) worse than 6/36 in a study eye; non-progressive VA loss better than 6/36 owing to any comorbidity was permitted provided that it did not affect the response to treatment or later surgical choices and that it was not under active follow-up (e.g. an old, isolated retinal scar no longer under review or amblyopia)
- any previous intraocular surgery, except uncomplicated phacoemulsification, at least 1 year before recruitment (this applied to both eyes, even if one was not in the trial, as it could affect the required treatment intensity and visit frequency for any glaucoma in the fellow eye)
- pregnancy at the time of recruitment or intention to become pregnant within the duration of the trial
- 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)
- recent involvement in another interventional research study (within 3 months) of any topic.

Recruitment

Internal pilot study

We conducted a 9-month internal pilot at Moorfields Eye Hospital (MEH) (the central trial site and largest recruiting site). This ensured that recruitment rates were adequate and that all procedures were in place, before roll-out to other sites. Data collected included number of eligible patients approached, proportion entering the trial and recruitment rates.

Recruitment strategy and identification of participants

Patients attending the hospital eye service 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 co-ordinator (along with written information). To maximise potential coverage of all eligible patients, a trial staff member was available daily to attend clinics and counsel potential subjects. Local trial staff screened all new referrals (by referral letter or electronic patient record) and identified those possibly eligible, with reminders for the clinic staff. Regular education of clinical staff and clinic-wide information posters for staff and patients raised awareness of the study and reminded clinicians of the opportunity for recruitment.[56]

Recruitment process and informed consent

Eligible patients were approached and introduced to the aims, methods, anticipated benefits and potential hazards of the study, and were eventually invited to participate by a member of the LiGHT team. Introducing the patients to the study and inviting them to participate was done either by face-to-face discussions with the trial team members or by the use of audiovisual material (video); the video conveyed the same information as the face-to-face discussions with the trial team members, but was delivered by the chief investigator (video content/script is shown in *Appendix 3*). The use of the video in the recruitment process maximised the time efficiency of the recruiters, as often more than one patient had to be approached simultaneously.

After the invitation to participate, ample time was given to the patients to consider participation. Written informed consent was obtained on a separate day, usually the day of the baseline assessment (see *Baseline assessment*), by either the good clinical practice (GCP)-trained local trial ophthalmologist or the local trial optometrist who had been delegated this duty by the chief investigator/principal investigator (PI) on the delegation log. Consent was obtained with the support of extensive clearly written information (in English) that had been reviewed and approved by our patient-led lay advisory group (LAG). Patients who had difficulty in giving informed consent did not form part of this study. A copy of the signed informed consent was given to the participant and the original signed form was retained at the study site.

If new safety information resulted in significant changes in the risk/benefit assessment, the consent form was reviewed and updated if necessary. All patients, including those already being treated, were given any new information, a copy of the revised form and reconsented to continue in the study.

Baseline assessment

At the baseline assessment, and after informed consent was provided, participants underwent VA testing, slit-lamp examination, automated VF testing [Humphrey Field Analyser Mark II (Carl Zeiss Meditec, Dublin, CA, USA) and the Swedish Interactive Threshold Algorithm standard 24-2 programme], HRT optic disc imaging, IOP measurement, gonioscopy, CCT measurement and assessment of the optic discs, maculae and fundi. The patients also completed the following baseline questionnaires: EuroQol-5 Dimensions, five-level version (EQ-5D-5L),[60] Glaucoma Utility Index (GUI),[61] Glaucoma Symptom Scale (GSS),[62] Glaucoma Quality of Life-15 (GQL-15; a visual function, rather than quality-of-life measure)[8] and a modified version of the Client Service Receipt Inventory (CSRI) questionnaire.[63]

Randomisation and masking

Following the 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 undertaken online on the same day by the clinical staff who obtained informed consent, using a web-based randomisation service (Sealed Envelope, London, UK) and 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. Following randomisation, the details of the treatment and specific arrangements and instructions were communicated to the patients by a member of the trial team. Owing to the pragmatic design of this trial, the patients and clinicians were unmasked to the treatment arm; however, all clinical measurements (IOP, VF, HRT) were carried out by masked observers and treatment decisions were masked by the use of a computerised evidence-based decision support algorithm.[56]

Treatment arm allocation

Laser-1st pathway

Selective laser trabeculoplasty was delivered to 360° of the trabecular meshwork with one 360° retreatment used as the first escalation of treatment, if required. To ensure quality control of SLT delivery and to minimise variation between surgeons, standardisation was achieved by a stringent protocol defining laser settings and technique, including the range of acceptable powers (see *Appendix 4*). All treating clinicians were given training before recruitment and had at least one laser treatment directly observed by the chief investigator. After two SLT treatments, if further treatment escalation was required, the Laser-1st pathway patients embarked on medical treatment and followed the Medicine-1st algorithms. Significant complications of laser treatment, if they occurred (e.g. corneal oedema, intraocular haemorrhage, severe uveitis, IOP spike > 15 mmHg, peripheral anterior synechiae), meant that a second treatment with SLT was contraindicated. Other new medical conditions (such as a new history of uveitis or rubeosis) also precluded repeat SLT.[56]

Medicine-1st pathway

Medical treatment of glaucoma involves several distinct steps that require standardisation: choice of drugs, number of agents permitted and rules for switching between or adding drugs. 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).[64–66] Surgery was offered once maximum treatment intensity was reached; this varied between patients, but required definition to minimise inter-surgeon variation (see *Maximum medical treatment*).

Choice of agent

No mainstream medications were prohibited, but medication classes for first-, second- or third-line treatment were defined as per NICE[1] and European Glaucoma Society guidance:[67]

- first line: prostaglandin analogue
- second line: beta-blocker (once in the morning or in a prostaglandin analogue combination)
- third or fourth line: topical carbonic anhydrase inhibitor or alpha-adrenoceptor agonist.

Systemic carbonic anhydrase inhibitors were permitted only as a temporising measure while awaiting surgery and did not influence treatment escalation. Cholinergic agonists were not accepted as topical medications for OAG.

Treatment changes

Treatment was escalated under the following circumstances:

- Strong evidence of progression (see *Defining progression*) irrespective of IOP.
- IOP above the target IOP (see *Adding/switching medication*) by > 4 mmHg[68] at a single visit (irrespective of evidence for progression).
- IOP above target by < 4 mmHg plus less strong evidence for progression (see *Defining progression*). If the IOP was above target by less than the threshold with no evidence for progression, then the target IOP was re-evaluated.

Adding/switching medication

The incremental escalation of the treatment protocol defined stepwise increases in treatment. Patients' medications were switched if the pre- and post-treatment IOP difference was no greater than the measurement error. If there was a greater reduction but the eye was still not at target, then the next medication was added. The progression of glaucomatous optic neuropathy (GON) when at target IOP, also triggered a stepwise increase in treatment and a lowering of the target.[56]

Maximum medical treatment

Maximum medical treatment (MMT) is the most intensive combination of eyedrops a given individual can reasonably, reliably and safely use. The MMT varies between patients depending on their comorbidities, side effects and patient-specific concordance factors. Although there is variation in the attitudes of surgeons to polypharmacy, it is widely accepted that additional medications result in a lower percentage reduction in IOP. Evidence shows there are profound reductions in compliance with complex dosage schedules. NICE guidance[15] recommends offering surgery after only two drugs have failed to control IOP. In the LiGHT trial, treatment with multiple different medications was limited and MMT was defined in terms of the maximum number of drugs (three) and dosages per day (five drops). The MMT was often less owing to drug intolerance, contraindications and patient factors.[56]

Disease stratification and initiation of treatment

The NICE-recommended thresholds were used for defining disease (OAG or OHT) for entry into the study, as well as in initiating treatment (see *Appendix 2*).[15] The patients' clinical evaluation and test outcomes were then 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,[69] with central-field loss severity criteria defined according to Mills *et al.*[70] (*Table 1*). Severity stratification determined the follow-up frequency.

Computerised decision algorithm

The follow-up and treatment escalation protocols were enabled by custom-written clinical decision support software (DSS), which permitted real-time decision-making based on the analysis of multiple clinical measures, including HRT optic disc analysis, VF assessment and IOP measurements. Predefined objective indicators of either disc or field deterioration [change in mean neuroretinal rim area, as determined by HRT, or VF glaucoma progression analysis (GPA)], or IOP above target all triggered earlier follow-up and/or increased treatment intensity.

Setting individual target intraocular pressure

Once the decision to treat was made, a treatment target IOP (target) was set. The target 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.

TABLE 1 Severity criteria for setting a treatment target IOP from the Canadian target IOP workshop[69] (with central field criteria defined according to Mills *et al.*[70])

	Definition for treatment target IOP				
Severity	Optic nerve		VF MD		Central (10°) scotoma on VF
OHT	Healthy		Any		No GON-related VF loss
Mild OAG	GON	+	> –6 dB	+	None
Moderate OAG	GON	+	< –6 dB and > –12 dB	or	At least one central 5° point < 15 dB but none < 0 dB and only one hemifield with a central point < 15 dB
Severe OAG	GON	+	< –12 dB	or	Any central 5° point with sensitivity < 0 dB. Both hemifields contain point(s) < 15 dB within 5° of fixation

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 a target IOP.[56] 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.[71] 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 illustrated in *Figure 1*. Greater reductions were required for greater disease severity as defined by Canadian glaucoma study criteria.[73]

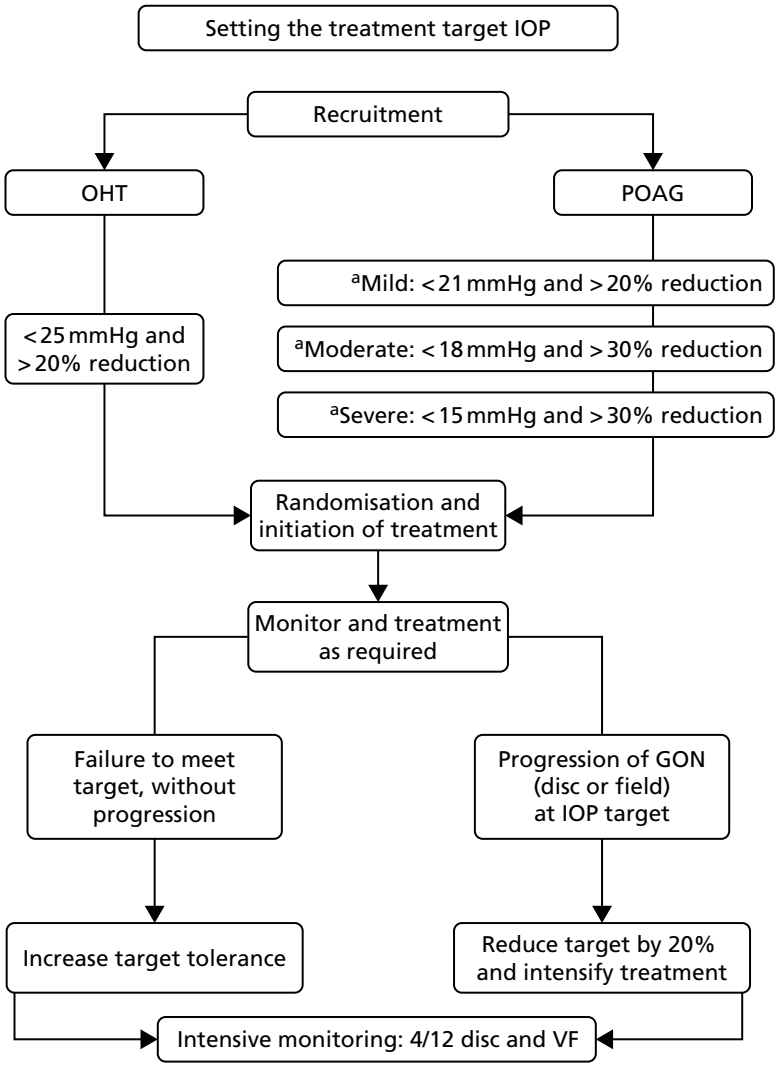

FIGURE 1 Process for target IOP setting. a, Disease stratification according to Mills *et al.*[70] POAG, primary open-angle glaucoma. Adapted by permission from BMJ Publishing Group Limited. The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. A multicentre randomised controlled trial: baseline patient characteristics, Konstantakopoulou E, Gazzard G, Vickerstaff V, Jiang Y, Nathwani N, Hunter R, Ambler G, Bunce C, volume 102, pp. 599–603, 2018.[72]

Failure to meet target intraocular pressure and target intraocular pressure re-evaluation

Diurnal fluctuation and measurement error both lead to variation in measured IOP. Kotecha *et al.*[68] have shown that inter-visit variation may nonetheless be as much as ± 4 mmHg.[68] To prevent an inappropriate escalation to a more intensive treatment, it is therefore important to repeat measurements that deviate only slightly from target. Criteria for failure to meet, and to reassess, target IOP follow those of the Canadian glaucoma study,[74] taking into account that inter-visit variation in IOP measurement may be as much as ± 4 mmHg:

- If IOP in an eye was ≥ 2 mmHg but < 4 mmHg above target on two consecutive visits and showed possible or definite progression, then the treatment was intensified and the target remained unchanged.
- If IOP in an eye was ≥ 2 mmHg and < 4 mmHg above target on two consecutive visits and showed no progression (with a minimum of three post-baseline follow-up VF tests required to confirm progression, as per EMGT I),[59] then the target was adjusted upwards. In this case the target IOP was revised to the mean of the previous three visits, during which progression did not occur. If VF testing had been carried out at fewer than three follow-up visits, additional visits were required to confirm stability before the target was relaxed.
- If IOP in an eye was ≥ 4 mmHg from target at any visit, then the eye was considered to have failed to reach target and treatment intensity was increased to the next level (unless already at the maximum), irrespective of any progression, unless the clinician identified poor concordance with treatment. In such cases the target remained unchanged. In the presence of poor concordance and in the absence of progression, additional measures to improve concordance before escalation of treatment were permitted, as in usual clinical practice.
- If the IOP of an eye on MMT was ≥ 2 mmHg from target and showed definite progression, then glaucoma drainage surgery was offered to the patient.
- If the IOP of an eye on MMT was ≥ 2 mmHg from target and showed possible progression, then the follow-up frequency was increased until progression was either confirmed or ruled out.
- If the IOP of an eye on MMT was ≥ 2 mmHg from target but below maximum IOP (maximum IOP is that above which surgery may be offered even without progression: OHT, 35 mmHg; mild glaucoma, 24 mmHg; moderate and severe glaucoma, 21 mmHg), and showed no progression (with at least three follow-up VFs), then the target was adjusted (revised to the mean of the previous three visits) with an increase in follow-up frequency. If VF testing had been carried out at fewer than three follow-up visits, additional visits were required to confirm stability.
- A patient with an eye with IOP above the maximum IOP may have been offered surgery without progression at the discretion of the treating surgeon.
- If there was progression and the IOP was at target, then the target IOP was reduced by 20% (according to the Canadian glaucoma study protocol),[74] with a lower limit of 8 mmHg, and treatment intensified accordingly.

Failure to meet target can be a result of poor concordance as well as a lack of drug efficacy. As is normal practice, compliance was discussed and patients were counselled at each visit, using validated 'ask–tell–ask' techniques.[75–77] Patients were given standard written information from the International Glaucoma Association, face-to-face instruction in eyedrop administration and the offer of further nurse-led support.

Where poor concordance was thought to be the contributing factor, education with written information and repeated face-to-face instruction in eyedrop administration was given. If the decision was made to educate rather than escalate a patient who was not at target, then the reason for an algorithm over-ride was recorded (non-concordance) and the patient recalled after 8 weeks for a repeat IOP check visit.[56]

Treatment escalation

To minimise bias for escalating treatment, standardised criteria for any additional intervention were used, in accordance a protocol following international guidelines by the European Glaucoma Society,[64] American Academy of Ophthalmology Preferred Practice Pattern[65] and the South East Asia Glaucoma Interest Group.[66] Treatment is escalated under the following circumstances:[56]

- Strong evidence of progression irrespective of IOP (see *Defining progression*).
- IOP above target by > 4 mmHg at a single visit (irrespective of evidence of progression).
- IOP above target by < 4 mmHg and less strong evidence of progression (see *Defining progression*). If the IOP is above target by < 4 mmHg with no evidence of progression, then the treatment target IOP is re-evaluated (see *Failure to meet target intraocular pressure and target intraocular pressure re-evaluation*).

The process for escalating treatment is shown in *Figures 2* and *3*.

More stringent criteria than those used for laser or medical treatment were applied before being referred for surgery. This reflected the greater risk to a patient's vision from surgical complications. Strong evidence of progression and/or failure to meet target was usually required in all but the most severe disease. However, extreme elevations of IOP could be an indication for surgery without progression, with lower thresholds in more damaged eyes. Any patient in whom IOP was at or above the maximum was reviewed (in person or remotely) by the PI, who decided whether or not surgery was indicated. In accordance with the principle of 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.

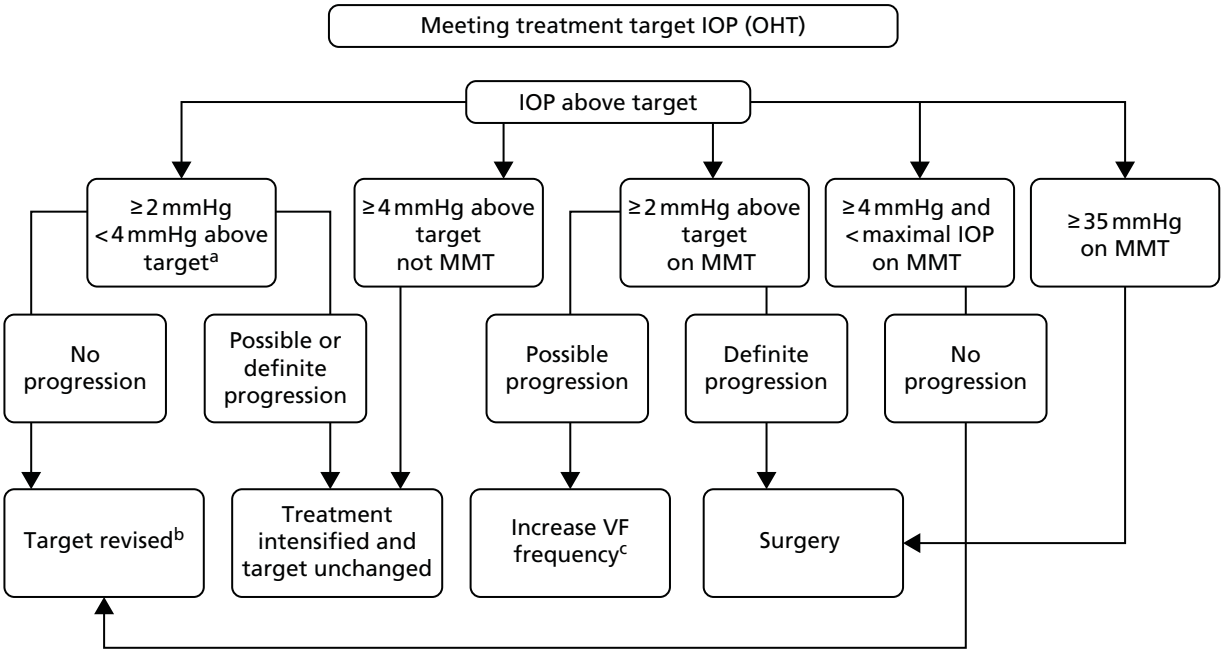

FIGURE 2 Process for escalating treatment in OHT. a, On two consecutive visits; b, as per protocol; and c, until progression confirmed/refuted. VF progression required three follow-up VF assessments. Maximal IOP, IOP above which surgery was offered even without progression or 35 mmHg for OHT. Adapted by permission from BMJ Publishing Group Limited. The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. A multicentre randomised controlled trial: baseline patient characteristics, Konstantakopoulou E, Gazzard G, Vickerstaff V, Jiang Y, Nathwani N, Hunter R, Ambler G, Bunce C, volume 102, pp. 599–603, 2018.[72]

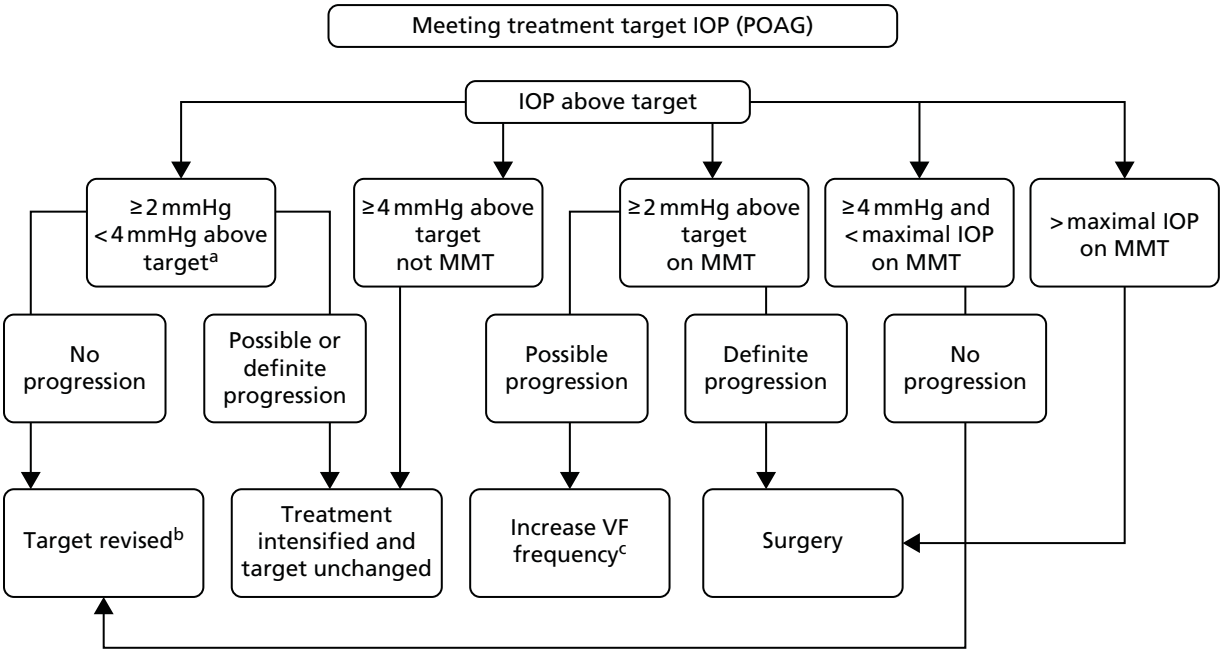

FIGURE 3 Process for escalating treatment in OAG. a, On two consecutive visits; b, as per protocol; and c, until progression confirmed/refuted. VF progression required three follow-up VF assessments. Maximal IOP, IOP above which surgery was offered even without progression or 35 mmHg for OHT. Adapted by permission from BMJ Publishing Group Limited. The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. A multicentre randomised controlled trial: baseline patient characteristics, Konstantakopoulou E, Gazzard G, Vickerstaff V, Jiang Y, Nathwani N, Hunter R, Ambler G, Bunce C, volume 102, pp. 599–603, 2018.[72]

Defining progression

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 data set' to determine VF progression was two reliable baseline VF measurements followed by three follow-up VF tests. 'Likely VF progression' was defined as ≥ 3 points on the Humphrey Visual Field (HVF) GPA software (Carl Zeiss Meditec, Dublin, CA, USA) at $p < 0.05$ for change on three consecutive occasions. 'Possible VF progression' was ≥ 3 points on Humphrey Visual Field GPA software at $p < 0.05$ for change on two consecutive occasions. VF series were independently assessed for progression using the automated algorithm software at each visit. Any treatment escalation triggered by worsening VF loss had to be agreed by a senior clinician after excluding retinal or neurological causes.[56]

Optic disc progression

Chauhan *et al.*[78] showed that sequential HRT three-disc assessment performed as well as, or better than, 'experts' judging monoscopic photos. Simultaneous stereoscopic disc photography has been considered a gold standard, but it is rarely available. Worsening of disc damage was defined as a rate of neuroretinal rim loss exceeding 1% of baseline rim area per year on a minimum of five repeat HRT images. This slope value was selected as approximately double that of age-related rim area loss and gave a similar specificity to VF trend analyses.[79]

Open-angle glaucoma progression

Progression of glaucoma is 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 ($p < 0.01$).

Algorithm over-ride

In the following cases the algorithm was over-ridden by the treating consultant if:

- 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 after for an IOP check.
- It was felt that it was in the patient's best interest to over-ride the algorithm's decision to either revise the target IOP (upwards or downwards) or to escalate treatment.

The reason for the over-ride was recorded.

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,[15] 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 the target IOP, without progression or treatment change, and who had no adverse reactions requiring earlier assessment, is shown in *Table 2*. Additional VF tests were permissible at any visit if clinically necessary to confirm possible progression. Variation in follow-up intervals was permitted to accommodate the clinician's judgement and/or patient choice.[56]

Participants in the Laser-1st arm were reviewed 2 and 8 weeks after SLT application. After the 8-week review in the Laser-1st group and for all treatment changes in the Medicine-1st arm, patients were reviewed at 2 months, following which their treatment was changed (with consequent early assessment of response to second treatment) or they entered a disease severity-tailored routine follow-up schedule. Follow-up of patients with severe OAG was at the discretion of the consultant ophthalmologist. If an eye showed 'possible progression', then the follow-up frequency was increased to every 3–4 months until progression was confirmed or ruled out with additional VF testing or HRT. No further tests were conducted at additional visits for IOP check alone. All contacts with medical professionals and optometrists were captured for cost data. Information on contact with health-care providers was collected via the CSRI, a validated method of collecting health-care cost data.[63]

Follow-up intervals were planned within the ranges specified by NICE guidance[15] and were independently determined on the basis of IOP control or adverse reactions, to minimise bias. The main driver for follow-up frequency was treatment in pursuit of control. Disease stability was considered using all available data, but testing for progression did not independently determine follow-up. Patients who required medication

TABLE 2 Routine follow-up frequency for patients who remain at target without progression or treatment change and have no adverse effects requiring earlier assessment

		Routine follow-up intervals in months						
Disease severity category	First visit	Second visit[a]	Third visit	Fourth visit	Fifth visit	Sixth visit	Seventh visit	Eighth visit
OHT	Randomisation and 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

a 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).

changes or additional laser treatment and patients who suffered AEs or showed progression of glaucoma were seen sooner and reverted to schedule when stable. The worse or more unstable of each patient's two eyes determined the follow-up interval, whereas treatment was individualised to the needs of each eye.

Follow-up clinical assessments

The schedule of assessments (all assessments were part of routine care) is shown in *Table 3*. After the full baseline assessment, all patients underwent VF testing and HRT to assess progression at each follow-up visit. The EuroQol-5 Dimensions (EQ-5D-5L) and other HRQoL questionnaires were assessed at baseline and 6-monthly thereafter, with additional questionnaires as outlined in *Questionnaires*.

Questionnaires

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

- EQ-5D-5L
- GUI
- GSS
- GQL-15.

TABLE 3 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

	Time of follow-up[a]							
Investigation	Baseline	First check[a]	Third visit (6 months)	First year	18 months	Second year	Patient specific[b]	Third year
Clinical examination (including disc and IOP)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dilated fundus examination	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes
Gonioscopy	Yes	–	–	–	–	–	–	Yes
VF test	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes
Optic nerve imaging (HRT)	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes
EQ-5D-5L	Yes	–	Yes	Yes	Yes	Yes	–	Yes
GUI	Yes	–	Yes	Yes	Yes	Yes	–	Yes
GSS	Yes	–	Yes	Yes	Yes	Yes	–	Yes
CSRI[c]	Yes	–	Yes	Yes	Yes	Yes	–	Yes

a First follow-up visit was at 2 weeks following SLT, followed by a visit at 2 months. First follow-up visit for the Medicine-1st pathway was at 2 months.
b Follow-up frequency may have varied depending on clinical findings at each visit.
c Modified CSRI questionnaire.

Notes
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 judgement and/or patient choice.
Reproduced from Gazzard *et al.*[58] © 2019 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license (http://creativecommons.org/licenses/by/4.0/).

Additionally, a modified CSRI was used and two questions regarding concordance. The content of the questionnaires used can be found as supplementary material [see URL: www.journalslibrary.nihr.ac.uk/programmes/hta/0910440/#/documentation (accessed 23 April 2019)]; a sample of each questionnaire completed is presented in *Appendix 5*. The patient and public involvement group reviewed the final questionnaire for layout and clarity to ensure ease of completion.

Questionnaire delivery and follow-up

The baseline questionnaires were self-completed by participants in a private room, at the time of enrolment, after informed consent had been given but before randomisation. Participants were required to have sufficient English knowledge that translation was not required [practical assistance with the layout (e.g. some questionnaires were printed double-sided, some questions had conditional formatting depending on the patients' response) and completion of the form were permitted].

Subsequent questionnaires were sent out by post for self-completion at 6-monthly intervals; up to two written reminders followed by one telephone follow-up were implemented in the case of non-response. In the event of a telephone follow-up, if the patient was willing, only the primary outcome measure was collected. Aiming to incentivise LiGHT participants to return the vital final questionnaire, a high street voucher worth £5.00 was sent by post along with the final set of questionnaires to each participant. The central site at MEH managed all questionnaires across all collaborating sites.

Follow-up has been extended beyond the primary study to look additionally at HRQoL outcomes at 6 years; questionnaires are will be posted to participants every 6 months for the duration of the extended period.

Adverse events and serious adverse events

An AE was defined as an unfavourable medical occurrence in a patient that was not necessarily caused by the treatment. GCP guidelines[67] were used to determine if AEs should be classified serious [serious adverse events (SAEs)]. AEs and SAEs were reported in accordance with standard operating procedures (SOPs) and GCP guidelines, to achieve standardisation across sites and between treatment arms, with an annual safety report to the Research and Ethics Committee.

Primary outcome measure

The primary outcome measure was HRQoL in patients with OAG or OHT treated with SLT first, compared with HRQoL in patients treated with topical medication first, measured using EQ-5D-5L utility scores at 3 years.

Secondary outcome measures

The secondary outcomes were as follows:[56]

- Treatment pathway health-care resource use, cost and cost-effectiveness. Health-care resource use was ascertained from the record of treatment episodes and additional health-care contacts using a modified CSRI.[63] The cost components included the cost of SLT, number of visits, number and type of medications and glaucoma surgeries, and clinical tests.
- Glaucoma-specific treatment-related QoL was measured using the GUI, from which quality-adjusted life-years (QALYs) can also be derived.
- 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 assessed by two questions shown to predict the probability of non-concordance.[80]

Reproduced with permission from The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. A multicentre randomised controlled trial: baseline patient characteristics, Konstantakopoulou E, Gazzard G, Vickerstaff V, Jiang Y, Nathwani N, Hunter R, Ambler G, Bunce C, volume 102, pp. 599–603, 2018 with permission from BMJ Publishing Group Ltd.[72]

Data collection and management

To standardise data collection and management, researchers were trained to follow specific SOPs for each stage of data handling. Identical electronic and hard-copy case report forms (CRFs) were designed according to a standard CRF template. A web-based database for the Priment Clinical Trials Unit, managed by the company 'SealedEnvelope', was used for database entry with direct data entry at the time of patient visit. This included extensive internal consistency and range checking, with a hard-copy backup CRF in case of information technology (IT) failure. Records were identifiable only by unique, confidential trial identification number with no patient-identifiable information included. All data were contemporaneously entered directly into the web-based database CRF.

Data from patient completed questionnaires received by post were scanned on receipt for e-copy back-up and entered onto the database within 1 week of receipt by the trial data management officer. Questionnaire data were from validated, standardised tools (EQ-5D-5L, GUI, GQL-15, GSS and CSRI) (see *Table 3*). The central site at MEH managed the inputting of data from all questionnaires across all collaborating sites.

Statistical analysis plan

The statistical analysis plan has been published previously.[81] All patients were analysed in the treatment arm to which they were randomised. All analyses were performed in Stata® version 14 (StataCorp LP, College Station, TX, USA).

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 EQ-5D-5L between the two arms at 36 months using a two-sample *t*-test at the 5% significance level, with 90% power, assuming a common standard deviation (SD) of 0.19[82] and a 15% loss to follow-up.[81]

Baseline

The baseline characteristics of each arm were summarised as means and SDs for continuous, symmetric variables, medians and interquartile ranges (IQRs) for continuous, skewed variables and frequencies and percentages for categorical variables. These summaries were based only on observed data. No significance testing was performed.

Primary outcome

The primary outcome measure was HRQoL measured using the EQ-5D-5L at 36 months. The EQ-5D-5L questionnaire 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-5L and whether one or two eyes were affected at baseline.

For the primary outcome, the unit of analysis was the patient. If both of a patient's eyes were included in the study, we used the worse eye at baseline for severity and baseline IOP covariates. The worse eye was defined using the MD at baseline, with the worse eye having the most negative MD.

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

Secondary outcomes

The secondary outcomes were analysed using regression methods appropriate for the type of outcome. These models were also adjusted using the covariates mentioned above. The results from all secondary analyses are presented as estimates with confidence intervals (CIs).

Exploratory analyses

We used mixed-effect models, using all patient outcome data over the 36 months, to investigate how the primary and secondary outcomes changed over time. Such models allow the analysis of repeated outcome measurements data (recorded every 6 months), as well as taking into account the correlation between measurements from the same patient. Standard regression models assume independence between observations, which typically means that separate models are required for each time point. The mixed-effect models allowed modelling all time points (baseline and 6, 12, 18, 24, 30 and 36 months) in a single model, by explicitly modelling both the within- and the between-patient variability.[83]

By using interaction terms between randomisation arm and time, we investigated differences between the groups over time.

We also used a similar mixed-effect model using all patient data over the 36 months, to evaluate the treatment effects at 36 months by using the exact times that the questionnaires were completed. Finally, using all the patient data over the 36 months, we used a mixed-effects model to explore the average treatment effect over the 36 months.

Analysis of missing data

Potential bias as a result of missing data was investigated by descriptively comparing the baseline characteristics of the trial participants with complete follow-up measurements with those who had incomplete follow-up or no outcome data.

Analysis of homogeneity

To explore the homogeneity (or otherwise) of the intervention effect on the primary outcome, we examined the treatment effect across the following: age (as a continuous measure); severity of glaucoma (using the two groups OHT/OAG used during randomisation process); baseline IOP (as a continuous measure); and sex. The results from these analyses should be treated as exploratory and hypothesis generating, as the trial was not powered for these analyses.

Sensitivity analyses

First, we ran sensitivity analyses that adjusted for variables associated with missingness. We performed logistic regression analyses (with missing 'yes' or 'no' as the outcome), to identify predictors of missing data. When predictors associated with both missing data and outcomes were found, we refitted the primary analysis model, adjusting for these predictors of missingness.

Second, to take into account any missing data, we used a multiple imputation approach. The imputation model included the outcome of interest, sociodemographic variables and any other variables potentially related to missingness and HRQoL. The imputations were performed separately by treatment arm.

Economic evaluation

The aim of the economic evaluation was to calculate the mean incremental cost per QALY of Laser-1st compared with Medicine-1st. Health and social care costs and QALYs were calculated for the within-trial period (36 months). The outputs were:

- mean total patient-level QALYs by trial arm
- mean cost per patient of laser treatment in the Laser-1st arm
- mean cost per patient of eyedrop treatment for glaucoma by trial arm
- mean cost per patient of surgery by trial arm
- mean total health-care cost per patient over 3 years by trial arm
- mean increment cost per QALY of Laser-1st compared with Medicine-1st and 95% CIs
- cost-effectiveness planes
- cost-effectiveness acceptability curves (CEACs).

Quality-adjusted life-years

Mean patient-level QALYs by trial arm were calculated as the area under the curve using patient-level responses to EQ-5D-5L at each follow-up time point[84] and the formula by Devlin *et al.*[85] Patients who died were imputed as zero from the date of death until the end of the trial. We assumed a straight line from the last follow-up time point until death. As the EQ-5D-5L is the primary outcome for the trial, mean patient responses at each follow-up time point are reported as part of the repeated-measures analysis. The mean incremental difference in QALYs was calculated using ordinary least squares regression and included covariates for randomisation arm, baseline EQ-5D-5L values, randomisation factors (severity and centre), baseline IOP and number of eyes affected at baseline.

Quality-adjusted life-years were discounted from 12 months to 3 years at an annual rate of 3.5%.[86] Ninety-five per cent CIs were calculated using bootstrapping, bias corrected and 5000 replications, given that we assume that the data are not normally distributed. Although there was a high rate of return for the EQ-5D-5L at 36 months (91%), data were missing for each time point, which meant that only 73% of patients had complete data across all time points for calculation of QALYs. Multiple imputation using chained equations was used to impute the data for 35 data sets, including age, highest education attainment, employment and diabetic status, included as variables identified as being predictive of missingness.

Cost of selective laser trabeculoplasty

The cost of SLT was calculated using bottom-up microcosting based on data collected from sites. Sites reported the cost of the machine maintenance costs, how sessions were run (dedicated sessions for SLT or as part of a routine session), the grade and number of staff for each session and the number of patients treated per session and per year. Staff wages and overheads were taken from the Personal Social Services Resource Unit (PSSRU).[87] The cost per patient of using the machine was based on an annuitised formula,[88] accounting for the number of patients seen in a 'typical' site per year and assuming a laser lifetime of 10 years. The number of SLTs per patient was reported.

Cost of drops for open-angle glaucoma and ocular hypertension

We report the mean cost of eyedrops by trial arm over 3 years. Information on eyedrops prescription, including drug name, dose, number of eyes, number of drops per eye and frequency, was collected as part of trial monitoring processes. Each prescription was costed using the *British National Formulary* (2018) to calculate the cost per bottle.[89] This was divided by the number of drops per bottle to calculate the cost per day. To calculate the number of days per medication, it was assumed that patients would take the medication from the day of prescription until the next medication change. The mean total cost per patient was then the cost per day of the prescribed eyedrops multiplied by the number of days the medication was prescribed for.

Total ophthalmology-related costs

In addition to eyedrops and laser, information was collected from the patient files on ocular surgery and planned and unplanned specialist ophthalmologist visits. These included a 2-week IOP check as part of the trial process; however, this check would not occur if the service was rolled out and hence this IOP check was removed from the primary analysis. Descriptive statistics for ophthalmology resource use are reported in *Chapter 3, Ocular-related costs*. Ocular surgery and ophthalmologist outpatient appointments were costed using the *NHS Reference Costs 2016–17*.[90] We report the mean cost per patient at 3 years for each type of ophthalmology cost, as well as total costs discounted at an annual rate of 3.5%[86] by trial arm. Ninety-five per cent bias-corrected CIs were calculated using bootstrapping and 5000 replications. Given that data were taken from patient files, it was not possible to identify missing data (it was assumed that if patients did not have an appointment or surgery reported, this was because none occurred). As a result, the intention to treat (ITT) was based on all the patients, assuming that the appointment data collected are correct.

Other health-care costs

Health-care resource use, including optician contacts, community health-care contacts and acute health-care contacts, was collected from a modified version of the CSRI[91] at baseline and at 6, 12, 18, 24, 30 and 36 months, asking about eye-related and non-eye-related resource use in the past 6 months. Information on inpatient stays and day cases was checked against SAE data. SAEs not reported in the CSRI were included in the total inpatient cost. Resource use was costed using unit costs from PSSRU[87] except for optometrist visits,[92] heart bypass surgery[90] and cancer deaths (*Table 4*).[93] Mean costs by trial arm at each time point were by ocular- and non-ocular-related costs over 3 years.

Total health and social care costs

The cost components included in the analysis were the cost of SLT, OAG medication and other health-care costs. We report the mean cost per patient in addition to an adjusted cost, adjusting for baseline service use using regression analysis. Mean costs were based on a complete-case analysis, with only optician and CSRI resource use excluding inpatient stays missing (an analysis imputing for missing CSRI data using chained equations has been included). The mean incremental difference in costs is calculated using ordinary least squares regression and includes covariates for randomisation arm, baseline EQ-5D-5L values, randomisation factors (severity and centre), baseline IOP and number of eyes affected at baseline. We used bias-corrected bootstrapping to calculate 95% CIs, given that we assumed that the data are not normally distributed. All costs are reported in 2016/17 Great British pounds.

Incremental cost-effectiveness ratio

The incremental cost-effectiveness ratio (ICER) was defined as the mean incremental cost of Laser-1st compared with Medicine-1st and divided by the mean incremental QALYs of laser treatment compared with eyedrops. The mean incremental differences were adjusted for baseline values, randomisation factors (severity and centre), baseline IOP and number of eyes affected at baseline. To account for the correlation between costs and QALYs, seemingly unrelated regression was used to calculate the numerator and denominator of the ICER. ICERs are reported for total costs, as defined in *Total health and social care costs*, and ophthalmology only costs, as defined in *Total ophthalmology-related costs*. Costs and QALYs from 12 months until 36 months are discounted at an annual rate of 3.5%.[86] The final results for total costs and QALYs are based on data imputed using chained equations for QALYs and CSRI, and using the missing at random methodology described in Leurent *et al.*[57] for calculating CEACs using bootstrapping and multiple imputation for 200 draws of each of the 35 imputed data sets for 7000 replications in total.

Cost-effectiveness acceptability curve

A CEAC is reported using the bootstrap imputed data (200 draws of each of the 35 imputed data sets for 7000 replications in total), for a range of values of willingness to pay for a QALY. We report the probability that Laser-1st is cost-effective compared with Medicine-1st at a willingness to pay for a QALY of £20,000 and £30,000 for (1) total costs and (2) ophthalmology only costs.

TABLE 4 Health-care unit costs used in the cost-effectiveness analysis

Resource use	Unit cost (£) (per contact)	Source
Trabeculectomy	1436	*NHS Reference Costs 2016–17*[90]
Ophthalmology appointments	91	*NHS Reference Costs 2016–17*[90]
Optometrist visit	52	Violato *et al.*[92]
Planned inpatient stay	3903	Curtis[87]
Unplanned inpatient stay: short duration[a]	628	Curtis[87]
Unplanned inpatient stay: long duration[b]	2953	Curtis[87]
A&E attendance: admitted	221	*NHS Reference Costs 2016–17*[90]
A&E attendance: not admitted	128	*NHS Reference Costs 2016–17*[90]
Outpatient attendance	137	Curtis[87]
GP contact: in practice	31	Curtis[87]
GP contact: telephone	24	Curtis[87]
GP contact: at home	80	Curtis[87]
GP practice nurse	36	Curtis[87]
Social care	59	Curtis[87]
Home care	26	Curtis[87]
Other community contacts	57	*NHS Reference Costs 2016–17*[90]
Cancer death	6129	Georghiou and Bardsley[93]

A&E, accident and emergency; GP, general practice.
a < 7 days.
b ≥ 7 days.
Note
All costs are reported in 2016/17 Great British pounds.

Secondary analyses

The following secondary analyses were conducted:

- For the primary analysis SLT was costed using microcosting. Some assumptions of the microcosting, for example the number of patients per site per year, or how sessions are run, may have an impact on the total cost. As a result, we planned to examine the impact of modifying the assumptions on the total cost of SLT per patient and hence the ICER. The cost of SLT as estimated from NHS reference costs[90] was used in the analysis.
- In the primary analysis we removed the cost of the 2-week IOP check, given that this was unlikely to occur in practice. One could hypothesise that patients obtained some minor benefit from this check and hence its costs could be included in the analysis. A secondary analysis including the 2-week IOP check has been included.
- QALYs were calculated using utility scores generated from the GUI[61] and the same methodology for calculating QALYs as above. The results were combined with the costs, as above, to report the mean incremental cost per QALY of Laser-1st compared with Medicine-1st, using the GUI.

Patient and public involvement: lay advisory group

Glaucoma patients and relatives from the Cochrane Eyes and Vision Group Consumer Panel formed our independent LAG. Consultation on trial design, choice of outcome measures, recruitment and treatment acceptability took place by e-mail and through online discussions via the Facebook social networking site (Facebook, Inc., Menlo Park, CA, USA; Group: 'Public Eye – LiGHT Trial Discussion Forum'). All of the suggestions made have been incorporated (e.g. requests to monitor all symptoms in detail, a safety concern about 'rapid loss of pressure control' after SLT and more explanation of the relationship between eyedrops and surgical failure). An 'expert patient' with treated glaucoma reviewed and commented on the study protocol as a service user member for the Trial Steering Committee (TSC) and another service user representative from the International Glaucoma Association was invited to join. The LAG contributed to the development of tailored information leaflets and consent forms with further consultation with service user groups and via the Friends of Moorfields charity. A survey of 100 new patients attending MEH to assess the acceptability of an invitation to participate in such a trial, before the commencement of the trial, had a 70% positive response.

Patients diagnosed and treated for glaucoma also provided input to a questionnaire sent in 2015 (see *Appendix 6*), allowing us to design an extension for the main LiGHT trial; the questionnaire looked into the views of these treated patients on current treatment options and their willingness to switch from eyedrops to laser.

As required by the NHS, in line with INVOLVE national guidelines and in accordance with UK Clinical Research Collaboration policy, the results are being communicated to patients, for example via NHS Choices and patient advocate groups (e.g. International Glaucoma Association), and the findings have been published in open access media.[58]

Study oversight and management

Study co-ordination in London

The Trial Management Team was composed of the chief investigator, central trial manager (CTM), central trial optometrist (CTO), central research optometrist (CRO), lead trial statistician and trial statistician, members of the University College London Priment Clinical Trials Unit, trial data officers, co-applicants and trial optometrists. The team met monthly on average to ensure the smooth running of the trial and troubleshooting. The duties of the CTM were to support the organisation of the study [investigator meetings, TSC and Data Management Committee (DMC) meetings, training, etc.] and have a study management role, including monitoring data collection according to established milestones, maintaining trial records, co-ordinating data management between local sites and the central clinical trial unit, facilitating user involvement in the project through LAG meetings and working alongside the CTO and facilitating the recruitment and follow-up of study participants.

Local organisation in centres

The chief investigator (consultant ophthalmologist) was the local PI at the central site (MEH), who co-ordinated the local ethics approval and sat on the TSC. The local study co-ordinator administrated the follow-up and recall of patients, liaising with the Trial Management Team. The local trial clinicians were an ophthalmologist, a fellow or an optometrist who were responsible for the recruitment, treatment and follow-up of trial participants. They had regular conference calls with the Trial Management Team for the duration of the study. The local trial clinicians were directly accountable to the local PIs. There were regular conference calls to all local clinicians and PIs to troubleshoot local issues. The chief investigator closely supervised the CTM, CTO and CRO with regular meetings.

Trial Steering Committee

The TSC was composed, in accordance with GCP, of an ophthalmologist as the independent TSC chairperson, a chief investigator, an independent clinician with relevant expertise, a sponsor representative, a Central and East London Comprehensive Local Research Network representative, an independent health economist, an independent statistician and two patient representatives. The trial manager, chief investigator, lead trial statistician and trial statistician were invited to report as required. The TSC met at least 6-monthly and minutes were taken.

Data and safety monitoring

Data and safety monitoring by the University College London Priment Clinical Trials Unit involved regular reports from the CTM, including recruitment and drop-out rates, adherence to SOPs, number failing to meet target or progressing, and AEs. The chief investigator maintained day-to-day responsibility for the trial with the CTM to ensure that the trial was conducted, recorded and reported in accordance with the protocol, GCP[94] guidelines and SOPs.

The DMC was composed of the following individuals in accordance with GCP guidelines: (1) a DMC chairperson, (2) an independent trial statistician and (3) two additional glaucoma or ophthalmic trials specialists. The DMC met annually (or more often if appropriate), timed to report to the TSC. During recruitment, interim reports were supplied to the DMC, together with any analyses it requested.

The above committees followed SOPs set by MEH and the University College London Priment Clinical Trials Unit, and complied with guidelines issued by the National Institute for Health Research (NIHR) Health and Technology Assessment panel for clinical trials.

Data monitoring

We completed double data entry for the EQ-5D-5L for all completed questionnaires for all time points. The second data entry was completed by a different individual to the person doing the first entry. The first data entry was then matched with the second data entry and any discrepancies were checked and resolved by referring back to the hard-copy questionnaire.

The trial research team performed checks on 100% of the clinical baseline and eligibility data. Monitoring activity across sites was carried out at scheduled intervals and was adapted to the demonstration of errors by the collaborating sites (see *Appendix 7*). Protocol deviations and violations were recorded throughout the study and appropriate action was taken to prevent similar events from taking place in the future.

Protocol amendments

A series of minor amendments have taken place after the commencement of the trial and were submitted to the funder, as well as gaining ethics approval. Below is a list of the major protocol amendments:

1. addition of audio-visual material to assist with recruitment of patients
2. collection of blood, tears and saliva samples
3. addition of the ocular response analyser (Reichert Ophthalmic Instruments, Inc., Buffalo, NY, USA) to the assessments
4. extension of the trial to 6 years
5. ocular surface disease questionnaire (extension only).

Chapter 3 Results

Recruitment

A total of 16,379 patients were assessed for eligibility; 15,483 were excluded as they did not meet the inclusion criteria. Of the 896 patients who were eligible across the six participating NHS centres, a total of 718 (1235 eyes) were recruited for the study (80.1% participation rate). A recruitment chart for the total recruitment period can be found in *Appendix 8*. A total of 178 eligible patients declined to participate. Of the patients who declined to participate, 43 did not want to have SLT, 17 did not want to take part in research, nine did not want to use eyedrops, three did not want to receive any treatment, one did not want to travel to the hospital and 105 did not provide an explanation.

Participant flow

A total of 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) (*Figure 4*). Two patients were randomised twice owing to failure, as a result of which the initial randomisation was not visible. Subsequently, a second randomisation was carried out; one of these patients had initially been randomised to medication (non-visible randomisation), but was subsequently randomised to, and received, SLT. The second patient was initially randomised to SLT (non-visible randomisation), but was later randomised to, and received, medication. Four patients who did not meet the eligibility criteria were randomised in error and were subsequently removed from the study (see *Appendix 9*).

Participant baseline characteristics

Reproduced with permission from The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. A multicentre randomised controlled trial: baseline patient characteristics, Konstantakopoulou E, Gazzard G, Vickerstaff V, Jiang Y, Nathwani N, Hunter R, Ambler G, Bunce C, volume 102, pp. 599–603, 2018 with permission from BMJ Publishing Group Ltd.[72]

Participant baseline characteristics are shown in *Table 5*. Of the 718 patients recruited, approximately 70% were based in London: 52% were recruited by MEH and almost 15% from Guy's and St Thomas' Hospital. The average age of the patients was 63.1 years (± 11.8 years), with more male patients recruited than female (55.3% male vs. 44.7% female). In total, 70% of all participants were white, and black was the second largest ethnic group (20%). Thirty per cent of patients reported a family history of glaucoma affecting at least one first-degree relative. Systemic hypertension (defined as the use of prescribed antihypertensive medication) was recorded in 35% of the patients. Use of systemic antihypertensive medication was recorded in these patients; of those, 5% were using beta-blockers, 16% were using calcium channel blockers and 14% were using angiotensin-converting enzyme inhibitors; 27% of all patients were on statins. In total, 11% of the patients were smokers at the time of recruitment. Approximately 30% of the LiGHT patients had a degree or equivalent qualification, 13% had achieved higher education, 12% had achieved Advanced Level or equivalent and 45% did not pursue an education beyond 16 years of age.

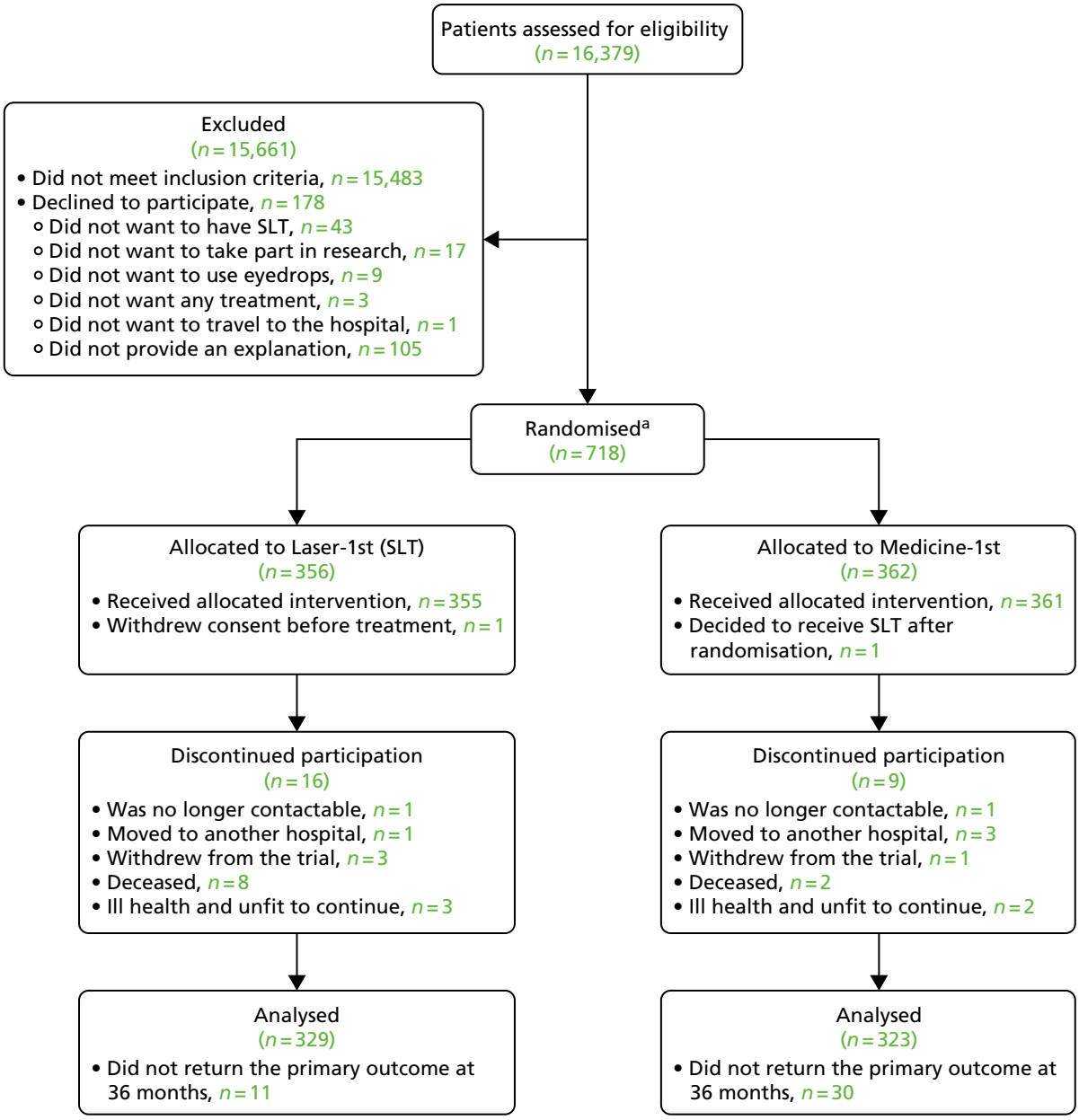

FIGURE 4 The LiGHT trial Consolidated Standards of Reporting Trials (CONSORT) flow diagram. a, Two patients were randomised twice owing to IT failure, as a result of which the initial randomisation was not visible, and subsequently a second randomisation was carried out. Reproduced from Gazzard *et al.*[58] © 2019 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license (http://creativecommons.org/licenses/by/4.0/).

TABLE 5 Baseline patient demographic characteristics

Characteristic	Total (*N* = 718), *n* (%)	Medicine-1st (*N* = 362), *n* (%)	Laser-1st (*N* = 356), *n* (%)
Centre			
MEH	374 (52.1)	187 (51.7)	187 (52.5)
Hinchingbrooke 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 (5.0)	19 (5.3)

TABLE 5 Baseline patient demographic characteristics (*continued*)

Characteristic	Total (*N* = 718), *n* (%)	Medicine-1st (*N* = 362), *n* (%)	Laser-1st (*N* = 356), *n* (%)
Age (years), mean (SD)	63.1 (11.8)	62.7 (11.6)	63.4 (12.0)
Sex, *n* (%)			
Male	397 (55.3)	197 (54.4)	200 (56.2)
Female	321 (44.7)	165 (45.6)	156 (43.8)
Ethnicity, *n* (%)[a]			
Asian	51 (7.1)	28 (7.7)	23 (6.5)
Black	146 (20.3)	69 (19.1)	77 (21.6)
White	501 (69.8)	258 (71.3)	243 (68.3)
Other	20 (2.8)	7 (1.9)	13 (3.7)
Diagnosis, *n* (%)			
OAG	555 (77.3)	282 (77.9)	273 (76.7)
OHT	163 (22.7)	80 (22.1)	83 (23.3)
General health conditions, *n* (%)			
Asthma	93 (13.0)	45 (12.4)	48 (13.5)
Hypertension	251 (35.0)	119 (32.9)	132 (37.1)
Diabetes	82 (11.4)	40 (11.1)	42 (11.8)
Angina	21 (2.9)	11 (3.0)	10 (2.8)
Cardiac arrhythmia	37 (5.2)	20 (5.5)	17 (4.8)
Medication, *n* (%)			
Statins	196 (27.3)	92 (25.4)	104 (29.2)
Systemic beta-blockers	34 (4.7)	12 (3.3)	22 (6.2)
Calcium channel blocker	116 (16.2)	60 (16.6)	56 (15.7)
ACE inhibitors	100 (13.9)	43 (11.9)	57 (16.0)
Corticosteroids	42 (5.9)	20 (5.5)	22 (6.2)
Family ocular history of glaucoma,[b] *n* (%)	214 (30.0)	107 (29.6)	107 (30.1)
Highest education achievement, *n* (%)			
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 (11.0)
GCSE	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)

ACE, angiotensin-converting enzyme; A level, Advanced level; GCSE, General Certificate of Secondary Education.

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, and 'other' ethnicity refers to Chinese and any other ethnic groups.

b First-degree relative.

A total of 301 patients (41.9%) had bilateral OAG, 161 patients (22.4%) had unilateral OAG (fellow eye healthy), 93 patients (13.0%) had OAG in one eye and OHT in the other eye, 124 patients (17.3%) had bilateral OHT and 39 patients (5.4%) had unilateral OHT (fellow eye healthy). A total of 555 patients (77.2%) were classified as having OAG (if at least one eye was affected by OAG) and 163 patients (22.7%) were classified as having OHT; both eyes were eligible for the trial in 517 patients (72.0%), only the right eye was eligible in 96 patients (13.4%), and only the left eye was eligible in 105 patients (14.6%); 55% of the better eyes were right eyes.[72]

The baseline patient characteristics were similar between the two groups in terms of age, sex distribution, ethnicity, general health and family history of glaucoma (see *Table 5*). There were small differences in the medication and education of the patients. The eye characteristics were also similar between the two treatment arms, with VA, VF MD, HRT optic disc rim area, IOP and CCT comparable between the two treatment arms (*Table 6*).

The baseline scores for QoL (EQ-5D-5L, GSS, GUI and GQL-15) are shown in *Table 7*. The two treatment arms had similar average EQ-5D-5L scores (Medicine-1st 0.92 ± 0.13, Laser-1st 0.91 ± 0.13; higher scores indicate better HRQoL), GUI scores (Medicine-1st 0.89 ± 0.11, Laser-1st 0.89 ± 0.12; higher scores indicate better HRQoL) and GQL-15 scores (Medicine-1st 18.7 ± 5.6, Laser-1st 18.9 ± 6.6; higher scores indicate worse HRQoL) at baseline. The Medicine-1st arm showed slightly higher average GSS scores at baseline than the Laser-1st arm (Medicine-1st 83.3 ± 16.6, Laser-1st 81.4 ± 17.2; higher scores indicate better HRQoL).

Primary outcome return rates

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 ITT analysis (with imputation used for missingness). 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.

TABLE 6 Baseline patient clinical characteristics

Characteristic	*N*	All eyes (*N* = 1235)	Medicine-1st (*N* = 622)	Laser-1st (*N* = 613)
Diagnosis, *n* (%)				
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)
Refractive error (spherical D), mean (SD)	1225	–0.23 (3.0)	–0.2 (2.7)	–0.3 (3.2)
VA, mean (SD)	1235	0.1 (0.12)	0.1 (0.1)	0.1 (0.2)
VF MD (dB), mean (SD)	1233	–3.0 (3.45)	–3.0 (3.6)	–3.0 (3.4)
HRT rim area, mean (SD)	1128	1.2 (0.4)	1.1 (0.4)	1.2 (0.4)
IOP, mean (SD)	1233	24.5 (5.1)	24.4 (5.0)	24.5 (5.2)
CCT (μm), mean (SD)	1229	551.1 (37.2)	551.6 (36.3)	550.7 (38.1)
PXF, *n* (%)	1233	17 (1.4)	12 (1.9)	5 (0.8)
Pseudophakia, *n* (%)	1233	72 (5.8)	33 (5.3)	39 (6.4)

PXF, pseudoexfoliation syndrome.

TABLE 7 Baseline questionnaire scores

Measure	Overall (*N* = 717), mean (SD)	Medicine-1st (*N* = 362), mean (SD)	Laser-1st (*N* = 355), mean (SD)
EQ-5D-5L index	0.91 (0.13)	0.92 (0.13)	0.91 (0.13)
GUI[a]	0.89 (0.12)	0.89 (0.11)	0.89 (0.12)
GSS[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)
GQL-15[a]	18.8 (6.1)	18.7 (5.6)	18.9 (6.6)
Subscales			
Central	2.5 (1.0)	2.5 (1.0)	2.5 (1.0)
Peripheral	8.5 (3.1)	8.4 (2.9)	8.5 (3.4)
Dark	7.9 (2.9)	7.9 (2.8)	7.9 (3.0)
Outdoor	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)

a *n* = 716.
b *n* = 710.

Losses to follow-up

A total of 16 patients in the Laser-1st arm and nine patients in the Medicine-1st arm discontinued participation (see *Figure 4*). In total, two patients were lost to follow-up and were no longer contactable, four patients moved to a different hospital, four patients withdrew from the trial, five patients could not continue participation owing to ill health and 10 patients died.

Quality of life

Primary outcome: EQ-5D-5L

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; $p = 0.23$] (*Table 8* and *Figure 5*).

TABLE 8 Primary (at 36 months) and secondary (across 36 months) analysis of HRQoL questionnaires

Measure	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-5L	336	0.89 (0.18)	337	0.90 (0.16)	0.01	–0.01 to 0.03	0.230
GUI	299	0.89 (0.13)	303	0.89 (0.13)	0.01	–0.01 to 0.03	
GSS	281	83.3 (17.3)	294	83.1 (17.7)	1.6	–0.8 to 4.0	
GQL-15	297	19.8 (7.8)	304	19.8 (7.2)	–0.4	–1.3 to 0.6	
QALY	263	2.70 (0.42)	261	2.74 (0.37)	0.025	0.02 to 0.07	0.289
QALY (discounted)	263	2.62 (0.41)	261	2.65 (0.36)	0.024	–0.02 to 0.07	0.286

continued

TABLE 8 Primary (at 36 months) and secondary (across 36 months) analysis of HRQoL questionnaires (*continued*)

Measure	Medicine-1st		Laser-1st		Adjusted mean difference[a]	95% CI	*p*-value
	n	Mean (SD)	*n*	Mean (SD)			
Repeated measures analysis across 36 months							
EQ-5D-5L							
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	–0.00 to 0.03	
GUI							
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	
GSS							
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	
GQL-15							
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	

a Laser-1st – Medicine-1st. Mean difference is adjusted for baseline score, severity, centre, baseline IOP and number of eyes affected at baseline.

Notes

EQ-5D-5L: higher scores represents a better QoL.
GUI: higher scores represents a higher QoL.
GSS: higher scores represent better outcomes.
GQL-15: higher sores represents poorer glaucoma QoL.

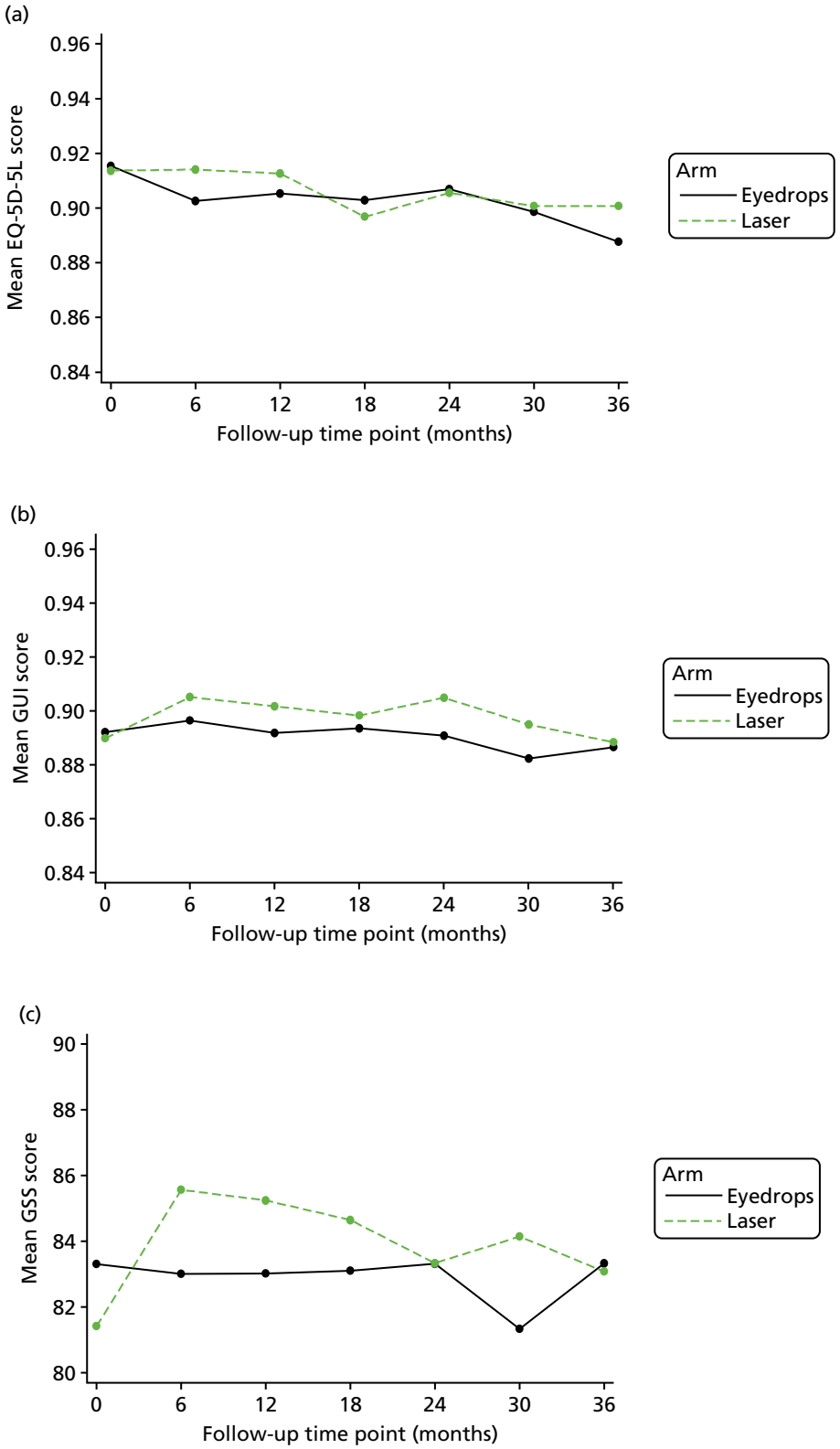

FIGURE 5 Mean (a) EQ-5D-5L, (b) GUI, (c) GSS and (d) GQL-15 scores at each time point, across 36 months. Time point '0' refers to pre-treatment. a, Higher scores on EQ-5D-5L, GUI and GSS indicate better HRQoL; b, higher scores on GQL-15 indicate worse HRQoL. Adapted by permission from BMJ Publishing Group Limited. The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. A multicentre randomised controlled trial: baseline patient characteristics, Konstantakopoulou E, Gazzard G, Vickerstaff V, Jiang Y, Nathwani N, Hunter R, Ambler G, Bunce C, volume 102, pp. 599–603, 2018.[72] (*continued*)

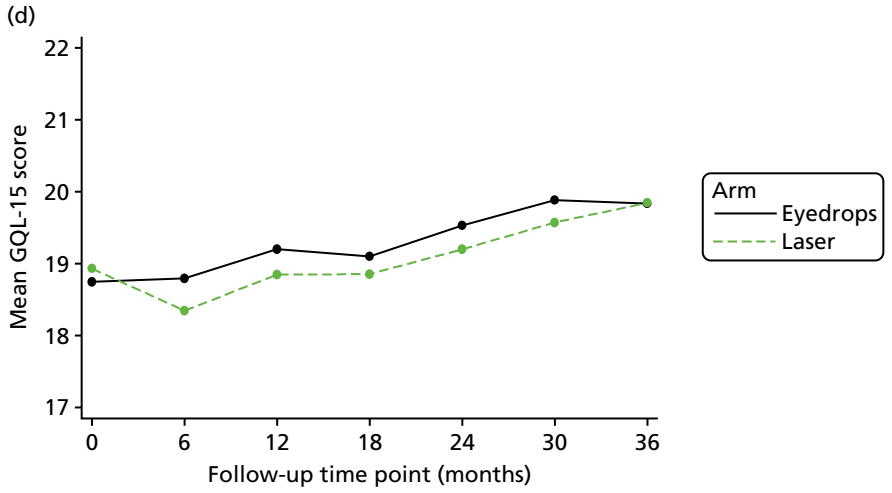

FIGURE 5 Mean (a) EQ-5D-5L, (b) GUI, (c) GSS and (d) GQL-15 scores at each time point, across 36 months. Time point '0' refers to pre-treatment. a, Higher scores on EQ-5D-5L, GUI and GSS indicate better HRQoL; b, higher scores on GQL-15 indicate worse HRQoL. Adapted by permission from BMJ Publishing Group Limited. The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. A multicentre randomised controlled trial: baseline patient characteristics, Konstantakopoulou E, Gazzard G, Vickerstaff V, Jiang Y, Nathwani N, Hunter R, Ambler G, Bunce C, volume 102, pp. 599–603, 2018.[72]

The results were confirmed in sensitivity analyses (see *Appendix 10*). Taking into account the outcome data from all time points across 36 months, the two treatment arms had similar EQ-5D-5L scores at 36 months [adjusted mean difference 0.02 (95% CI –0.00 to 0.03) and 0.01 (95% CI –0.01 to 0.02), when using exact times of questionnaire returns).

Secondary outcomes: Glaucoma Utility Index, Glaucoma Symptom Scale and Glaucoma Quality of Life-15

The average score on the GUI was 0.89 (SD 0.13) in the Laser-1st arm, compared with 0.89 (SD 0.13) in the Medicine-1st arm (adjusted mean difference 0.007, 95% CI –0.010 to 0.025) (see *Table 8* and *Figure 5*). The mean GSS score at 36 months was 83.3 (SD 17.3) in the Laser-1st arm, compared with 83.1 (SD 17.7) in the Medicine-1st arm (adjusted mean difference 1.595, 95% CI –0.797 to 3.988). Mean GQL-15 scores at 36 months were similar (19.8 in the Laser-1st arm and 19.8 in the Medicine-1st arm, adjusted mean difference –0.368, 95% CI –0.605 to 1.341). Secondary HRQoL outcomes (GUI, GSS and GQL-15) generally suggested slightly better HRQoL in the Laser-1st cohort (see *Table 8*). Repeated-measures analysis showed worse GSS scores in the Medicine-1st arm at five out of six time points over 36 months.

Pathway clinical effectiveness

At 12 months, 606 eyes (98.9%) were available for analysis in the Medicine-1st arm and 608 eyes (97.8%) in the Laser-1st arm. At 24 months, 564 eyes (92.0%) were available for analysis in the Medicine-1st arm and 576 eyes (92.6%) in the Laser-1st arm. 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.

Visual function

Measures of visual function at 36 months are shown in *Table 9* for both treatment arms. VA at 36 months was comparable between the two treatment arms [0.08 (SD 0.17) log of the minimum angle of resolution (logMAR) for Medicine-1st compared with 0.07 (0.18) for Laser-1st]. In both treatment arms, patients with moderate and severe OAG showed worse VA than those with OHT and mild OAG [logMAR for the Medicine-1st and Laser-1st arms, respectively: severe OAG, 0.16 (SD 0.23) and 0.15 (SD 0.18); moderate OAG, 0.12 (SD 0.16) and 0.11 (SD 0.24); mild OAG, 0.06 (SD 0.15) and 0.08 (SD 0.17); and OHT, 0.08 (SD 0.19) and 0.02 (SD 0.15)].

TABLE 9 Visual acuity, IOP and VF MD and pattern SD at 36 months

	Medicine-1st, mean (SD)	Laser-1st, mean (SD)
VA (logMAR) at 36 months	0.08 (0.17)	0.07 (0.18)
OHT	0.08 (0.19)	0.02 (0.15)
Mild OAG	0.06 (0.15)	0.08 (0.17)
Moderate OAG	0.12 (0.16)	0.11 (0.24)
Severe OAG	0.16 (0.23)	0.15 (0.18)
VF MD at 36 months	–3.21 (3.76)	–3.19 (3.92)
OHT	–0.94 (1.92)	–1.05 (1.98)
Mild OAG	–2.14 (1.95)	–1.99 (1.93)
Moderate OAG	–7.21 (1.92)	–7.96 (2.04)
Severe OAG	–10.50 (5.01)	–10.24 (4.93)
VF pattern SD at 36 months	3.98 (3.29)	3.91 (3.23)
OHT	2.00 (1.19)	2.11 (1.31)
Mild OAG	3.01 (1.94)	2.84 (1.63)
Moderate OAG	7.56 (2.89)	8.40 (3.03)
Severe OAG	10.41 (2.77)	9.63 (2.58)
IOP at 36 months	16.29 (3.87)	16.63 (3.62)
OHT	18.7 (3.73)	18.2 (3.73)
Mild OAG	15.7 (3.45)	16.4 (3.17)
Moderate OAG	14.7 (3.49)	14.4 (3.07)
Severe OAG	15.5 (4.17)	15.5 (4.16)

VF MD was also comparable between the two treatment arms at 36 months [–3.21 (SD 3.76) dB for Medicine-1st compared with –3.19 (SD 3.92) dB for Laser-1st]; VF MD values among those with OHT, as well as those with mild, moderate or severe OAG, were similar in the two treatment arms. VF pattern SD was similar between the two treatment arms at 36 months [3.98 (SD 3.29) dB for Medicine-1st, compared with 3.91 (SD 3.23) dB for Laser-1st]. IOP was reduced from baseline levels for both groups and showed comparable measures at 36 months across all severity categories [16.3 mmHg (SD 3.9) for Medicine-1st, compared with 16.6 mmHg (SD 3.6) for Laser-1st] (see *Table 9*).

Achieving target intraocular pressure

A total of 91% of patients treated with Laser-1st achieved target IOP at the first planned visit, compared with 89.6% of those treated with Medicine-1st (*Table 10*). Over 36 months, target IOP was achieved at 93.0% of visits in the Laser-1st arm, compared with 91.3% of visits in the Medicine-1st arm.

At 12 months, 94.7% of eyes ($n = 576$) in the Laser-1st arm met or were below the target IOP, compared with 96.2% of the eyes in the Medicine-1st arm (see *Table 10*). In the first 12 months after treatment, the proportion of eyes that were consistently at target IOP among patients with OHT or mild or moderate OAG was higher in the Medicine-1st arm, but, among those with severe OAG, the proportion of eyes achieving target IOP was similar in both arms (91.3% in the Medicine-1st arm vs. 91.5% in the Laser-1st arm). This trend was reversed at the end of the second year of the trial, when 96.0% of eyes in the Laser-1st arm ($n = 553$) were at target IOP, compared with 94.1% of eyes the Medicine-1st arm ($n = 531$). Similarly, more eyes with severe OAG, treated with Medicine-1st, were at target IOP compared with those treated

TABLE 10 Control of IOP over 12, 24 and 36 months

	Medicine-1st	Laser-1st
Eyes achieving target IOP at first planned visit (%)[a]	89.6	91.0
Proportion of visits at target IOP over 36 months (%)	91.3	93.0
Eyes at target IOP at 12 months, % (*n*)	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, % (*n*)	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, % (*n*)	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, mean (SD)	2.5 (1.4)	2.3 (1.0)

a Out of a total of 615 eyes for Medicine-1st and 605 eyes for Laser-1st.

with Laser-1st (89.5% vs. 87.5%, respectively). At 36 months, a total of 95% of eyes (*n* = 509) were at target IOP in the Laser-1st pathway, compared with 93.1% of eyes (*n* = 499) in the Medicine-1st pathway. The proportion of eyes at target IOP among patients with OHT or mild or moderate OAG was higher in the Laser-1st arm than in the Medicine-1st arm, but, among those with severe OAG, a higher proportion of eyes treated with Medicine-1st were at target IOP (85.7% in the Medicine-1st arm vs. 84.6% in the Laser-1st arm). IOP appears to have fluctuated marginally more in the Medicine-1st arm than in the Laser-1st arm (2.5 mmHg vs. 2.3 mmHg).

Treatment intensity to achieve target intraocular pressure

In the first year after treatment, 85.9% of eyes (*n* = 522) treated with Laser-1st were at target IOP without the use of IOP-lowering eyedrops (*Table 11*). This reduced to 81.6% (*n* = 470) after the second year and to 78.2% (*n* = 419) at the end of the trial, at 36 months. In comparison, in the Medicine-1st arm, 82.2% of eyes (*n* = 498) were being treated with a single medication at 12 months, falling to 71.5% of eyes (*n* = 403) at 24 months and 64.6% of eyes (*n* = 346) at 36 months. The benefit of not using any eyedrops to control IOP was lost for 103 eyes in the Laser-1st arm, whereas 152 eyes in the Medicine-1st arm lost the benefit of a single drop per eye and had to add a second medication to control their IOP.

At the end of the first year, a total of 701 SLT procedures had taken place, with 521 eyes having had a single SLT and 90 eyes having had two SLTs (see *Table 11*). During the second year, a further 32 SLTs were performed for on eyes that had been treated with SLT during the first 12 months. During the third year of the trial, 35 eyes underwent a second SLT and one eye underwent a third SLT (protocol deviation; see *Appendix 9*).

TABLE 11 Intensity of treatment to achieve target IOP

	Medicine-1st, *n* (%)	Laser-1st, *n* (%)
Number of SLT treatments per eye at 12 months[a]	4	701
One SLT treatment	4	521(85.3)
Two SLT treatments	0	90 (14.7)
Three SLT treatments[b]	0	0
Number of medications per eye at target IOP at 12 months[b]		
No medication	6 (1.0)	522 (85.9)
One medication	498 (82.2)	49 (8.1)
Two medications	67 (11.1)	4 (0.7)
Three medications	11 (1.8)	1 (0.1)
Four medications	1 (0.2)	0 (0.0)
Number of SLT treatments per eye at 24 months[a]	4	733
One SLT treatment	4	489 (80)
Two SLT treatments	0	122 (20)
Three SLT treatments[b]	0	0
Number of medications per eye at target IOP at 24 months[b]		
No medication	14 (2.5)	470 (81.6)
One medication	403 (71.5)	73 (12.7)
Two medications	94 (16.7)	8 (1.4)
Three medications	18 (3.2)	2 (0.3)
Four medications	2 (0.4)	0 (0.0)
Number of SLT treatments per eye at 36 months[a]	6[a]	770
One SLT treatment	6	453 (74.0)
Two SLT treatments	0	157 (26.0)
Three SLT treatments[b]	0	1 (0.2)
Number of medications per eye at target IOP at 36 months[b]		
No medication	16 (3.0)	419 (78.2)
One medication	346 (64.6)	64 (12.0)
Two medications	99 (18.5)	21 (3.9)
Three medications	35 (6.5)	4 (0.8)
Four medications	3 (0.6)	1 (0.2)

a Includes eyes that were not at target IOP.
b includes eyes that had undergone trabeculectomy.

At the end of the trial, at 36 months, target IOP was achieved without IOP medication in 78.2% of the eyes ($n = 419$) treated with Laser-1st (see *Table 11*); of these, 76.6% ($n = 321$) had required only one SLT application. Of the Laser-1st patients, 74.2% ($n = 233$, 95% CI 69.3% to 78.6%) were eyedrop free at 36 months. A total of 64.6% ($n = 346$) of the eyes treated with Medicine-1st were being treated with a single medication at 36 months.

Control of disease

More treatment escalations took place in the Medicine-1st arm ($n = 348$) than in the Laser-1st arm ($n = 299$). Thirty-six eyes in the Medicine-1st arm showed algorithm-confirmed disease deterioration (three eyes converted from OHT to OAG and in 33 eyes OAG progressed), compared with 23 eyes in the Laser-1st arm (two eyes showed OHT conversion to OAG and in 21 eyes OAG worsened) (*Table 12*).

Over the 36-month duration of the trial, target IOP was revised in 38 eyes, in 33 patients, in the Medicine-1st arm (total 38 IOP revisions) and in 38 eyes, in 37 patients, in the Laser-1st arm (total 41 IOP revisions) (see *Table 12*). IOP was revised downwards in 31 eyes (16 in the Medicine-1st arm and 15 in the Laser-1st arm) because of objective signs of disease deterioration/progression despite the IOP target being met. The vast majority of the downward revisions of target IOP (28 out of 31) were for eyes with OAG. Additionally, in 48 cases (22 in the Medicine-1st arm and 26 in the Laser-1st arm), the IOP target was revised upwards, despite the initial IOP target not having been met repeatedly, because there was no evidence of disease deterioration/progression. There were proportionally more upwards 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). Eleven eyes (1.8%) required IOP-lowering surgery (trabeculectomy) in the Medicine-1st arm, compared with none in the Laser-1st arm.

TABLE 12 Treatment escalations, disease progression, IOP target revisions and glaucoma surgeries, describing overall control of the disease

	Medicine-1st	Laser-1st
Treatment escalations over 36 months (*n*)[a]	348	299
Disease progression during the trial, % (*n*)	5.8 (36)	3.8 (23)
From OHT to OAG (*n*)[b]	3	2
OAG progression (*n*)	33	21
Algorithm defined VF progression	27	18
Algorithm defined optic disc progression	3	2
Algorithm-defined VF and disc progression	3	1
IOP target revisions	38 (38 eyes, 33 patients)	41 (38 eyes, 37 patients)
Upwards IOP revisions over 36 months (*n*)	22	26
OHT	4	5
Mild OAG	8	14
Moderate OAG	7	1
Severe OAG	3	6
Downwards IOP revisions over 36 months (*n*)	16	15
OHT	1	2
Mild OAG	5	5
Moderate OAG	6	5
Severe OAG	4	3
Glaucoma surgeries (*n*)		
Trabeculectomy	11	0
Trabeculectomy revision	7 (5 eyes)	0

a Treatment escalations initiated by the algorithm and the clinicians.
b Conversion of OHT to OAG required a DSS-derived sign of progression and verification by a consultant ophthalmologist.

Safety profile

Adverse events

A total of 1196 AEs were reported for the Medicine-1st arm, compared with 900 in the Laser-1st arm, although the number of patients reporting at least one AE was balanced (260 patients in the Medicine-1st arm vs. 261 in the Laser-1st arm) (*Table 13*). On average, four AEs were reported per patient treated with Medicine-1st compared with three AEs per patient treated with Laser-1st.

TABLE 13 Adverse events

Summary	Medicine-1st		Laser-1st		Total	
Total number of AEs	1196		900		2096	
Number of patients reporting at least one AE	260		261		521	
Number of AEs reported per person, median[a] (IQR)	4 (2–8)		3 (1–5)		3 (2–7)	
	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)
Systemic AEs/symptoms	298	115 (31.8)	236	98 (27.6)	534	213 (29.7)
Pulmonary problems	23	14 (3.9)	24	12 (3.4)	47	26 (3.6)
Cardiac events	6	5 (1.4)	8	5 (1.4)	14	10 (1.4)
Heart block	1	1 (0.3)	0	0 (0)	1	1 (0.0)
Cardiac arrhythmia	5	4 (1.1)	8	5 (1.4)	13	9 (1.3)
Drug-related events	148	52 (14.4)	87	23 (6.5)	235	75 (10.5)
Impotence	10	3 (0.8)	7	4 (1.1)	17	7 (1.0)
Depression	18	9 (2.5)	14	4 (1.1)	32	13 (1.8)
Somnolence/tiredness	60	31 (8.6)	34	17 (4.8)	94	48 (6.7)
Nightmares	21	11 (3.0)	15	4 (1.1)	36	15 (2.1)
Generalised skin rash	18	11 (3.0)	13	8 (2.3)	31	19 (2.6)
Taste disturbance	21	18 (5.0)	4	3 (0.8)	25	21 (2.9)
Other[b]	121	82 (22.7)	117	78 (22.0)	238	160 (22.3)
Ophthalmic AEs	809	241 (66.6)	492	188 (53.0)	1388	429 (59.8)
Aesthetic eyedrop side effects	117	56 (15.5)	12	7 (2.0)	129	63 (8.8)
Change in iris colour	6	4 (1.1)	1	1 (0.3)	7	5 (0.7)
Periocular pigmentation	24	16 (4.4)	4	4 (1.1)	28	20 (2.8)
Excessive lash growth	87	48 (13.3)	7	5 (1.4)	94	53 (7.4)
Ophthalmic allergic reactions	33	17 (4.7)	18	13 (3.7)	51	30 (4.2)
Periocular skin rash	16	10 (2.8)	5	5 (1.4)	21	15 (2.1)
Allergy	17	11 (3.0)	13	8 (2.3)	30	19 (2.6)
Uveitis	1	1 (0.3)	2	2 (0.6)	3	3 (0.4)
Reactivation of herpes	1	1 (0.3)	1	1 (0.3)	2	2 (0.3)
Other[c]	744	118 (32.6)	459	117 (33.0)	1041	235 (32.8)

continued

TABLE 13 Adverse events (*continued*)

Summary	Medicine-1st		Laser-1st		Total	
Laser-related AEs	2	1 (0.3)	172	122 (34.4)	180	123 (17.2)
IOP spike post SLT[d]	0	0	6	6 (1.7)	6	6 (0.8)
Inflammation	0	0 (0)	1	1 (0.3)	1	1 (0.1)
Discomfort	1	1 (0.3)	92	82 (23.1)	93	83 (11.6)
Blurred vision	0	0 (0)	23	21 (5.9)	23	21 (2.9)
Change in refraction	0	0 (0)	5	4 (1.1)	5	4 (0.6)
Other[c]	1	1 (0.3)	51	47 (13.2)	52	48 (6.7)

a Of those with at least one AE.
b Includes ocular irritation, discomfort, dry eye, unspecified retinal haemorrhages, vision changes, flashes, floaters, conjunctivitis, blepharitis, vascular occlusions, diabetic retinopathy and macular pathology.
c See *Appendix 11*.
d IOP spike defined as > 5 mmHg; only one eye received treatment.

Overall, systemic AEs were similar between the two treatment arms (see *Table 13*): 26 cardiac AEs in the Medicine-1st arm vs. 28 in the Laser-1st arm and six pulmonary systemic AEs in the Medicine-1st arm vs. eight in the Laser-1st arm. Eyedrop-related systemic AEs (impotence, depression, somnolence/tiredness, taste disturbance, skin rash and nightmares) were reported more often and by more patients in the Medicine-1st arm [148 events reported by 52 patients (14.4%)] than in the Laser-1st arm [87 events reported by 23 patients (6.5%)].

There were more ophthalmic eyedrop-related AEs reported by patients in the Medicine-1st arm (150 aesthetic side effects and topical allergic reactions reported by 73 patients) than reported by patients in the Laser-1st arm (30 events reported by 20 patients). There were a total of 80 treatment changes (not escalations) attributable to eyedrop side effects or intolerances during the course of the trial; 69 changes to treatment were applied to 59 eyes in 41 patients (11.3% of patients) treated with Medicine-1st and 11 changes to treatment were applied to seven eyes in four patients (1.1% of patients) treated with Laser-1st.

Transient discomfort, blurred vision, photophobia and hyperaemia after the SLT treatment were reported by 34.4% ($n = 122$) of the patients in the Laser-1st arm and were of a transient nature. AEs (including variations in the number of laser shots, visualisation of angle, breaks taken and discomfort) were reported for 14 patients during the SLT procedure.

There were no sight-threatening complications of SLT (see *Table 13*). Cases of reactivation of herpes simplex keratitis (one in each treatment arm) and uveitis (two in the Laser-1st arm and one in the Medicine-1st arm) were comparable in the two treatment arms. In only six eyes in six patients was a post-SLT IOP rise noted (> 5 mmHg), identified on the day of laser treatment. Only one of these eyes required treatment. There were no peripheral anterior synechiae.

Serious adverse events

Overall, serious adverse events were balanced between the two treatment arms (*Table 14*); there were 97 events in the Medicine-1st arm, reported by 69 patients, and 107 events in the Laser-1st arm, 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 the Laser-1st arms (three and two, respectively), as were cardiac events (seven and nine, respectively). There were few and balanced cerebrovascular accidents (one in the Medicine-1st arm and with two in the Laser-1st arm). There were more cancer diagnoses ($n = 15$) and deaths ($n = 8$) in the Laser-1st arm than in the Medicine-1st arm (nine and two events, respectively).

TABLE 14 Serious adverse events

	Medicine-1st		Laser-1st		Total	
Total number of events	97		107		204	
Total number of patients reporting	69		64		133	
	Events, *n*	*n* (%)	Events, *n*	*n* (%)	Events, *n*	*n* (%)
Ocular	9	6 (1.7)	10	8 (2.2)	17	14 (1.9)
CRVO/BRVO	1	1	1	1	2	2
Retinal detachment	1	1	3	2	4	3
Anterior chamber surgery	1	1	0	0	1	1
Posterior segment surgery	1	1	0	0	1	1
Corneal ulcer	1	1	0	0	1	1
CNV	2	2	3	3	5	5
Angle closure requiring intervention	2	1	2	1	4	2
Post-traumatic uveitis	0	0	1	1	1	1
Pulmonary problems[a]	3	3 (0.8)	2	2 (0.5)	5	5 (0.7)
Cerebrovascular accidents	1	1 (0.3)	2	2 (0.5)	3	3 (0.4)
Cardiac events[a]	7	7 (1.9)	9	8 (2.2)	16	15 (2.1)
Cancer	9	8 (2.2)	15	13 (3.6)	24	21 (2.9)
Death	2	2 (0.5)	8	8 (2.2)	10	10 (1.4)
Other systemic	66	50 (15.3)	61	43 (12.1)	127	93 (13)

BRVO, branch retinal vein occlusion; CNV, choroidal neovascularisation; CRVO, central retinal vein occlusion.
a Requiring hospitalisation.

Ocular comorbidities and cataract

Ocular comorbidities developing during the course of the trial are shown in *Table 15*. Overall, these were balanced between the two arms and not related to the treatment. Twenty-five cataract extractions were carried out in 17 patients treated in the Medicine-1st arm and 13 cataract extractions were carried out in 11 patients treated in the Laser-1st arm.

Concordance/compliance

At baseline, concordance with treatment was lower among patients who were to be treated with Medicine-1st than among those allocated to treatment with Laser-1st (the proportion taking their eyedrops correctly was 75% vs. 92.5%, respectively). By the end of the trial, at 36 months, self-reported concordance had improved and was similar between the two treatment arms (99% of eyedrops used correctly) (*Tables 16* and *17*).

TABLE 15 Ocular comorbidities developed during the trial and cataract surgeries

	Medicine-1st (*n*)		Laser-1st (*n*)		Total (*N*)	
	Events	Patients reporting	Events	Patients reporting	Events	Patients reporting
Ocular comorbidities	12		16		28	22
Central retinal artery occlusion	3	2	1	1	4	3
Branch retinal artery occlusion	1	1	2	1	3	2
Diabetic retinopathy	0	0	1	1	1	1
Diabetic macular oedema	0	0	3	2	3	2
Retinal detachment/tear	1	1	3	2	4	3
Anterior chamber surgery	1	1	0	0	1	1
Posterior segment surgery[a]	1	1	0	0	1	1
Corneal ulcer	1	1	0	0	1	1
CNV	2	2	3	3	5	5
Angle closure requiring intervention[b]	2	1	2	1	4	2
Post-traumatic uveitis	0	0	1	1	1	1
Cataract surgeries	25	17	13	11	38	28

CNV, choroidal neovascularisation.
a Not related to retinal detachment.
b One patient in the Medicine-1st arm underwent phacoemulsification in both eyes and one patient in the Laser-1st arm received laser peripheral iridotomy in both eyes.

Note
Some of the above comorbidities were reported as AEs, some as SAEs and are included in the relevant tables.

TABLE 16 Responses of patients treated with Laser-1st regarding the use of their eyedrops

	Follow-up time point (months)						
	Baseline	6	12	18	24	30	36
What percentage of your eyedrops do you think you took correctly (in past month)?							
Total responses (*n*)	10	41	49	61	62	65	77
Median (IQR)	92.5 (75–100)	99 (90–100)	98 (90–75)	99 (80–100)	99 (85–100)	99 (90–100)	99 (90–100)
I'm the sort of person who follows doctors' orders exactly							
Total responses (*n*)	351	324	311	299	300	286	299
Strongly agree, *n* (%)	266 (75.8)	245 (75.6)	226 (72.7)	212 (70.9)	209 (69.7)	203 (71.0)	210 (70.2)
Somewhat agree, *n* (%)	77 (21.9)	70 (21.6)	74 (23.8)	73 (24.4)	80 (26.7)	74 (25.9)	79 (26.4)
Neither agree nor disagree, *n* (%)	7 (2.0)	5 (1.5)	8 (2.6)	10 (3.3)	6 (2.0)	4 (1.4)	7 (2.3)
Somewhat disagree, *n* (%)	0 (0)	1 (0.3)	3 (1)	2 (0.7)	4 (1.3)	5 (1.8)	2 (0.7)
Strongly disagree, *n* (%)	1 (0.3)	3 (0.9)	0 (0)	2 (0.7)	1 (0.3)	0 (0)	1 (0.3)

TABLE 17 Responses of patients treated with Medicine-1st, regarding the use of their eyedrops

	Follow-up time point (months)						
	Baseline	6	12	18	24	30	36
What percentage of your eyedrops do you think you took correctly (in past month)?							
Total responses (*n*)	11	319	298	289	290	284	286
Median (IQR)	75 (25–100)	99 (90–100)	99 (90–100)	99 (95–100)	99 (90–100)	99 (93–100)	99 (90–100)
I'm the sort of person who follows doctors' orders exactly							
n	354	324	305	302	290	293	294
Strongly agree, *n* (%)	249 (70.3)	247 (76.2)	226 (74.1)	221 (73.2)	211 (72.8)	219 (74.7)	211 (71.8)
Somewhat agree, *n* (%)	82 (23.2)	73 (22.5)	73 (23.9)	73 (24.2)	75 (25.9)	68 (23.2)	78 (26.5)
Neither agree nor disagree, *n* (%)	16 (4.5)	1 (0.3)	5 (1.6)	5 (1.7)	2 (0.7)	4 (1.4)	3 (1)
Somewhat disagree, *n* (%)	5 (1.4)	2 (0.6)	1 (0.3)	2 (0.7)	1 (0.3)	2 (0.7)	1 (0.3)
Strongly disagree, *n* (%)	2 (0.6)	1 (0.3)	0 (0)	1 (0.3)	1 (0.3)	0 (0)	1 (0.3)

Cost-effectiveness

Throughout the 36 months of the trial, patients treated with Medicine-1st made 2907 ophthalmology outpatient visits and patients treated with Laser-1st made 3441 visits. The latter includes visits at 2 weeks after the SLT treatment, which served as a safety check. None of these visits revealed a pathology that changed the course of management. A detailed table summarising all of the medical contacts is shown in *Appendix 12* (see *Table 28*).

Quality-adjusted life-years

Descriptive statistics for the EQ-5D-5L are reported in *Table 8*. In the complete-case analysis, the Laser-1st arm had a mean of 2.63 adjusted and discounted QALYs across 3 years ($n = 261$, 95% CI 2.60 to 2.66), with 2.61 QALYs in the Medicine-1st arm ($n = 263$, 95% CI 2.57 to 2.64) with an adjusted difference of 0.025 (95% CI –0.020 to 0.070; $p = 0.277$). In the multiple imputation analysis, there was an adjusted difference of 0.014 [standard error (SE) 0.220, 95% CI –0.029 to 0.057; $p = 0.526$].

Cost of selective laser trabeculoplasty

There were a range of different models for delivering SLT across the different sites. Although all sites had a dedicated laser session, this was usually attended by a mixture of patients, some receiving other types of laser treatment. The procedure was performed by ophthalmologists of a range of grades, covering registrar through to consultant. Supporting staff may have been a health-care assistant or a lower-grade nurse. Sessions tended to last 4 hours, with sites treating between five and eight patients at each session. Depending on the number of sessions, sites may treat between 350 and 200 patients a year with the laser (the laser can be used for procedures other than just SLT).

At a cost of £38,995 for the machine, and an annual maintenance cost of £6395, the cost per patient for the machine, annuitising for a 10-year lifespan, is £32 per patient if one assumes that each site sees 300 patients per year (Lumenis, 2018, personal communication). Alternatively, the per patient cost is £55 if one assumes that each site sees 200 patients per year. If it is assumed that the procedure is carried out by a consultant, takes 30 minutes and there is a mixed model of care between nurses and health-care assistants (half and half), the total staff cost is £64 per patient . If the procedure takes 45 minutes, it is £97 per patient, using the same mix of staff (overheads and oncosts are included in the salary costs).

As a result, the total cost of a SLT is likely to be between £96 and £151 depending on the assumptions made. We have used the upper estimate of £151 as the cost per patient for a SLT to use the more conservative estimate. Descriptive statistics for SLTs are reported in *Table 11*. The average total cost per patient for SLT is reported in *Table 18*.

Ocular-related costs

Descriptive statistics for eyedrops, surgery and IOP appointments are reported in *Table 11*. Total ophthalmology costs collected from patient files are reported in *Tables 11* and *18*. Patients randomised to Laser-1st had significantly higher costs for SLT and scheduled ophthalmology checks (excluding the 2-week IOP check). Patients randomised to Medicine-1st had significantly higher costs for eyedrops, ocular surgery (including preoperative assessment) and IOP checks. The ophthalmology-related costs in the Medicine-1st arm were £451 (95% CI –£580 to –£322) higher in the unadjusted analysis and £447 (95% CI –£573 to –£322) higher in the adjusted analysis with bootstrapped bias-corrected CIs. There were no significant differences between the two groups in community eye-related costs collected using the CSRI (*Table 19*).

Other health-care resource use

There were no significant differences between the two arms in health-care costs collected using the CSRI (*Table 20*), with a difference of –£319 (95% –£757 to £118) for the adjusted analysis with 95% bias-corrected bootstrapped CIs. If missing data are imputed using chained equations, then the adjusted discounted difference is £36 (95% CI –£366 to £437).

Inpatient costs have been calculated separately, given that information on inpatient stays could be supplemented with SAE data. The mean inpatient cost over 3 years (discounted) for patients randomised to Medicine-1st is £799 (SD £2592), with a mean cost of £1095 (SD £3252) for patients randomised to Laser-1st and an adjusted difference of £336 (95% CI –£97 to £770), with CIs calculated from bias-corrected bootstrap.

TABLE 18 Total average cost per patient of ophthalmology-related appointments taken from patient files over 3 years (unadjusted)

Cost component	Medicine-1st (*n* = 362), mean (SD)	Laser-1st (*n* = 356), mean (SD)	Difference, mean (95% CI)
SLT	3 (22)	208 (82)	205 (196 to 213)
Eyedrops	526 (202)	61 (144)	–465 (–491 to –440)
Ocular surgery	242 (709)	109 (386)	–134 (–218 to –50)
Preoperative assessment	17 (50)	8 (32)	–9 (–15 to –3)
Postoperative assessment	1 (14)	0.3 (5)	–0.5 (–2 to 1)
IOP checks[a]	170 (290)	34 (111)	–135 (–168 to –103)
Scheduled checks	446 (144)	535 (150)	90 (68 to 111)
Unscheduled checks	26 (86)	21 (57)	–5 (–16 to 5)
3-year check	63 (42)	67 (40)	4 (–2 to 10)
Total	1495 (1083)	1044 (608)	–451 (–580 to –322)

a Excluding 2-week IOP check.
Note
Costs are in 2016/17 Great British pounds.

TABLE 19 Eye-related costs taken from completed CSRI over 3 years (discounted and unadjusted)

Cost component	Medicine-1st, mean (SD)		Laser 1st, mean (SD)		
	Baseline ($n = 354$)	3 years ($n = 223$)	Baseline ($n = 348$)	3 years ($n = 217$)	Difference, mean (95% CI)
Optometrist	49 (37)	125 (95)	47 (39)	139 (111)	14 (–7 to 35)
Community costs[a] (eye related)	7 (16)	23 (43)	7 (16)	19 (50)	–4 (–12 to 5)
Total (£)	56 (43)	133 (109)	54 (45)	141 (130)	8 (–14 to 30)

a Community costs include general practitioner, primary care nurse and social care.
Notes
Costs are in 2016/17 Great British pounds.
Baseline values are 6 months prior to randomisation.

TABLE 20 Costs collected using the CSRI for non-eye-related health-care resource use over 3 years (discounted and unadjusted)

Cost component	Medicine-1st, mean (SD)		Laser-1st, mean (SD)		
	Baseline ($n = 354$)	3 years ($n = 224$)	Baseline ($n = 348$)	3 years ($n = 231$)	Difference, mean (95% CI)
General practitioner[a]	47 (65)	138 (171)	48 (79)	133 (133)	–5 (–36 to 26)
Social care	4 (40)	27 (109)	2 (15)	26 (134)	–1 (–25 to 22)
A&E attendances	9 (40)	60 (163)	13 (51)	51 (147)	–9 (–39 to 22)
Acute outpatient[b]	115 (182)	525 (683)	97 (172)	436 (706)	–89 (–227 to 49)
Day cases	256 (610)	1184 (2071)	230 (602)	920 (1577)	–264 (–619 to 90)
Total (£)	425 (712)	1776 (2538)	386 (719)	1389 (2100)	–387 (–815 to 41)

A&E, accident and emergency.
a Including practice nurse.
b Excludes eye-related costs.
Notes
Costs are in 2016/17 Great British pounds.
Baseline values are 6 months prior to randomisation.
Inpatient data includes SAE costs.

Total health and social care costs

Total costs include the cost of SLTs, eyedrops, eye-related costs and non-eye-related health and social care costs. Including all costs with no imputation, the total adjusted cost for patients randomised to Medicine-1st over 3 years, discounted, is £3993 (SE £215, 95% CI £3571 to £4414) and for Laser-1st it is £3890 (SE £245, 95% CI £3409 to £4371), with a difference of –£103 (SE £325, 95% CI –£739 to £534; $p = 0.752$). Including imputed missing community data, the difference in costs is –£105 (SE £348, 95% CI –£788 to £579; $p = 0.764$).

Incremental cost-effectiveness ratio and cost-effectiveness acceptability curve

For ophthalmology and total costs, Laser-1st dominates Medicine-1st in that it results in more QALYs for a lower cost. For ophthalmology-only costs, the results of the multiple imputation (QALYs imputed only) and bootstrap, accounting for correlation between costs and QALYs using seemingly unrelated regression, are that Laser-1st results in an average cost saving of –£458 per patient, with 95% of iterations falling between –£585 and –£345, and 0.014 additional QALYs, with 95% of bootstrap replications falling

between –0.018 and 0.046. If non-eye-related costs are also included, the average cost saving of Laser-1st is –£126 per patient, with 95% of bootstrap replications falling between –£796 and £487.

The CEAC is presented in *Figure 6*. If ophthalmology-only costs are included, at a £20,000 and £30,000 willingness to pay for a QALY, there is a 97% and 93% probability, respectively, that Laser-1st is cost-effective compared with Medicine-1st over 3 years, discounted and adjusted. For all health-care-related costs, including non-eye-related costs, at both a £20,000 and a £30,000 willingness to pay for a QALY, there is a 68% chance that Laser 1st is cost-effective compared with Medicine-1st, discounted and adjusted, over 3 years.

Sensitivity analysis

- If the SLT cost was at the lower end of the microcosting estimate, Laser-1st would result in a £176 cost saving compared with eyedrops for all health-care costs. The cost of a SLT based on NHS reference costs[90] is £188. If this value is used, Laser-1st results in £89 in cost savings if all health-care costs are included.
- The average cost of the 2-week check following SLT in the Laser-1st arm was £128 and £20 in the Medicine-1st arm, with the 2-week check costing an additional £108 for patients randomised to Laser-1st. If the 2-week check is included in the analysis, Laser-1st results in £18 of cost savings if all health-care costs are included.
- In the complete-case analysis, the Laser-1st arm results in a mean of 2.63 adjusted and discounted QALYs over 3 years ($n = 261$, 95% CI 2.60 to 2.65), with 2.61 QALYs in the Medicine-1st arm ($n = 263$, 95% CI 2.57 to 2.62) and an adjusted difference of 0.032 (95% CI –0.003 to 0.068; $p = 0.075$). Laser-1st dominates Medicine-1st, with lower costs and more QALYs.

Protocol deviations and violations

A list of protocol deviations and violations is shown in *Appendix 9.*

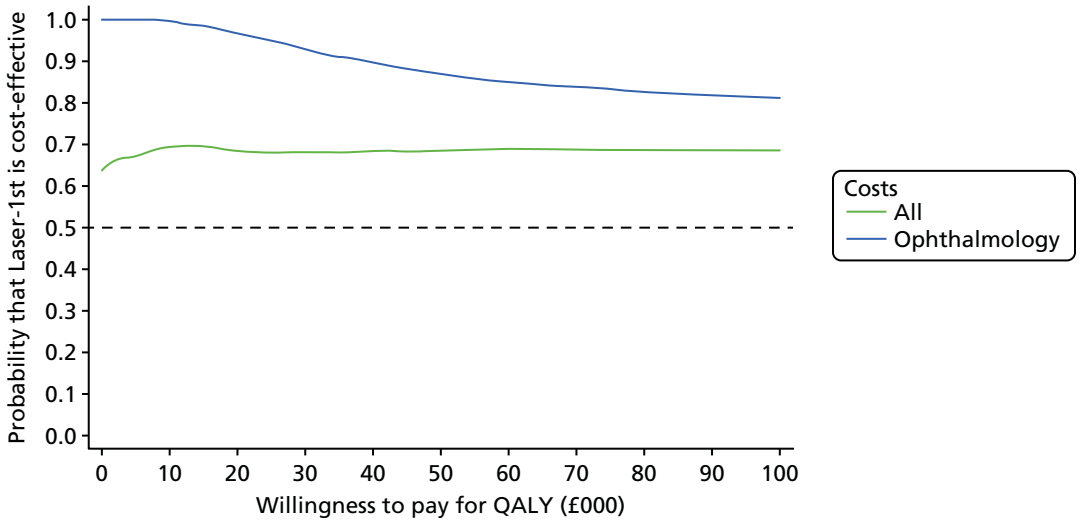

FIGURE 6 Cost-effectiveness acceptability curve of Laser-1st compared with Medicine-1st based on bootstrapped, imputed, discounted and adjusted data: ophthalmology costs and all health-care costs. Reproduced from Gazzard *et al.*[58] © 2019 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license (http://creativecommons.org/licenses/by/4.0/).

Chapter 4 Health economic decision model

Introduction

We collected costs and monitored QoL over the 3-year time horizon of the trial. However, it is possible that further costs and benefits will accrue beyond the time horizon of the trial.

Aim

The aim of the economic evaluation was to calculate the mean incremental cost per QALY of Laser-1st compared with Medicine-1st for the lifetime of the patient. Health service costs and QALYs were calculated for the lifetime of patients, drawing on data from the trial and the literature where appropriate.

Methods

Design

In the lifetime model, cost-effectiveness was calculated in terms of the incremental cost per QALY of Laser-1st compared with Medicine-1st. The model was developed and populated based on available evidence, including the data collected during the trial. Based on previously identified models[73] and expert clinical input, the proposed design is a Markov state-transition model that allows movement between glaucoma states. Values for the model have predominantly been taken from data collected from the trial. A systematic search of the literature was also conducted to ratify the evidence from the trial with that in the wider literature. Estimates for mortality have been derived from national data sets.[75]

The model has cycles of 6 months' duration and calculates expected costs and outcomes for a hypothetical cohort of patients with the same age, sex, ethnicity and deprivation composition as patients enrolled in the LiGHT trial. The number of cycles was determined by the number of years between the first cycle and when all patients in the model had died. Costs and QALYs have been discounted at 3.5% per year, in line with NICE guidelines.[76] The health states in the model were OHT, mild glaucoma, moderate glaucoma, severe glaucoma and death. Health states were defined with associated costs and utility values.

Transition probabilities were obtained from the LiGHT trial findings for the first 3 years of the model and a combination of published studies and LiGHT trial findings for the remaining years of the analysis. Given the duration of follow-up in the trial, health status utility and annual costs associated with each Markov state were based on within-trial data; mean utilities and costs for each state were calculated based on the patient-level data in the 3-year follow-up period in the study. These values were utilised in the long-run model. The within-trial values were also compared and supplemented with data from published studies (see Traverso *et al.*[77]), if appropriate. We undertook deterministic (one-way, two-way, multiway) analyses and a probabilistic sensitivity analysis (PSA), the latter assuming appropriate distributions and parameter values.[79] The values from the PSA were used to construct a CEAC, which shows the probability that Laser-1st is cost-effective compared with Medicine-1st over the full lifetime of patients for a range of values of the NHS's willingness to pay for an additional QALY.

The costs of the treatment pathway were also estimated using a Markov model that estimated the cost of eyedrops, surgery and SLT and the costs for patients who were 'drops free'. This model was run in conjunction with the aforementioned model and the results were combined.

Markov model structure

The model structure is presented in *Figure 1*. Generally speaking, OAG is a non-reversible condition, which is reflected in the model structure, in which it was not possible for patients to return to a less severe glaucoma state at the end of each cycle. However, in reality, it is expected that a number of patients will break this assumption as a result of fluctuation within patients, measurement error and other procedures (e.g. cataract surgery), rather than true improvement. Only two patients in the trial were at a better state at 36 months than at baseline (both in the medication arm). These patients were removed from the analysis, assuming measurement error.

Patients in both arms progressed through health states until the entire cohort entered the 'death' state. The rate of progression was calculated based on patients severity at the 36-month follow-up compared with baseline. Cycle-specific transition probability was calculated using the method and formula set out in Briggs *et al.*[79] of $r = -[\ln(1 - P)]/t$ and transition probability $= 1 - \exp(-rt)$, where r is the rate, P is the probability of an event and t is time.

The model was developed in Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA).

Costing of the treatment pathway

The second and third Markov models were developed to capture treatment costs, including the costs of eyedrops, surgery and SLT. The model structures for each pathway are shown in *Figures 7* and *8*. The costs estimated in the model were combined with the health state costs in the disease state model (*Figure 9*).

The cost of eyedrops depended on whether the patient was receiving first, second, third or fourth escalation treatment. The model allowed for patients to remain in each eyedrops subcategory after each cycle or progress to the next treatment escalation. Patients could stay in the surgery state for only one cycle, following which they moved into the eyedrops-free window. Patients could also remain in the eyedrops-free state for multiple cycles.

The Laser-1st pathway included a state for patients who received SLT and allowed a number of patients to undergo a second laser treatment, although this transition could be made only once, in line with the trial protocol.

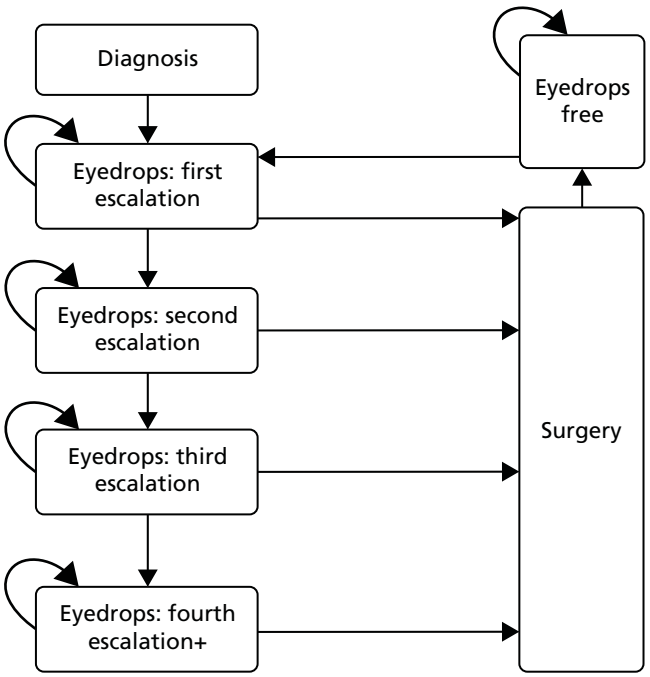

FIGURE 7 Medicine-1st treatment pathway.

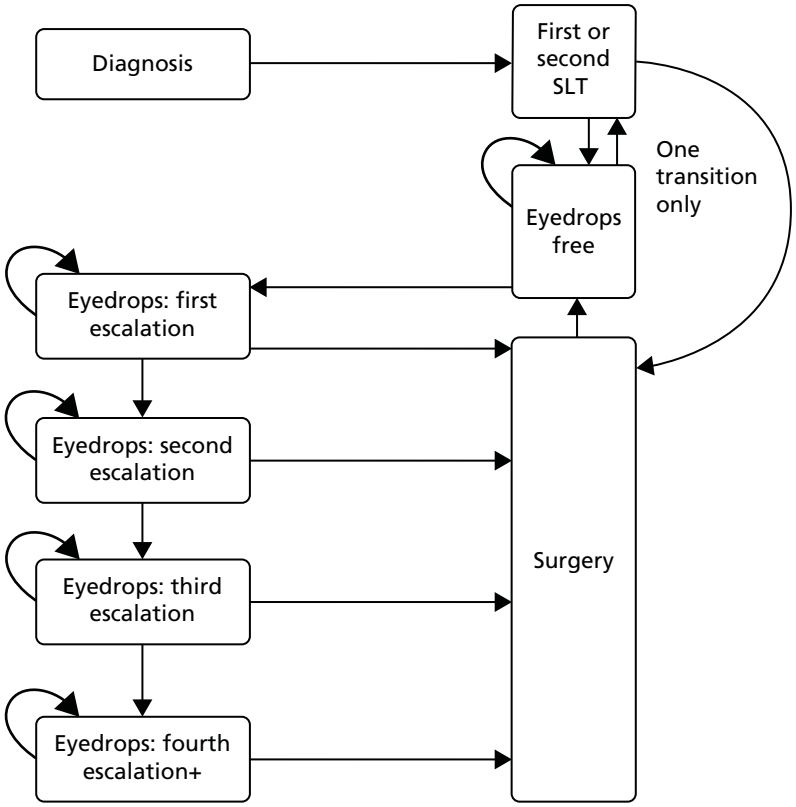

FIGURE 8 Laser-1st treatment pathway.

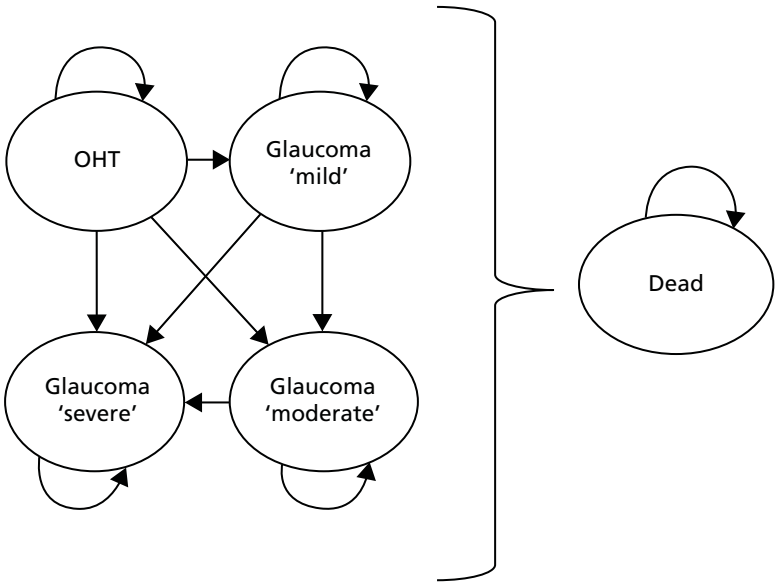

FIGURE 9 Markov model structure.

Eyedrops treatment

The cost of eyedrops was calculated as the average for patients who received their first, second, third and fourth escalation of treatment by eyedrops. The fourth escalation group was inclusive of subsequent lines of medical therapy.

Time-to-eyedrops analysis

The proportion of people moving into each of the eyedrops escalations was based on the number of changes made to patients' eyedrops medication over the 3 years of the trial by trial arm. The same methodology for calculating cycle-specific transition probabilities, as described in *Markov model structure*, was used.

Time-to-surgery analysis

We conducted a survival analysis with Weibull distribution to calculate the probability of surgery in each cycle by trial arm. The Weibull model was calculated and applied in the model using the methodology in Briggs *et al.*,[79] to extrapolate beyond the time horizon of the trial.

Literature search

A literature search was undertaken to identify previous economic evaluations with modelling components in OHT and glaucoma, and epidemiological studies of utility scores, costs or disease progression in OHT and glaucoma. We searched the following databases: York Centre for Reviews and Dissemination database, cost-effectiveness registry, The Cochrane Library and MEDLINE. Search terms relating to costs, utility tariffs, QALYs and glaucoma were used.

Population

Patients with a diagnosis of OAG or OHT with a decision to treat made by a consultant glaucoma specialist. The age, sex, ethnicity and socioeconomic deprivation of patients was assumed to be the same as the patients enrolled in the LiGHT trial.

Intervention and comparator

Intervention

Initial treatment with SLT: Laser-1st.

Comparator

Current standard initial treatment with topical medication alone: Medicine-1st.

Perspective

Costs were from the perspectives of NHS England and Personal and Social Services (PSS).

Time horizon

The time horizon for the model was the lifetime (maximum 30 years) for a hypothetical cohort of patients distributed across age bands in line with the trial population. All costs and QALYs were discounted by 3.5%, in line with NICE guidance.[76]

Cycle length

The cycle length in the model was 6 months. The cycle length specifies the time interval at which the cohort can change health state.

Health states

Health states in the model were used to allocate costs and consequences as a result of various events. Events within a state were assumed to happen at the start of the 6-month cycle and, hence, costs and

consequences for the period were calculated from the first time that the patient entered a state. There were five health states in the model as follows:

1. OHT
2. glaucoma 'mild'
3. glaucoma 'moderate'
4. glaucoma 'severe'
5. death.

The health states in the model are displayed in *Figure 1*. The mild, moderate and severe glaucoma health states and OHT were defined in accordance with the structured protocols applied (see *Table 1*). The definitions were based on the Canadian IOP guidelines.[69] The definition of health states from any costs and QALYs assigned from the literature was carefully compared with the health state definitions used in the trial for suitability. In particular, the 'severe' state as defined in the trial was likely to be less severe than in other trials because of the nature of the recruitment selection process, as a result of which patients with more severe disease were not considered suitable for the study.

Death was an absorbing state in the model, meaning that any individual can move into this state from any other state within the model. Once a patient entered the death state in the model, no costs or utilities were applied.

Costs

Individual costs included in the model were as follows:

- Cost of SLT: the mean cost per patient of SLT in the Laser-1st arm was £151 per SLT based on the figure reported in the trial-based health economic evaluation (see *Cost-effectiveness analysis*).
- Cost of trabeculectomy: the cost of trabeculectomy was taken from NHS reference costs 2016/17[90] and as a day-case cost.
- Cost of eyedrops: the cost of eyedrops was calculated using trial data and the average cost per patient at each eyedrop change.
- Health state costs: health-care costs were calculated as the average 36 months' health and social costs for patients with OHT or one of the three OAG health states at 36 months and by trial arm. They included all costs, excluding SLT, eyedrops and surgery (trabeculectomy). They included the cost of ophthalmology appointments, including IOP checks.

Quality-adjusted life-years

Quality-adjusted life-years for each health state were calculated based on patients' OHT and OAG severity at 35 months and the mean GUI[61] for those patients by trial arm. Utility values collected using the EQ-5D-5L were applied in the sensitivity analysis.

Cost-effectiveness analysis

We calculated the total costs and QALYs for patients with OAG and OHT treated by Laser-1st compared with Medicine-1st.

The ICER was calculated as the ratio of the difference in total cost for a patient over a lifetime for the intervention and the comparator, and the difference in total QALYs for a patient over a lifetime for the treatment and the comparator:[79]

$$\text{ICER} = (\text{Total cost}_{\text{intervention}} - \text{Total cost}_{\text{comparator}}) / (\text{QALY}_{\text{intervention}} - \text{QALY}_{\text{comparator}}). \quad (1)$$

All future benefits (QALYs) and costs were discounted in line with NICE guidance[76] to capture time preferences for costs and benefits.

Sensitivity analysis

We undertook deterministic (one-way, two-way and multiway) analyses and a PSA, the latter assuming appropriate distributions and parameter values.[79] The values from the PSA were used to construct a CEAC, which showed a probability that Laser 1st is cost-effective compared with Medicine-1st over the full lifetime of patients, for a range of values of the NHS's willingness to pay for an additional QALY.

Probabilistic sensitivity analysis and cost-effectiveness acceptability curve

We conducted a full PSA to generate a CEAC and calculate the probability that a given option was cost-effective compared with a range of prestated comparators based on 1000 iterations of the model. All values in the model were assigned appropriate distributions and parameter values.[79]

Deterministic

We varied input variables, either individually or in combination, whereas other variables are held at their baseline value.

Results

Inputs for model

The inputs for the model are reported in *Table 21*. There was a significant reduction in the rate of surgery in the Laser-1st arm compared with the Medicine-1st arm (hazard ratio 0.156, 95% CI 0.046 to 0.527).

TABLE 21 Inputs for model: 1-year values

Variable	Mean	SE	Distribution	Source
Age at time 0	63			
Patients OHT at time 0 (%)	30			
Patients mild at time 0 (%)	49			
Patients moderate at time 0 (%)	15			
Patients severe at time 0 (%)	6			
Transition probabilities variables (1 year) *Laser-1st*				
OHT to mild	0.07	0.04	Beta	
OHT to moderate	0.04	0.04	Beta	
OHT to severe	0.02	0.02	Beta	
Mild to moderate	0.08	0.04	Beta	
Mild to severe	0.04	0.03	Beta	
Moderate to severe	0.22	0.12	Beta	
Second SLT	0.10	0.03	Beta	
Medicine free to first-line medicine	0.07	0.02	Beta	
First- to second-line medicine	0.17	0.06	Beta	
Second- to third-line medicine	0.05	0.04	Beta	
Third- to fourth-line medicine	0.01	0.02	Beta	

TABLE 21 Inputs for model: 1-year values (*continued*)

Variable	Mean	SE	Distribution	Source
Medicine-1st				
1-year probability of OHT to mild	0.10	0.05	Beta	
1-year probability of OHT to moderate	0.03	0.03	Beta	
1-year probability of OHT to severe	0.01	0.02	Beta	
1-year probability of mild to moderate	0.07	0.04	Beta	
1-year probability of mild to severe	0.06	0.03	Beta	
1-year probability of moderate to severe	0.17	0.13	Beta	
First- to second-line medicine	0.15	0.03	Beta	
Second- to third-line medicine	0.07	0.02	Beta	
Third- to fourth-line medicine	0.03	0.02	Beta	
Medicine free after surgery to first-line medicine	0.15	0.03	Beta	
Time to surgery (3-month rates)				
Laser-1st	–1.86	0.62	LogNormal	
Constant	–10.88	1.61	LogNormal	
Gamma	2.85	0.57	LogNormal	
Resource cost (per year)				
Laser-1st OHT	£1087	824	Gamma	
Laser-1st mild	£798	217	Gamma	
Laser-1st moderate	£1162	598	Gamma	
Laser-1st severe	£1109	637	Gamma	
Medicine-1st OHT	£772	283	Gamma	
Medicine-1st mild	£874	197	Gamma	
Medicine-1st moderate	£1072	422	Gamma	
Medicine-1st severe	£1500	744	Gamma	
Cost of medicine first line	£152	50	Gamma	
Cost of medicine second line	£159	70	Gamma	
Cost of medicine third line	£179	74	Gamma	
Cost of medicine fourth line	£180	74	Gamma	
Surgery	£1454	299	Gamma	*NHS Reference Costs 2016–17*[90]
Utility of Markov states per cycle				
Laser-1st OHT	0.9034	0.02	Beta	
Laser-1st mild	0.905	0.013	Beta	
Laser-1st moderate	0.8622	0.021	Beta	
Laser-1st severe	0.88	0.023	Beta	
Medicine-1st OHT	0.8934	0.022	Beta	
Medicine-1st mild	0.9085	0.011	Beta	
Medicine-1st moderate	0.8762	0.02497	Beta	
Medicine-1st severe	0.8455	0.0206	Beta	

Literature search

A total of 1506 papers were identified as part of the literature search. Thirty-four papers[45,46,48,50,52–54,73,95–120] were identified as being relevant to the model, and included information on transition probabilities, utilities and costs. Overall, data from the trial fit better with the model than data that could be extracted from the 34 papers identified to be relevant. The best utility scores were those from the trial because we were able to derive trial-arm specific utilities and from the GUI. The values were similar to values published elsewhere in the literature; for example, Hernández *et al.*[103] reported utilities of 0.8015, 0.8015, 0.7471 and 0.7133 for OHT and mild, moderate and severe glaucoma, respectively. Stein *et al.*[95] reported values of 0.92, 0.89 and 0.86 for mild, moderate and severe glaucoma, respectively. The values reported in Hernández *et al.*[103] were used in a sensitivity analysis for the model.

Cost-effectiveness analysis

The average lifetime cost for Laser-1st based on 1000 runs of the PSA was £17,541 per patient, with an average cost per patient of £20,435 for the Medicine-1st arm and a difference of –£2894. Laser-1st resulted in an average QALY of 12.5 over the lifetime time horizon, compared with 12.3 for Medicine-1st (difference of 0.2 QALYs). Laser-1st dominated Medicine-1st in that it was cost saving and resulted in additional QALYs.

There was a 90% probability that Laser-1st is cost-effective compared with medication at a willingness to pay £20,000 for a QALY (*Figure 10*).

Sensitivity analysis

If the utility health state values were substituted for those from Hernández *et al.*,[103] there was no difference in QALYs between the two groups (an average of 10.6 QALYs per patient over the lifetime time horizon).

Conclusion

When costs, outcomes and surgery rates were projected to a lifetime time horizon, there was a 90% probability that Laser-1st is cost-effective. This is similar to the findings of trial-based analysis, strengthening the finding that Laser-1st is cost saving compared with Medicine-1st.

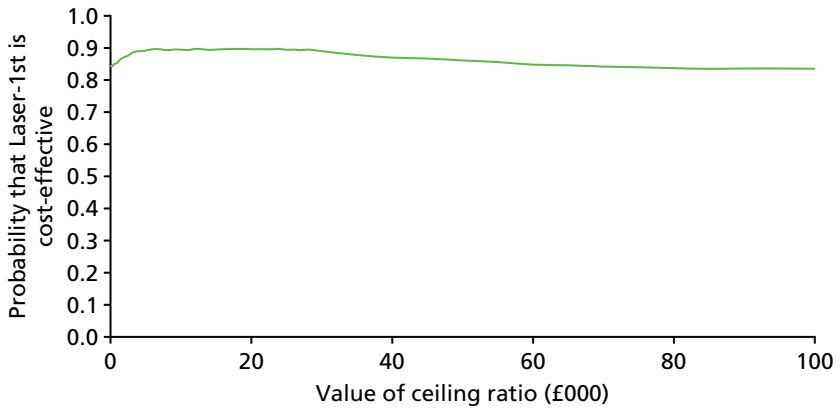

FIGURE 10 Cost-effectiveness acceptability curve: probability that Laser-1st is cost-effective for a range of values of willingness to pay for a QALY.

Chapter 5 Discussion and conclusions

Summary of findings

This multicentre randomised controlled trial compared initial treatment of OAG or OHT using SLT followed by medication, if required, with the use of IOP-lowering medication alone. Patient HRQoL, clinical efficacy and cost-effectiveness were investigated in six NHS settings in the UK. The study demonstrates that initial SLT is cost-effective, with better clinical outcomes and a trend towards better HRQoL compared with the prescription of IOP-lowering eyedrops from the outset.

Quality of life

The Laser-1st and Medicine-1st treatment arms showed comparable EQ-5D-5L scores at the trial's end point, at 36 months. 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. Indeed, VA, VF MD and VF pattern SD were comparable between the two treatment arms at 36 months (see *Table 9*), and this was reflected in similar EQ-5D-5L scores between the two pathways (see *Table 8*). The above average baseline HRQoL,[82,121–123] weak sensitivity of the EQ-5D-5L to detect glaucoma-specific effects on HRQoL[82,123,124] and relatively short duration of this trial, compared with the time for disease progression, may have contributed to the lack of superiority of the EQ-5D-5L in the Laser-1st approach. Recent data on patient self-reported outcome measures (including EQ-5D-5L) now confirm that these may not be sensitive enough to function as primary end points in clinical trials.[125]

Glaucoma-specific instruments (e.g. GUI and GQL-15) are better at capturing differences in glaucoma severity than the effect of treatment side effects on patients' HRQoL. Indeed, the QoL of patients with glaucoma has been related to the extent of VF loss when using the GQL-15.[8,121,126,127] The GUI attributes less weight to local side effects and provides generic health outcome measures and measures of glaucoma severity.[61] The lack of a significant difference in the GUI and GQL-15 in this study was, therefore, somewhat expected; each eye was treated to target and stringent controls over disease progression minimised any substantial differences in disease severity.

The GSS evaluates a visual and an ocular comfort-related domain. The six non-visual ophthalmic symptoms are formed around an ocular comfort domain (burning/smarting/stinging, tearing, dryness, itching, soreness/tiredness and a feeling of something in the eye), and are related to treatment side effects and their measures. The patients were asked to rate their difficulties around blurry/dim vision, hard to see in daylight, hard to see in dark places and haloes around lights, in relation to the four visual ophthalmic symptoms. The GSS has been shown to correlate well with traditional measures of visual function (such as VA and VF),[62] which in this study's end point were comparable between the two treatment arms. Repeated-measures analysis showed 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. Better GSS scores for the Laser-1st arm may represent differences that arise from eyedrop use (64.6% of the patients in the Medication-1st arm were using only one drop per day) (see *Table 11*), but potentially reflect differences in baseline scores between the two treatment arms (83.3 for the Medicine-1st arm and 81.4 for the Laser 1st arm) (see *Table 7*).

Clinical efficacy

The treatments were equally effective in lowering IOP and reaching the target IOP for the first time, with 89.6% of the Medicine-1st eyes reaching target at the first planned follow-up visit, compared with 91.0%

of the Laser-1st eyes (see *Table 10*). By 3 years, however, 95% of the Laser-1st eyes were at target IOP, compared with 93.1% of the eyes treated with Medicine-1st. Although Medicine-1st provided more eyes at target IOP at 12 months (96.2% for Medicine-1st compared with 94.7% for Laser-1st) (see *Table 10*), Laser-1st achieved more eyes at target IOP over the second and the third years of treatment. Interestingly, the percentage of eyes with severe OAG that were at target IOP after the second and third years of treatment was higher in the Medicine-1st arm than in the Laser-1st arm (89.5% compared with 87.5%, respectively, at 24 months and 85.7% compared with 84.6%, respectively at 36 months); the proportions of severe OAG eyes achieving IOP target at 12 months were comparable (91.3% and 91.5%, respectively). A possible explanation may be the limit to which SLT may reduce IOP; severe OAG is likely to have low IOP targets, which may be easier to achieve with more than one medication. A number of studies have reported that SLT reduces IOP by 15–32%,[128–134] and another study found a reduction of up to 29.4% at 6 months, up to 30% at 12 months, up to 27.8% at 2 years and up to 25.1% at 3 years.[135]

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. IOP control with topical medication (eyedrops) may rely on patient concordance with treatment; indeed, one report[94] found that IOP-lowering eyedrops were available to patients for only 69% of the time, whereas concordance has been reported to range between 76% and 86%. More discouraging figures have been reported for patients on multiple eyedrops.[136,137] In this trial, however, self-reported concordance was very high, with patients' concordance reportedly improving during the 36 months of treatment (see *Tables 16* and *17*). SLT has also been proposed to provide better diurnal IOP stability, because of its continuous effect on the trabecular meshwork, in contrast to the episodic administration of medication.[138–141] This trial showed a comparable IOP fluctuation between Medicine-1st and Laser-1st (2.5 mmHg and 2.3 mmHg, respectively).

By 36 months, 78.2% (95% CI 74.7% to 81.4%) of the eyes treated with Laser-1st were at target without the need for any topical IOP-lowering medication (eyedrops). In comparison, in 64.6% of eyes treated with Medicine-1st only a single eyedrop was necessary to control IOP. Primary SLT gave eyedrop-free IOP control for at least 36 months to 74.2% of patients (95% CI 69.3% to 78.6%), substantially higher than reported in previous studies that used less stringent success criteria and which used SLT exclusively as the primary treatment.[37,142–144] Prior treatment and more severe disease have been suggested to reduce the magnitude of IOP lowering with SLT,[37,38,142–144] possibly explaining the results of this trial in treatment-naive patients. Pre-trial activities with glaucoma patients (LAG) identified eyedrop-free disease control as the most desired outcome, with 90% of a patient focus group feeling that even unilateral eyedrop freedom is beneficial. Concerns about eyedrop use, particularly associated with challenges from cognitive and physical impairment, were rated as a priority by patients in the James Lind Alliance survey of sight loss research questions.[145]

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 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) (see *Table 12*). Additionally, there were more treatment escalations over 36 months in the Medicine-1st arm (348, compared with 299 in the Laser-1st arm).

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. By 36 months, 11 eyes in the Medicine-1st arm, but none in the Laser-1st arm, had required IOP-lowering surgery.

Safety

This trial demonstrates a greater safety of SLT than previously reported, with low rates of SLT-related AEs.[143] Rates of systemic AEs were balanced between the two treatment arms, indicating a safe treatment

pathway for both Medicine-1st and Laser-1st (i.e. no excess cardiac or pulmonary events in the Medicine-1st arm and no systemic AEs as a result of SLT) (see *Tables 13* and *14*). Differences in the rates of cancer diagnoses and deaths between the two treatment arms (see *Table 14*) are attributable to chance, with no medical link between the treatments that were administered and the events that took place.

Eyedrop-related systemic and ophthalmic AEs were reported by more patients and more often in the Medicine-1st arm (see *Table 13*). Ophthalmic AEs led to a change in treatment for 11.3% of the patients treated with Medicine-1st, when IOP was otherwise well controlled.

Selective laser trabeculoplasty resulted in at least one transient AE in 34.4% of the patients treated with Laser-1st. Out of 776 SLT procedures, one patient developed an IOP spike requiring treatment, compared with reported rates of up to 28.8%, possibly because treatment was administered at an earlier stage of disease in this trial.[143] The IOP check conventionally done 2 weeks after SLT did not change management for any of the patients and consequently appears unnecessary.

The ocular comorbidities developed during the trial spanned a range of conditions commonly seen in patients of the age group of this cohort (retinal vascular occlusions, diabetic retinopathy, retinal tears and detachments, macular degeneration, etc.) (see *Table 15*). The rate of cataract surgery was lower in the Laser-1st arm (13 eyes in the Laser-1st arm, compared with 25 eyes in the Medicine-1st arm) (see *Table 15*), supporting existing evidence that IOP-lowering eyedrops are associated with a greater incidence of nuclear cataract and earlier need for surgical removal.[12,59,146–148]

Economic evaluation

The Laser-1st approach resulted in a significant reduction in the cost of surgery and IOP-lowering medication, with an overall cost saving to the NHS of £451 per patient in specialist ophthalmology costs. The trial-based economic evaluation found that there is a 97% probability that SLT is a cost-effective treatment for OAG and OHT at a £20,000 willingness to pay for a QALY, from an ophthalmology cost perspective. Resource use information was collected from patient files and trial monitoring data and hence is likely to be complete, with limited bias as a result of loss to follow-up or missing data. Including non-eye-related health-care costs alongside ophthalmology costs, the average cost per patient for Laser-1st remained less than that for Medicine-1st, but the differences between the two groups were not significant, with the wide CIs resulting in a 68% probability that Laser-1st is cost-effective compared with Medicine-1st. Non-ocular health-care cost data were, however, based on self-reported health-care resource use and may be unreliable or incomplete. Expensive systemic AEs unrelated to OHT or OAG, such as cancer, may have also skewed the cost results. In the health economic decision model, in which costs and utilities are projected for the lifetime of patients, there is a 90% probability that Laser-1st is cost-effective compared with Medicine-1st at a willingness to pay £20,000 for a QALY health-care cost perspective, with an average cost saving per patient to the NHS of £2894.

Previous economic assessments have attempted to estimate the relative costs of SLT using only economic modelling or estimates of the treatment costs, instead of a direct cost assessment plus modelling.[50,51,53] Compared with mono or multiple drug therapy, and allowing for repetition of SLT within 2–3 years, cost savings have been predicted at 6 years for a Canadian health-care system.[46] The present study, conducted in a NHS setting following pragmatic clinical approaches for the treatment of OAG/OHT, indicates that SLT is cost-effective over a 3-year period and is likely to remain cost-effective over the lifetime of the patients. These findings have important implications for patients and health-care systems. Patients are concerned about the use of IOP-lowering eyedrops,[145] and widespread uptake of the Laser-1st strategy would lead to an eyedrop-free interval of at least 36 months for three-quarters of patients, while also providing savings for the NHS. If necessary, additional SLT may further increase the duration of this eyedrop-free window. Patients with OAG have an average life expectancy from diagnosis of 9–13 years,[149–151] and so an eyedrop-free period of ≥ 3 years may significant increase the quality of their remaining life. The requirement for

intense medical or surgical regimes may be deferred or completely averted by SLT and potentially with improved surgical success rates and still lower cost.[31,33,34]

The health economic decision model has some limitations. First, the mortality rate used is not glaucoma specific. Rather, the same all-cause mortality rate was applied across all health states. This is a reasonable assumption given that studies have not found a difference in all-cause mortality rates between patients with and without glaucoma.[149] There is, however, an increased risk of cardiovascular disease in older patients (aged > 75 years), which was not incorporated into the model. This is unlikely to have made a significant impact on the results of the model, given the small difference in OAG progression between the two arms.

The lifetime economic model originally set out to include variables from other studies in the literature, including costs, utilities and disease progression. As noted in other studies that have modelled the progression of OAG, there is heterogeneity in how OHT and OAG are defined, making it difficult to incorporate such values into glaucoma models.[73] Burr *et al.*[73] conducted a systematic review of studies for glaucoma progression and identified 1-year progression probabilities for mild to moderate glaucoma, moderate to severe glaucoma and severe glaucoma to visually impaired. The progression values for the two health states that overlap with our model for Medicine-1st patients are different from those observed in the LiGHT trial; higher for mild to moderate progression (0.2 in Burr *et al.*[73] vs. 0.07 in the LiGHT trial) and lower for moderate to severe progression (0.07 in Burr *et al.*[73] vs. 0.17 in the LiGHT trial). This difference is likely to be a result of differences in the populations used to determine transitions probabilities, as the values for Burr *et al.*[73] are from observational studies of people at different stages of OAG, whereas the LiGHT trial recruited patients newly diagnosed with OHT or OAG. It may also be as a result of differences in how the various stages are defined, with Burr *et al.*[73] restricting the definition to mean definition score only, omitting an OHT health state and including an additional visual impairment state. Costs were also more suitably obtained from the trial or NHS reference costs[90] given that most studies report costs for medication for OHT and OAG health states, or the costs for eyedrops progression, ophthalmology appointments and trabeculectomy (glaucoma surgery) only.[77] Our model is novel, in that we were able to project medication and trabeculectomy costs over the lifetime of patients while modelling the health-care costs associated with OHT and OAG health states separately, using LiGHT trial data. As discussed, our utility values for health states are similar to those quoted in other studies;[73,95,103] modifying these has limited impact on the results, particularly as using published data means that we are unable to use utilities specific to trial arms.

Strengths and limitations

This study mirrored pragmatic clinical practice by tailoring treatment to the patient. Individual IOP targets were based on pre-treatment IOP and disease severity, and adapted both to treatment response and to progression of the disease. Consequently, the concluding findings on disease progression, achievement of target IOP and cost are highly relevant to normal clinical practice. 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.

This trial was unmasked. An unmasked design was essential to capture any treatment effects on patients' perception, which is clinical reality. As an important benefit of SLT is an eyedrop-free treatment window; a study design requiring a treatment arm with placebo eyedrops would have prevented assessment of benefits attributable to IOP control without the use of medication. The impact of treatment on subsequent medication-taking behaviours and concordance was also of interest and will be fully revealed in the extension of this trial. Similarly, treating clinicians had to be unmasked to be able to choose appropriate treatment escalations.

The EQ-5D-5L questionnaire, a generic tool eliciting utility values in multiple settings, may not have been the most sensitive tool to investigate HRQoL in the two treatment arms for a 3-year trial, but is a requirement for a NICE cost–utility analysis. OAG can be asymptomatic, even at levels sufficient to make driving unsafe.[152] 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.

Chapter 6 Conclusions

In summary, this trial shows that treating newly diagnosed OAG and OHT patients with SLT can safely provide predominantly eyedrop-free IOP control over a minimum of 3 years, with less intense treatment, fewer AEs and a reduced need for ocular surgery at a lower cost per QALY than standard medical therapy alone, with a similar effect on patients' generic HRQoL.

Implications for health care

The results of this randomised controlled trial are widely generalisable, as patients with OHT and both low- and high-pressure OAG were included, from a range of backgrounds and ethnic origins. This trial focused on newly diagnosed, treatment-naive patients with OHT and/or mild or moderate OAG; the results should, therefore, be interpreted with caution in relation to the efficacy of SLT in advanced OAG stages, or in eyes previously treated for high IOP. There are important implications for resource-poor health-care settings, where access to medication is a major barrier to glaucoma treatment. Adequate eyedrop-free IOP control for years after is a promising treatment paradigm for regions of Africa where glaucoma prevalence is high. Longer follow-up, already under way, will permit us to answer further questions regarding the effect of prior SLT on later medication-taking behaviour, treatment intensity and longitudinal HRQoL.

The data support a change in practice; however, clinicians need to consider the perceived necessity of monitoring visits by the patient, in the absence of daily medication, as has been suggested by in the past for other chronic illnesses.[153] Primary SLT is a safe, clinically efficient and cost-effective alternative to eyedrops that can be offered as a first-line treatment to patients with OAG or OHT, in need of IOP reduction.

Recommendations for research

This study addresses the initial 36-month period after initiation of treatment for OAG and/or OHT. OAG and OHT are chronic conditions and treatment is almost always lifelong. Longitudinal research into the clinical efficacy of SLT as a first-line treatment could specify the long-term differences (if any) of disease progression, treatment intensity and ocular surgery rates between a Laser-1st and a Medicine-1st pathway, as well as any effect on subsequent medication-taking behaviours. Longitudinal HRQoL in OAG and OHT will also help clinicians understand the impact medical treatment has on patients over a longer period of time, where more intense medical treatment might become necessary.

Acknowledgements

We are thankful to all the patients who participated in this trial. Our particular recognitions and remembrances are for Dominic Carrington (MEH research technician), who sadly and suddenly passed away shortly before the completion of the study.

Members of the Trial Steering Committee

Independent chairperson: Professor John Sparrow, Honorary Professor, University of Bristol.

Chief investigator: Mr Gus Gazzard, Consultant Ophthalmic Surgeon, MEH.

Trial manager: Dr Amanda Davis, MEH.

Independent clinician with relevant expertise: Professor James Morgan, Professor of Ophthalmology, Cardiff University.

Independent statistician: Dr Marta (Garcia-Finana) Van der Hoek, Reader in Biostatistics, University of Liverpool.

Lead statistician: Dr Gareth Ambler, Senior lecturer in Medical Statistics, University College London.

Patient and public involvement representative: Ms Shelia Page, expert patient.

Independent members of the Data Monitoring Committee

Independent statistician: Professor Chris Rogers, Professor of Medical Statistics and Clinical Trials, University of Bristol.

Independent clinician: Mr John Salmon, Consultant Ophthalmologist, Oxford Eye Hospital.

Independent triallist: Professor Caroline Free, Professor of Primary Care and Epidemiology, London School of Hygiene and Tropical Medicine.

Project management group

Mr Gus Gazzard was the chief investigator of the trial; Dr Amanda Davis was the CTM of the trial (with temporary covers from Ms Ayse Barnes and Ms Danielle Reid); Mr Neil Nathwani was the trial's CTO; Dr Evgenia Konstantakopoulou was the trial's CRO; Dr Gareth Ambler was the lead trial statistician; Ms Victoria Vickerstaff was the trial statistician; and Ms Taniya Chowdhury was the trial data officer.

Staff facilitating recruitment and data collection

Moorfields Eye Hospital: Ms Emily Dowse, Ms Karine Girard-Claudon, Ms Seetal Savania-Dholakia and Ms Gurveen Panesar (optometrists); Mr Emerson Tingco, Ms Kanom Bibi, Mr Charles Amoah, Mr Dominic Carrington, Mr Mohamed Illiyas and Mr Yoganand Jeetun (technicians); and Ms Taniya Chowdhury, Ms Varshini Parayoganathan and Ms Nana Fatimah Ogunfemi (data officers).

Guy's and St' Thomas' Hospital: Mr Sheng Lim (local PI); Mr Arij Daas, Ms Panayiota Founti and Mr Pouya Alaghband (research fellows); and Ms Priya Morjaria, Mr Andrew Ho, Ms Jenny Lee, Mr Kishan Patel, Mr Sandip Patel and Ms Seema Rajoria (optometrists).

Royal Victoria Hospital Belfast: Ms Sarah Wilson (local PI); Ms Karen Gillvray and Ms Angela Knox (research fellows); and Ms Tricia Douglas, Ms Katie Graham and Ms Deirdre Burns (optometrists).

Hinchingbrooke Hospital: Professor Rupert Bourne (local PI); and Ms Jane Kean (optometrists).

York Hospital: Mr Timothy Manners (local PI); and Ms Archana Airody (research fellow).

Norfolk and Norwich University Hospital: Mr David Broadway (local PI); and Mr Nuwan Niyadurupola (research fellow).

Contributions of authors

Gus Gazzard (Chief Investigator, Consultant Ophthalmic Surgeon) led the initial conception and design of the trial and writing of the protocol, acquired funding and ethics approval, is the chief investigator, had complete involvement and oversight of the trial, provided clinical expertise and was a major contributor to writing the manuscript.

Evgenia Konstantakopoulou (Research Optometrist) was involved in the day-to-day running of the trial, data collection and data interpretation, wrote the manuscript together with Gus Gazzard and was responsible for the production of the final report.

David Garway-Heath (Professor of Ophthalmology) co-designed the trial and the trial protocol, provided expert advice on clinical and methodological aspects and was involved in the drafting and critical revision of the manuscript.

Anurag Garg (Research Fellow) was involved in the acquisition of the data, data analysis and interpretation, contributed to the writing of *Chapter 3* and critically reviewed the manuscript.

Victoria Vickerstaff (Senior Research Fellow) was involved in the design of the statistical analysis plan and the writing of the relevant paper, the data analysis, wrote parts of *Chapter 2*, provided guidance on the writing of *Chapter 3* and critically reviewed the manuscript.

Rachael Hunter (Associate Professor Health Economics) contributed to the design of the outcome measures and data collection as well as the health economics analysis, wrote *Chapter 4* and parts of *Chapter 3*.

Gareth Ambler (Associate Professor) was involved in the design of the statistical analysis plan and the writing of the relevant paper, contributed to the design of the outcome measures, the data to be collected and the data analysis, and was involved in the critical revision of the manuscript.

Catey Bunce (Reader Medical Statistics) contributed to the design of the outcome measures and the data to be collected, provided expert advice on statistical and methodological aspects of the trial and was involved in the critical revision of the manuscript.

Richard Wormald (Consultant Ophthalmologist) was involved in the critical revision of the study design and protocol, provided expert advice on clinical and methodological aspects of the trial and was involved in the critical revision of the manuscript.

Neil Nathwani (Research Optometrist) was involved in the design of the trial, data collection, data interpretation and critical revision of the manuscript. He was responsible for the clinical running of the trial in the central site.

Keith Barton (Consultant Ophthalmologist) was involved in the drafting of the protocol and critical revision of the study design and manuscript, and provided clinical expertise.

Gary Rubin (Professor of Ophthalmology) was involved in the drafting of the study design, provided expert advice on clinical and methodological aspects of the trial, and was involved in the critical revision of the manuscript.

Stephen Morris (Professor Health Economics) contributed to the design of the outcome measures and the data to be collected, and the critical revision of the manuscript.

Marta Buszewicz (Associate Professor in Primary Care) contributed to the original trial design, provided methodological guidance and was involved in the critical revision of the manuscript.

Publications

Vickerstaff V, Ambler G, Bunce C, Xing W, Gazzard G, LiGHT Trial Study Group. 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. https://doi.org/10.1186/s13063-015-1047-9

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. *Br J Ophthalmol* 2018;**102**:593–8. https://doi.org/10.1136/bjophthalmol-2017-310877

Konstantakopoulou E, Gazzard G, Vickerstaff V, Jiang Y, Nathwani N, Hunter R, *et al.* The laser in glaucoma and ocular hypertension (LiGHT) trial. A multicentre randomised controlled trial: baseline patient characteristics. *Br J Ophthalmol* 2018;**102**:599–603. https://doi.org/10.1136/bjophthalmol-2017-310870

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;**393**:1505–16.

Data-sharing statement

All available data can be obtained from the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data are vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives. More about the background to this citation can be found here: https://understandingpatientdata.org.uk/data-citation.

References

1. Baasanhu J, Johnson GJ, Burendei G, Minassian DC. Prevalence and causes of blindness and visual impairment in Mongolia: a survey of populations aged 40 years and older. *Bull World Health Organ* 1994;**72**:771–6.
2. Bunce C, Wormald R. Leading causes of certification for blindness and partial sight in England & Wales. *BMC Public Health* 2006;**6**:58. https://doi.org/10.1186/1471-2458-6-58
3. Haymes SA, Leblanc RP, Nicolela MT, Chiasson LA, Chauhan BC. Risk of falls and motor vehicle collisions in glaucoma. *Invest Ophthalmol Vis Sci* 2007;**48**:1149–55. https://doi.org/10.1167/iovs.06-0886
4. Haymes SA, LeBlanc RP, Nicolela MT, Chiasson LA, Chauhan BC. Glaucoma and on-road driving performance. *Invest Ophthalmol Vis Sci* 2008;**49**:3035–41. https://doi.org/10.1167/iovs.07-1609
5. Parrish RK, Gedde SJ, Scott IU, Feuer WJ, Schiffman JC, Mangione CM, Montenegro-Piniella A. Visual function and quality of life among patients with glaucoma. *Arch Ophthalmol* 1997;**115**:1447–55. https://doi.org/10.1001/archopht.1997.01100160617016
6. Nelson P, Aspinall P, O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. *Br J Ophthalmol* 1999;**83**:546–52. https://doi.org/10.1136/bjo.83.5.546
7. Gutierrez P, Wilson MR, Johnson C, Gordon M, Cioffi GA, Ritch R, *et al.* Influence of glaucomatous visual field loss on health-related quality of life. *Arch Ophthalmol* 1997;**115**:777–84. https://doi.org/10.1001/archopht.1997.01100150779014
8. Nelson P, Aspinall P, Papasouliotis O, Worton B, O'Brien C. Quality of life in glaucoma and its relationship with visual function. *J Glaucoma* 2003;**12**:139–50. https://doi.org/10.1097/00061198-200304000-00009
9. Higginbotham EJ, Gordon MO, Beiser JA, Drake MV, Bennett GR, Wilson MR, *et al.* The Ocular Hypertension Treatment Study: topical medication delays or prevents primary open-angle glaucoma in African American individuals. *Arch Ophthalmol* 2004;**122**:813–20. https://doi.org/10.1001/archopht.122.6.813
10. 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. *Arch Ophthalmol* 2002;**120**:701–13. https://doi.org/10.1001/archopht.120.6.701
11. Gordon MO, Kass MA. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol* 1999;**117**:573–83. https://doi.org/10.1001/archopht.117.5.573
12. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002;**120**:1268–79. https://doi.org/10.1001/archopht.120.10.1268
13. 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* 2015;**385**:1295–304. https://doi.org/10.1016/S0140-6736(14)62111-5
14. Ederer F, Gaasterland DA, Dally LG, Kim J, VanVeldhuisen PC, Blackwell B, *et al.* The Advanced Glaucoma Intervention Study (AGIS): 13. Comparison of treatment outcomes within race: 10-year results. *Ophthalmology* 2004;**111**:651–64. https://doi.org/10.1016/j.ophtha.2003.09.025

15. National Institute for Health and Care Excellence. *NICE: Guidance on Glaucoma: Diagnosis and Management of Chronic Open Angle Glaucoma and Ocular Hypertension*. London: NICE; 2010. URL: www.nice.org.uk/CG85fullguideline (accessed 22 August 2018).
16. Royal College of Ophthalmologists. *Focus in Ophthalmology – Glaucoma Management*. URL: www.mrcophth.com/focus1/Glaucoma%20Management.htm (accessed 10 July 2015).
17. National Institute for Health and Care Excellence. *Review of Clinical Guideline (CG85) – Glaucoma: Diagnosis and Management of Chronic Open Angle Glaucoma and Ocular Hypertension: Costing Report*. London: NICE; 2009. URL: www.nice.org.uk/guidance/cg85/documents/glaucoma-review-proposal-consultation-document2 (accessed July 2010).
18. Kirwan JF, Nightingale JA, Bunce C, Wormald R. Beta blockers for glaucoma and excess risk of airways obstruction: population based cohort study. *BMJ* 2002;**325**:1396–7. https://doi.org/10.1136/bmj.325.7377.1396
19. Fukuchi T, Wakai K, Suda K, Nakatsue T, Sawada H, Hara H, *et al.* Incidence, severity and factors related to drug-induced keratoepitheliopathy with glaucoma medications. *Clin Ophthalmol* 2010;**4**:203–9. https://doi.org/10.2147/OPTH.S9716
20. Alm A, Grierson I, Shields MB. Side effects associated with prostaglandin analog therapy. *Surv Ophthalmol* 2008;**53**:S93–105. https://doi.org/10.1016/j.survophthal.2008.08.004
21. 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. *Am J Geriatr Pharmacother* 2003;**1**:75–81. https://doi.org/10.1016/S1543-5946(03)90003-1
22. Sharkawi E, Franks W. Glaucoma and mortality. *Ophthalmology* 2008;**115**:213–14. https://doi.org/10.1016/j.ophtha.2007.03.088
23. Roughead EE, Kalisch LM, Pratt NL, Killer G, Barnard A, Gilbert AL. Managing glaucoma in those with co-morbidity: not as easy as it seems. *Ophthalmic Epidemiol* 2012;**19**:74–82. https://doi.org/10.3109/09286586.2011.638743
24. Nordstrom BL, Friedman DS, Mozaffari E, Quigley HA, Walker AM. Persistence and adherence with topical glaucoma therapy. *Am J Ophthalmol* 2005;**140**:598–606. https://doi.org/10.1016/j.ajo.2005.04.051
25. Tsai JC. Medication adherence in glaucoma: approaches for optimizing patient compliance. *Curr Opin Ophthalmol* 2006;**17**:190–5. https://doi.org/10.1097/01.icu.0000193078.47616.aa
26. Tsai JC. A comprehensive perspective on patient adherence to topical glaucoma therapy. *Ophthalmology* 2009;**116**:30–6. https://doi.org/10.1016/j.ophtha.2009.06.024
27. Rahman MQ, Montgomery DM, Lazaridou MN. Surveillance of glaucoma medical therapy in a Glasgow teaching hospital: 26 years' experience. *Br J Ophthalmol* 2009;**93**:1572–5. https://doi.org/10.1136/bjo.2008.151522
28. 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. *Arch Ophthalmol* 2002;**120**:714–20. https://doi.org/10.1001/archopht.120.6.714
29. Rahman MQ, Abeysinghe SS, Kelly S, Roskell NS, Shannon PR, Abdlseaed AA, Montgomery DM. Persistence of glaucoma medical therapy in the Glasgow Glaucoma Database. *Br J Ophthalmol* 2011;**95**:966–70. https://doi.org/10.1136/bjo.2010.188607
30. Broadway D, Grierson I, Hitchings R. Adverse effects of topical antiglaucomatous medications on the conjunctiva. *Br J Ophthalmol* 1993;**77**:590–6. https://doi.org/10.1136/bjo.77.9.590

31. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile. *Arch Ophthalmol* 1994;**112**:1437–45. https://doi.org/10.1001/archopht.1994.01090230051020

32. Broadway D, Hitchings R, Grierson I. Topical antiglaucomatous therapy: adverse effects on the conjunctiva and implications for filtration surgery. *J Glaucoma* 1995;**4**:136. https://doi.org/10.1097/00061198-199504000-00012

33. Broadway DC, Chang LP. Trabeculectomy, risk factors for failure and the preoperative state of the conjunctiva. *J Glaucoma* 2001;**10**:237–49. https://doi.org/10.1097/00061198-200106000-00017

34. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. *Arch Ophthalmol* 1994;**112**:1446–54. https://doi.org/10.1001/archopht.1994.01090230060021

35. Alvarado JA, Katz LJ, Trivedi S, Shifera AS. Monocyte modulation of aqueous outflow and recruitment to the trabecular meshwork following selective laser trabeculoplasty. *Arch Ophthalmol* 2010;**128**:731–7. https://doi.org/10.1001/archophthalmol.2010.85

36. Kagan DB, Gorfinkel NS, Hutnik CM. Mechanisms of selective laser trabeculoplasty: a review. *Clin Experiment Ophthalmol* 2014;**42**:675–81. https://doi.org/10.1111/ceo.12281

37. McIlraith I, Strasfeld M, Colev G, Hutnik CM. Selective laser trabeculoplasty as initial and adjunctive treatment for open-angle glaucoma. *J Glaucoma* 2006;**15**:124–30. https://doi.org/10.1097/00061198-200604000-00009

38. Nagar M, Ogunyomade A, O'Brart 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. *Br J Ophthalmol* 2005;**89**:1413–17. https://doi.org/10.1136/bjo.2004.052795

39. Khouri AS, Lari HB, Berezina TL, Maltzman B, Fechtner RD. Long term efficacy of repeat selective laser trabeculoplasty. *J Ophthalmic Vis Res* 2014;**9**:444–8. https://doi.org/10.4103/2008-322X.150814

40. 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 Afr J Ophthalmol* 2014;**21**:205–9. https://doi.org/10.4103/0974-9233.134668

41. Avery N, Ang GS, Nicholas S, Wells A. Repeatability of primary selective laser trabeculoplasty in patients with primary open-angle glaucoma. *Int Ophthalmol* 2013;**33**:501–6. https://doi.org/10.1007/s10792-013-9729-3

42. Barton K. Bleb dysesthesia. *J Glaucoma* 2003;**12**:281–4. https://doi.org/10.1097/00061198-200306000-00018

43. Budenz DL, Hoffman K, Zacchei A. Glaucoma filtering bleb dysesthesia. *Am J Ophthalmol* 2001;**131**:626–30. https://doi.org/10.1016/S0002-9394(00)00901-6

44. 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. *Br J Ophthalmol* 2018;**102**:922–8. https://doi.org/10.1136/bjophthalmol-2017-310902

45. Kobelt G, Jönsson L. Modeling cost of treatment with new topical treatments for glaucoma. Results from France and the United Kingdom. *Int J Technol Assess Health Care* 1999;**15**:207–19. https://doi.org/10.1017/S0266462399015299

46. Lee R, Hutnik CM. Projected cost comparison of selective laser trabeculoplasty versus glaucoma medication in the Ontario Health Insurance Plan. *Can J Ophthalmol* 2006;**41**:449–56. https://doi.org/10.1016/S0008-4182(06)80006-2

47. Slade J. *Eye Health Data Summary – A Review of Published Data in England*. Vision UK; 2014.

48. 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. *Arch Ophthalmol* 2006;**124**:12–19. https://doi.org/10.1001/archopht.124.1.12

49. Taylor HR. Glaucoma: where to now? *Ophthalmology* 2009;**116**:821–2. https://doi.org/10.1016/j.ophtha.2009.01.042

50. Dirani M, Crowston JG, Taylor PS, Moore PT, Rogers S, Pezzullo ML, *et al.* Economic impact of primary open-angle glaucoma in Australia. *Clin Experiment Ophthalmol* 2011;**39**:623–32. https://doi.org/10.1111/j.1442-9071.2011.02530.x

51. Seider MI, Keenan JD, Han Y. Cost of selective laser trabeculoplasty vs topical medications for glaucoma. *Arch Ophthalmol* 2012;**130**:529–30. https://doi.org/10.1001/archophthalmol.2012.355

52. Guedes RA, Guedes VM, Gomes CE, Chaoubah A. Maximizing cost-effectiveness by adjusting treatment strategy according to glaucoma severity. *Medicine* 2016;**95**:e5745. https://doi.org/10.1097/MD.0000000000005745

53. 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. *Curr Med Res Opin* 2008;**24**:2905–18. https://doi.org/10.1185/03007990802379996

54. Rolim de Moura C, Paranhos A, Wormald R. Laser trabeculoplasty for open angle glaucoma. *Cochrane Database Syst Rev* 2007;**4**:CD003919. https://doi.org/10.1002/14651858.CD003919.pub2

55. 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. *Br J Ophthalmol* 2018;**102**:593–8. https://doi.org/10.1136/bjophthalmol-2017-310877

56. National Institute for Health Research. *Health-related Quality of Life in Two Treatment Pathways for Newly Diagnosed Open Angle Glaucoma and Ocular Hypertension: An Unmasked, Multi-centre, Randomised Controlled Trial of Initial Selective Laser Trabeculoplasty versus Conventional Medical Therapy*. Southampton: National Institute for Health Research. URL: www.journalslibrary.nihr.ac.uk/programmes/hta/0910440/#/ (accessed 7 May 2019).

57. Leurent B, Gomes M, Faria R, Morris S, Grieve R, Carpenter JR. Sensitivity analysis for not-at-random missing data in trial-based cost-effectiveness analysis: a tutorial. *PharmacoEconomics* 2018;**36**:889–901. https://doi.org/10.1007/s40273-018-0650-5

58. 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. *Lancet* 2019;**393**:1505–16. https://doi.org/10.1016/S0140-6736(18)32213-X

59. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. *Ophthalmology* 1999;**106**:2144–53. https://doi.org/10.1016/S0161-6420(99)90497-9

60. 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). *Qual Life Res* 2011;**20**:1727–36. https://doi.org/10.1007/s11136-011-9903-x

61. Burr JM, Kilonzo M, Vale L, Ryan M. Developing a preference-based Glaucoma Utility Index using a discrete choice experiment. *Optom Vis Sci* 2007;**84**:797–808. https://doi.org/10.1097/OPX.0b013e3181339f30

62. 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**:861–6. https://doi.org/10.1001/archopht.116.7.861

63. 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**:323–7. https://doi.org/10.1093/fampra/cmi027

64. European Glaucoma Society. *Terminology and Guidelines for Glaucoma 3rd Edn*. 2008. URL: www.eugs.org/eng/guidelines.asp (accessed 12 May 2015).

65. American Academy of Ophthalmology. *Primary Open-Angle Glaucoma: Preferred Practice Pattern*. San Francisco, CA: American Academy of Ophthalmology; 2005.

66. South East Asia Gluacoma Interest Group (SEAGIG). *South East Asia Gluacoma Interest Group: Asia Pacific Glaucoma Guidelines*. Hong Kong: SEAGIG; 2003.

67. Medicines and Healthcare products Regulatory Agency (MHRA). *Good Clinical Practice*. London: MHRA; 2010.

68. 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**:4229–36. https://doi.org/10.1167/iovs.08-2955

69. Damji KF, Behki R, Wang L, Target IOP Workshop participants. Canadian perspectives in glaucoma management: setting target intraocular pressure range. *Can J Ophthalmol* 2003;**38**:189–97. https://doi.org/10.1016/S0008-4182(03)80060-1

70. 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**:24–30. https://doi.org/10.1016/j.ajo.2005.07.044

71. Lee JR, Kim S, Lee JY, Back S, Lee KS, Kook MS. Is myopic optic disc appearance a risk factor for rapid progression in medically treated glaucomatous eyes with confirmed visual field progression? *J Glaucoma* 2016;**25**:330–7. https://doi.org/10.1097/ijg.0000000000000218

72. Konstantakopoulou E, Gazzard G, Vickerstaff V, Jiang Y, Nathwani N, Hunter R, *et al.* The laser in glaucoma and ocular hypertension (LiGHT) trial. A multicentre randomised controlled trial: baseline patient characteristics. *Br J Ophthalmol* 2018;**102**:599–603. https://doi.org/10.1136/bjophthalmol-2017-310870

73. Burr JM, Mowatt G, Hernández R, Siddiqui MA, Cook J, Lourenco T, *et al.* The clinical effectiveness and cost-effectiveness of screening for open-angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(41). https://doi.org/10.3310/hta11410

74. Canadian Glaucoma Study Group. Canadian Glaucoma Study: 1. Study design, baseline characteristics, and preliminary analyses. *Can J Ophthalmol* 2006;**41**:566–75. https://doi.org/i06-057

75. Office for National Statistics. *Death Registrations Summary Tables – England and Wales*. Newport: Office for National Statistics; 2016.

76. National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal*. London: NICE; 2008.

77. Traverso CE, Walt JG, Kelly SP, Hommer AH, Bron AM, Denis P, *et al.* Direct costs of glaucoma and severity of the disease: a multinational long term study of resource utilisation in Europe. *Br J Ophthalmol* 2005;**89**:1245–9. https://doi.org/10.1136/bjo.2005.067355

78. Chauhan BC, Hutchison DM, Artes PH, Caprioli J, Jonas JB, LeBlanc RP, *et al.* Optic disc progression in glaucoma: comparison of confocal scanning laser tomography to optic disc photographs in a prospective study. *Invest Ophthalmol Vis Sci* 2009;**50**:1682–91. https://doi.org/10.1167/iovs.08-2457

79. Briggs A, Sculpher M, Claxton K. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press; 2006.

80. Chang DS, Friedman DS, Frazier T, Plyler R, Boland MV. Development and validation of a predictive model for nonadherence with once-daily glaucoma medications. *Ophthalmology* 2013;**120**:1396–402. https://doi.org/10.1016/j.ophtha.2013.01.002

81. Vickerstaff V, Ambler G, King M, Nazareth I, Omar RZ. Are multiple primary outcomes analysed appropriately in randomised controlled trials? A review. *Contemp Clin Trials* 2015;**45**:8–12. https://doi.org/S1551-7144(15)30053-7

82. Aspinall PA, Johnson ZK, Azuara-Blanco A, Montarzino A, Brice R, Vickers A. Evaluation of quality of life and priorities of patients with glaucoma. *Invest Ophthalmol Vis Sci* 2008;**49**:1907–15. https://doi.org/10.1167/iovs.07-0559

83. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. *Stat Med* 1997;**16**:2349–80. https://doi.org/10.1002/(SICI)1097-0258(19971030)16:20<2349::AID-SIM667>3.0.CO;2-E

84. Hunter RM, Baio G, Butt T, Morris S, Round J, Freemantle N. An educational review of the statistical issues in analysing utility data for cost-utility analysis. *PharmacoEconomics* 2015;**33**:355–66. https://doi.org/10.1007/s40273-014-0247-6

85. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5D-5L value set for England. *Health Econ* 2018;**27**:7–22. https://doi.org/10.1002/hec.3564

86. National Institute for Health and Care Excellence. *Guides to the Methods of Technology Appraisal*. London: NICE; 2013. URL: www.nice.org.uk/process/pmg9/chapter/foreword (accessed 7 May 2019).

87. Curtis L. *Unit Costs of Health and Social Care 2017*. Canterbury: PSSRU, University of Kent; 2017.

88. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes: Fourth Edition*. Oxford: Oxford University Press; 2015.

89. Joint Formulary Committee. *British National Formulary (Online)*. London: BMJ Group and Pharmaceutical Press. URL: www.medicinescomplete.com (accessed 15 July 2018).

90. Department of Health and Social Care (DHSC), Finance and Costing Team. *National Schedule of Reference Costs 2016–17*. London: DHSC; 2018.

91. Beecham JK, Knapp MRJ. Costing Psychiatric Interventions. In Thornicroft G, Brewin C, Wing JK, editors. *Measuring Mental Health Needs*. London: Edward Gaskell Publishers; 1992. pp. 200–24.

92. Violato M, Dakin H, Chakravarthy U, Reeves BC, Peto T, Hogg RE, *et al.* Cost-effectiveness of community versus hospital eye service follow-up for patients with quiescent treated age-related macular degeneration alongside the ECHoES randomised trial. *BMJ Open* 2016;**6**:e011121. https://doi.org/10.1136/bmjopen-2016-011121

93. Georghiou T, Bardsley M. *Exploring the Cost of Care at the End of Life*. London: Nuffield Trust; 2014.

94. Schwartz GF, Quigley HA. Adherence and persistence with glaucoma therapy. *Surv Ophthalmol* 2008;**53**:S57–68. https://doi.org/10.1016/j.survophthal.2008.08.002

95. Stein JD, Kim DD, Peck WW, Giannetti SM, Hutton DW. Cost-effectiveness of medications compared with laser trabeculoplasty in patients with newly diagnosed open-angle glaucoma. *Arch Ophthalmol* 2012;**130**:497–505. https://doi.org/10.1001/archophthalmol.2011.2727

96. Rahman MQ, Beard SM, Discombe R, Sharma R, Montgomery DM. Direct healthcare costs of glaucoma treatment. *Br J Ophthalmol* 2013;**97**:720–4. https://doi.org/10.1136/bjophthalmol-2012-302525

97. Holmstrom S, Buchholz P, Walt J, Wickstrom J, Aagren M. The cost-effectiveness of bimatoprost, latanoprost and timolol in treatment of primary open angle glaucoma in five European countries. *Curr Med Res Opin* 2006;**22**:897–905. https://doi.org/10.1185/030079906X104687

98. Crane GJ, Kymes SM, Hiller JE, Casson R, Martin A, Karnon JD. Accounting for costs, QALYs, and capacity constraints: using discrete-event simulation to evaluate alternative service delivery and organizational scenarios for hospital-based glaucoma services. *Med Decis Making* 2013;**33**:986–97. https://doi.org/10.1177/0272989X13478195

99. Li EY, Tham CC, Chi SC, Lam DS. Cost-effectiveness of treating normal tension glaucoma. *Invest Ophthalmol Vis Sci* 2013;**54**:3394–9. https://doi.org/10.1167/iovs.12-11549

100. Stewart WC, Stewart JA, Mychaskiw MA. Cost-effectiveness of latanoprost and timolol maleate for the treatment of glaucoma in Scandinavia and the United Kingdom, using a decision-analytic health economic model. *Eye* 2009;**23**:132–40. https://doi.org/10.1038/sj.eye.6702964

101. van Gestel A, Webers CA, Severens JL, Beckers HJ, Jansonius NM, Hendrikse, *et al.* The long-term outcomes of four alternative treatment strategies for primary open-angle glaucoma. *Acta Ophthalmol* 2012;**90**:20–31. https://doi.org/10.1111/j.1755-3768.2011.02318.x

102. Boodhna T, Crabb DP. More frequent, more costly? Health economic modelling aspects of monitoring glaucoma patients in England. *BMC Health Serv Res* 2016;**16**:611. https://doi.org/10.1186/s12913-016-1849-9

103. Hernandez R, Burr JM, Vale L, Azuara-Blanco A, Cook JA, Banister K, *et al.* Monitoring ocular hypertension, how much and how often? A cost-effectiveness perspective. *Br J Ophthalmol* 2016;**100**:1263–8. https://doi.org/10.1136/bjophthalmol-2015-306757

104. Kaplan RI, De Moraes CG, Cioffi GA, Al-Aswad LA, Blumberg DM. Comparative cost-effectiveness of the baerveldt implant, trabeculectomy with mitomycin, and medical treatment. *JAMA Ophthalmol* 2015;**133**:560–7. https://doi.org/10.1001/jamaophthalmol.2015.44

105. Thomas S, Hodge W, Malvankar-Mehta M. The cost-effectiveness analysis of teleglaucoma screening device. *PLOS ONE* 2015;**10**:e0137913. https://doi.org/10.1371/journal.pone.0137913

106. Xu X, Ma YY, Zou HD. Cost–utility analysis of cataract surgery in advanced glaucoma patients. *J Glaucoma* 2016;**25**:e657–62. https://doi.org/10.1097/IJG.0000000000000313

107. Blumberg DM, Vaswani R, Nong E, Al-Aswad L, Cioffi GA. A comparative effectiveness analysis of visual field outcomes after projected glaucoma screening using SD-OCT in African American communities. *Invest Ophthalmol Vis Sci* 2014;**55**:3491–500. https://doi.org/10.1167/iovs.14-14014

108. Orme M, Collins S, Loftus J. Long-term medical management of primary open-angle glaucoma and ocular hypertension in the UK: optimizing cost-effectiveness and clinic resources by minimizing therapy switches. *J Glaucoma* 2012;**21**:433–49. https://doi.org/10.1097/IJG.0b013e31821dac2a

109. Rein DB, Wittenborn JS, Lee PP, Wirth KE, Sorensen SW, Hoerger TJ, *et al.* The cost-effectiveness of routine office-based identification and subsequent medical treatment of primary open-angle glaucoma in the United States. *Ophthalmology* 2009;**116**:823–32. https://doi.org/10.1016/j.ophtha.2008.12.056

110. Stewart WC, Leech J, Sharpe ED, Kulze J, Ellyn J, Day DG. An economic analysis of switching to latanoprost from a beta-blocker or adding brimonidine or latanoprost to a beta-blocker in open-angle glaucoma or ocular hypertension. *Am J Manag Care* 2002;**8**:S240–8.

111. Vaahtoranta-Lehtonen H, Tuulonen A, Aronen P, Sintonen H, Suoranta L, Kovanen N, *et al.* Cost effectiveness and cost utility of an organized screening programme for glaucoma. *Acta Ophthalmol Scand* 2007;**85**:508–18. https://doi.org/10.1111/j.1755-3768.2007.00947.x

112. Burr J, Hernandez R, Ramsay C, Prior M, Campbell S, Azuara-Blanco A, *et al.* Is it worthwhile to conduct a randomized controlled trial of glaucoma screening in the United Kingdom? *J Health Serv Res Policy* 2014;**19**:42–51. https://doi.org/10.1177/1355819613499748

113. van Gestel A, Schouten JS, Beckers HJ, Severens JL, Hendrikse F, Webers CA. The long term effectiveness and cost-effectiveness of initiating treatment for ocular hypertension. *Acta Ophthalmol* 2014;**92**:513–23. https://doi.org/10.1111/aos.12328

114. Burr J, Azuara-Blanco A, Avenell A, Tuulonen A. Medical versus surgical interventions for open angle glaucoma. *Cochrane Database Syst Rev* 2012;**9**:CD004399. https://doi.org/10.1002/14651858.CD004399.pub3

115. Burr JM, Botello-Pinzon P, Takwoingi Y, Hernandez R, Vazquez-Montes M, Elders A, *et al.* Surveillance for ocular hypertension: an evidence synthesis and economic evaluation. *Health Technol Assess* 2012;**16**(29). https://doi.org/10.3310/hta16290

116. Hernandez RA, Burr JM, Vale LD. Economic evaluation of screening for open-angle glaucoma. *Int J Technol Assess Health Care* 2008;**24**:203–11. https://doi.org/10.1017/S0266462308080288

117. Kymes SM, Plotzke MR, Kass MA, Boland MV, Gordon MO. Effect of patient's life expectancy on the cost-effectiveness of treatment for ocular hypertension. *Arch Ophthalmol* 2010;**128**:613–18. https://doi.org/10.1001/archophthalmol.2010.83

118. Kymes SM, Plotzke MR, Li JZ, Nichol MB, Wu J, Fain J. The increased cost of medical services for people diagnosed with primary open-angle glaucoma: a decision analytic approach. *Am J Ophthalmol* 2010;**150**:74–81. https://doi.org/10.1016/j.ajo.2010.01.037

119. Kymes SM, Kass MA, Anderson DR, Miller JP, Gordon MO. Management of ocular hypertension: a cost-effectiveness approach from the Ocular Hypertension Treatment Study. *Am J Ophthalmol* 2006;**141**:997–1008. https://doi.org/10.1016/j.ajo.2006.01.019

120. Peeters A, Schouten JS, Webers CA, Prins MH, Hendrikse F, Severens JL. Cost-effectiveness of early detection and treatment of ocular hypertension and primary open-angle glaucoma by the ophthalmologist. *Eye* 2008;**22**:354–62. https://doi.org/10.1038/sj.eye.6702637

121. van Gestel A, Webers CA, Beckers HJ, van Dongen MC, Severens JL, Hendrikse F, Schouten JS. The relationship between visual field loss in glaucoma and health-related quality-of-life. *Eye* 2010;**24**:1759–69. https://doi.org/10.1038/eye.2010.133

122. Szende A, Janssen B, Cabases J, editors. *Self-Reported Population Health: An International Perspective Based on EQ-5D*. London: SpringerOpen; 2014. https://doi.org/10.1007/978-94-007-7596-1

123. Kobelt G, Jonsson B, Bergström A, Chen E, Lindén C, Alm A. Cost-effectiveness analysis in glaucoma: what drives utility? Results from a pilot study in Sweden. *Acta Ophthalmol Scand* 2006;**84**:363–71. https://doi.org/10.1111/j.1600-0420.2005.00621.x

124. Tosh J, Brazier J, Evans P, Longworth L. A review of generic preference-based measures of health-related quality of life in visual disorders. *Value Health* 2012;**15**:118–27. https://doi.org/10.1016/j.jval.2011.08.002

125. Jones L, Garway-Heath DF, Azuara-Blanco A, Crabb DP, United Kingdom Glaucoma Treatment Study Investigators. 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* 2019;**126**:682–9.

126. Medeiros FA, Gracitelli CP, Boer ER, Weinreb RN, Zangwill LM, Rosen PN. Longitudinal changes in quality of life and rates of progressive visual field loss in glaucoma patients. *Ophthalmology* 2015;**122**:293–301. https://doi.org/10.1016/j.ophtha.2014.08.014

127. Goldberg I, Clement CI, Chiang TH, Walt JG, Lee LJ, Graham S, Healey PR. Assessing quality of life in patients with glaucoma using the Glaucoma Quality of Life-15 (GQL-15) questionnaire. *J Glaucoma* 2009;**18**:6–12. https://doi.org/10.1097/IJG.0b013e3181752c83

128. Gracner T. Intraocular pressure response of capsular glaucoma and primary open-angle glaucoma to selective Nd:YAG laser trabeculoplasty: a prospective, comparative clinical trial. *Eur J Ophthalmol* 2002;**12**:287–92. https://doi.org/10.1177/112067210201200406

129. Shazly TA, Latina MA. Intraocular pressure response to selective laser trabeculoplasty in the first treated eye vs the fellow eye. *Arch Ophthalmol* 2011;**129**:699–702. https://doi.org/10.1001/archophthalmol.2011.108

130. Shazly TA, Latina MA, Dagianis JJ, Chitturi S. Effect of prior cataract surgery on the long-term outcome of selective laser trabeculoplasty. *Clin Ophthalmol* 2011;**5**:377–80. https://doi.org/10.2147/OPTH.S17237

131. Gracner T, Falez M, Gracner B, Pahor D. [Long-term follow-up of selective laser trabeculoplasty in primary open-angle glaucoma.] *Klin Monbl Augenheilkd* 2006;**223**:743–7. https://doi.org/10.1055/s-2006-926725

132. Melamed S, Ben Simon GJ, Levkovitch-Verbin H. Selective laser trabeculoplasty as primary treatment for open-angle glaucoma: a prospective, nonrandomized pilot study. *Arch Ophthalmol* 2003;**121**:957–60. https://doi.org/10.1001/archopht.121.7.957

133. Koucheki B, Hashemi H. Selective laser trabeculoplasty in the treatment of open-angle glaucoma. *J Glaucoma* 2012;**21**:65–70. https://doi.org/10.1097/IJG.0b013e3182027596

134. Lai JS, Chua JK, Tham CC, Lam DS. Five-year follow up of selective laser trabeculoplasty in Chinese eyes. *Clin Experiment Ophthalmol* 2004;**32**:368–72. https://doi.org/10.1111/j.1442-9071.2004.00839.x

135. Leahy KE, White AJ. Selective laser trabeculoplasty: current perspectives. *Clin Ophthalmol* 2015;**9**:833–41. https://doi.org/10.2147/OPTH.S53490

136. Robin AL, Covert D. Does adjunctive glaucoma therapy affect adherence to the initial primary therapy? *Ophthalmology* 2005;**112**:863–8. https://doi.org/10.1016/j.ophtha.2004.12.026

137. Robin AL, Novack GD, Covert DW, Crockett RS, Marcic TS. Adherence in glaucoma: objective measurements of once-daily and adjunctive medication use. *Am J Ophthalmol* 2007;**144**:533–40. https://doi.org/10.1016/j.ajo.2007.06.012

138. 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. *J Glaucoma* 2009;**18**:157–60. https://doi.org/10.1097/IJG.0b013e3181752c97

139. Elsås T, Junk H, Johnsen H. Diurnal intraocular pressure after successful primary laser trabeculoplasty. *Am J Ophthalmol* 1991;**112**:67–9. https://doi.org/10.1016/S0002-9394(14)76215-4

140. Greenidge KC, Spaeth GL, Fiol-Silva Z. Effect of argon laser trabeculoplasty on the glaucomatous diurnal curve. *Ophthalmology* 1983;**90**:800–4. https://doi.org/10.1016/S0161-6420(83)34479-1

141. 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. *J Glaucoma* 2014;**23**:e138–43. https://doi.org/10.1097/IJG.0000000000000026

142. Nagar M, Luhishi E, Shah N. Intraocular pressure control and fluctuation: the effect of treatment with selective laser trabeculoplasty. *Br J Ophthalmol* 2009;**93**:497–501. https://doi.org/10.1136/bjo.2008.148510

143. 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. *Surv Ophthalmol* 2015;**60**:36–50. https://doi.org/10.1016/j.survophthal.2014.06.006

144. Li X, Wang W, Zhang X. Meta-analysis of selective laser trabeculoplasty versus topical medication in the treatment of open-angle glaucoma. *BMC Ophthalmol* 2015;**15**:107. https://doi.org/10.1186/s12886-015-0091-2

145. The James Lind Alliance. *Priorities for Glaucoma Research*. Southampton: James Lind Alliance; 2015. URL: www.jla.nihr.ac.uk/priority-setting-partnerships/sight-loss-and-vision/top-10-priorities/glaucoma-top-10.htm (accessed 3 May 2019).

146. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E, Early Manifest Glaucoma Trial Group. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol* 2003;**121**:48–56. https://doi.org/10.1001/archopht.121.1.48

147. Wu SY, Nemesure B, Hennis A, Schachat AP, Hyman L, Leske MC, Barbados Eye Studies Group. Open-angle glaucoma and mortality: the Barbados Eye Studies. *Arch Ophthalmol* 2008;**126**:365–70. https://doi.org/10.1001/archophthalmol.2007.77

148. Stewart WC, Stewart JA, Nasser QJ, Nassar QJ, Mychaskiw MA. Cost-effectiveness of treating ocular hypertension. *Ophthalmology* 2008;**115**:94–8. https://doi.org/10.1016/j.ophtha.2007.01.040

149. Lee AJ, Wang JJ, Kifley A, Mitchell P. Open-angle glaucoma and cardiovascular mortality: the Blue Mountains Eye Study. *Ophthalmology* 2006;**113**:1069–76. https://doi.org/10.1016/j.ophtha.2006.02.062

150. Quigley HA, Tielsch JM, Katz J, Sommer A. Rate of progression in open-angle glaucoma estimated from cross-sectional prevalence of visual field damage. *Am J Ophthalmol* 1996;**122**:355–63. https://doi.org/10.1016/S0002-9394(14)72062-8

151. Saunders LJ, Russell RA, Kirwan JF, McNaught AI, Crabb DP. Examining visual field loss in patients in glaucoma clinics during their predicted remaining lifetime. *Invest Ophthalmol Vis Sci* 2014;**55**:102–9. https://doi.org/10.1167/iovs.13-13006

152. Saunders LJ, Russell RA, Crabb DP. Practical landmarks for visual field disability in glaucoma. *Br J Ophthalmol* 2012;**96**:1185–9. https://doi.org/10.1136/bjophthalmol-2012-301827

153. Patterson BL, Charlton P, Richard S. Non-attendance in chronic disease clinics: a matter of non-compliance? *J Nurs Healthc Chronic Illn* 2010;**2**:63–74. https://doi.org/10.1111/j.1752-9824.2010.01048.x

Appendix 1 Recruiting sites

TABLE 22 Recruiting sites, local PIs and screening start and end dates

Participating centre	Local PI	Screening start date	Screening end date
MEH, City Road Campus	Mr Gus Gazzard	October 2012	October 2014
MEH at St George's Hospital	Mr Gus Gazzard	October 2012	October 2014
MEH at Northwick Park Hospital	Mr Nicholas Strouthidis	October 2012	October 2014
	Mr Hari Jayaram		
Royal Victoria Hospital, Belfast	Ms Sarah Wilson	November 2013	October 2014
Guy's and St Thomas' Hospital	Mr Sheng Lim	July 2013	October 2014
Hinchingbrooke Hospital	Professor Rupert Bourne	July 2013	October 2014
Norfolk and Norwich University Hospitals NHS Foundation Trust	Mr David Broadway	July 2013	October 2014
York Hospital	Mr Timothy Manners	November 2013	October 2014
	Ms Joanna Liput		

Appendix 2 Definitions of open-angle glaucoma, ocular hypertension and treatment requirements

We have used the NICE recommended thresholds for initiating treatment,[1] with stringent diagnostic definitions of disease (OAG or OHT) for entry into the study.

Diagnosis of open-angle glaucoma and treatment requirements

Primary OAG is defined as an open drainage angle (no iridotrabecular contact on non-indentation gonioscopy in primary position, trabecular meshwork visible over 360°), with no secondary causes (such as trauma):

- and reproducible glaucomatous VF defects as tested by the Swedish Interactive Threshold Algorithm on the Humphrey Visual Field Analyser (i.e. reproducible defect, in at least, of two or more contiguous points with a p-value < 0.01 loss or greater, or three or more contiguous points with a p-value < 0.05 loss or greater, or abnormal Glaucoma Hemifield Test)
- or GON with localised absence of the neuroretinal rim, or cup disc ratio of ≥ 0.7, or asymmetry of cup disc ratio of ≥ 0.2 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 are eligible (as for EMGT I[82]).

Subjects with GON and IOP in the normal range are therefore eligible. 'Phasing' (diurnal IOP pressure measurements) will be performed at the discretion of the treating clinician, and, if performed, the maximum IOP recorded will be used as that day's measurement.

Diagnosis of ocular hypertension and treatment requirements

Ocular hypertension with IOP > 21 mmHg and requiring treatment as per NICE guidelines.[1] NICE OHT guidelines treat four categories of OHT on the basis of CCT and age (the rest are monitored for 3–5 years).

Appendix 3 Video script

This video has been designed to inform you about a research study that is ongoing at Moorfields Eye Hospital. The video will introduce you to glaucoma and ocular hypertension, the various treatment options that are available and will eventually invite you to take part in a research study investigating the quality of your life after treatment. We would be grateful if you could spend 5–10 minutes watching this video.

Glaucoma is a disease of the optic nerve, which connects the eye to the brain. Glaucoma slowly progresses over a period of years; at the early stages people may not notice anything abnormal, but in advanced disease people may notice loss of vision. At the early stages, glaucoma can be treated with eyedrops or a laser treatment, which aim to control the condition and minimise future damage. Early diagnosis is important because any damage cannot be reversed. If glaucoma is left untreated, it can cause visual impairment. Glaucoma may be caused by raised eye pressure, but sometimes glaucoma develops despite a normal pressure inside the eyes, owing to a poorer blood supply or a weaker optic nerve.

Ocular hypertension is a condition where the pressure of the eyes is above normal limits, without, however, this causing any damage to the optic nerve. Some people have higher pressures than others. It has been shown that ocular hypertension puts people at a higher risk for developing glaucoma. Some people with ocular hypertension may, however, never develop glaucoma.

The pressure of your eyes is important, as your eyes function properly under a certain amount of pressure. If this pressure increases the optic nerve can be damaged. The amount of damage may depend on how high the pressure is, how long it lasts, and whether there is a poor blood supply or other weaknesses of the optic nerve. By lowering the pressure damage is slowed down.

At the moment, in the NHS, nearly all patients who have glaucoma or ocular hypertension are treated by eyedrops. Once started, eyedrops usually have to be continued for life. Not all patients like using eyedrops daily, however, and these patients might be suitable to a gentle laser therapy called selective laser trabeculoplasty. This laser treatment is not experimental; it is used commonly in the UK and for a number of years in the United States and its efficacy has been proven. At the moment the laser treatment is not offered as a first-line treatment in the NHS.

This study is designed to investigate the quality of life in patients treated first time either with eyedrops or with laser and is being funded by the National Institute for Health Research. The study will use questionnaires that the patients will have to fill in every 6 months. A secondary aim is to assess the cost of these treatments to the NHS.

Because we don't know which treatment will prove preferable for the patients' quality of life or which treatment is more cost-effective for the NHS, patients in this study will be assigned randomly to one of the two treatments and the two groups will then be compared. This type of study is called a randomised controlled trial, where half the patients will be randomly assigned by a computer to eyedrops and half will be assigned to laser treatment. If we assigned you to a group we might show preference to a specific treatment and if you were to choose, you might be biased towards one treatment.

Participation in this study is entirely voluntary. If you decide not to take part this will have no effect on the quality of care you receive at Moorfields Eye Hospital. If you decide to take part you will only be asked to attend the clinic one extra time compared with the usual clinic, but we can reimburse your travel expenses. The reason we will ask you to come one extra time is to give you time to think about the study and allow you to ask us any questions you might have.

If you decide to take part in this study you will be monitored by our specially trained optometrist and you will do the exact same tests you would do in a normal clinic. This is because the study is a real-life study, investigating your quality of life. This study will last in total 5 years, but each patient will be monitored for 6 years after the treatment is started. For this period of time you will be asked to attend the clinic between five and seven times. If you do not take part in the study you will be asked to attend the clinic six to seven times. After the end of the study you will continued to be monitored by the glaucoma clinics at Moorfields Eye Hospital as usual.

If you decide to take part you will be asked to fill in a questionnaire about your health and about your eyes. You will then be assigned to having drops or laser and you will be seen a few weeks later to assess if the treatment is working, just as we would if you were not in the study. Twice a year we will send you a questionnaire by post, which after filling in you can return to us in a pre-paid envelope that we will also send.

As every treatment, the treatments in this study might have some side effects. Eyedrops are used for approximately 30 years and can have mild or more severe side effects. Drops can cause mild discomfort or redness of the eyes, which usually settle soon, but in some cases they might make asthma worse. We will make sure we ask you all the necessary questions about your health before prescribing any drops. Some types of eyedrops should not be given to pregnant women. Any woman who is pregnant or who is planning to become pregnant should therefore not take part in this study. If a woman taking part in the study becomes pregnant she should let the research team know immediately. If the drops are not lowering your eye pressure enough you will be offered different or additional eyedrops.

The laser has been used successfully for 10–20 years. It is not a surgery and it is safe, easy and painless to deliver. In some people it might cause a small discomfort for a few days, which can be treated with anti-inflammatory eyedrops. Very rarely the laser might cause the eyes to be blurry for a few weeks or it may cause the pressure of the eyes to increase. If this happens we will give you drops to use for a few days. Laser treatment is effective in 80–90% of patients and its effect might wear off after a few years. If this happens the laser can be repeated once more. If for some reason we still need to reduce your eye pressure we will give you drops.

This study has no direct risks or benefits to you, as it is designed to mimic normal clinical practise. This means that you will be doing exactly what you would be doing in a normal glaucoma clinic and nothing additional to that. If during the study you decide you don't want to take part any more you can withdraw without providing a reason and without this affecting your care at Moorfields Eye Hospital. If you choose to withdraw you will then be monitored by a normal clinic. If you decide to take part you will be assigned an ID and all the information will be kept strictly confidential.

Two of the patients who have already taken part in our study have kindly agreed to explain the reasons they decided to participate and their experience so far.

Having explained why Moorfields Eye Hospital is conducting this study I hope you will be willing to consider taking part. My colleagues will now give you an information sheet about this study and will be able to answer any further questions you might have in relation to the study.

Thank you very much for your time.

Appendix 4 Selective laser trabeculoplasty delivery protocol

Training was given to all treating surgeons before recruitment and at least one laser treatment was observed by the chief investigator. The treating surgeon was the local PI or a fellowship-trained glaucoma specialist who was eligible to apply for a UK consultant surgeon post or for inclusion on the UK General Medical Council specialist register and who had performed at least 25 previous SLT treatments.

Selective laser trabeculoplasty was delivered to 360° of the trabecular meshwork, with one 360° retreatment as the first escalation of treatment if required. The model of SLT laser used was not restricted, and the wavelength and spot size were the same. To minimise variation between surgeons, standardisation was achieved by a stringent protocol defining laser settings and technique.

Pretreatment with iopidine (0.5% or 1%) at least 15 minutes before treatments was mandatory, unless contraindicated for medical reasons, in which case alternative medications such as oral acetazolamide [Apraclonidine (Novartis Pharmaceuticals UK Ltd)] could be 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 400 μm spot size were used, with the laser energy varied from 0.3 mJ to 1.4 mJ by the clinician using any laser gonioscopy lens (as long as the appropriate magnification was observed, e.g. 'Latina' was acceptable but 'Magnaview' was not). The desired end point was the production of a few fine 'champagne bubbles'; larger gas bubbles and trabecular meshwork blanching were not acceptable, and if seen the operator should have titrated the power downwards in 0.1-mJ increments. Pigmented trabecular meshwork will have required lower energy (from 0.3 mJ to 1.2 mJ) than non-pigmented and it was advisable to start treatments at 0.4 mJ. The Goldmann applanation tonometry IOP was measured 1 hour after treatment.

After treatment with SLT, patients were not asked to use anti-inflammatory eyedrops routinely; however, they were provided with a bottle of topical non-steroidal anti-inflammatory eyedrops for use only if they were in significant discomfort, despite simple oral analgesia such as paracetamol. [This is now standard practice in most units worldwide (Mark Latina, Tufts University School of Medicine, MA, USA, personal communication).] Topical steroids were not to be permitted post laser. Demonstrations of correct eyedrop technique were given at baseline and whenever needed thereafter.

Any rise in IOP of > 10 mmHg or that puts the patient at risk of visual loss was treated at the discretion of the treating ophthalmologist 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 necessitating medical treatment or an extra visit alone would constitute an AE and be independently logged as such.

The first post-SLT follow-up was at 2 weeks for an IOP check and assessment of potential side effects. No reintervention/treatment escalation decisions for non-response were made at this point; a further follow-up 6 weeks later was scheduled to allow time for the full effects of laser to occur. Patients at target 8 weeks after SLT were subsequently reviewed as per the interval determined by the severity category. Patients not at target after a single SLT received another treatment of 360° (100 spots) at the same energy settings, with re-evaluation after 2 weeks. After retreatment, a 6-week follow-up was given whether at target or not, unless, in the opinion of the treating clinician, a dangerously high IOP posed a significant risk to vision, in which case earlier follow-up was allowed to avoid an unsafe delay in medical therapy.

It is possible that an IOP rise following SLT could be severe enough to prevent a safe repeat of SLT should the target not have been met in future, particularly with more severe glaucoma. In this case, treatment escalation with eyedrops rather than repeating the SLT was permitted. This required an algorithm over-ride and thus was automatically logged and monitored. This may have occurred as an immediate (but transient) or persistent post-SLT pressure rise. Any immediate IOP rise > 40 mmHg despite pre-treatment iopidine or any rise of > 5 mmHg that persisted 8 weeks after laser would usually prevent further SLT treatment. After two SLT treatments, participants in the Laser-1st pathway embarked on medical treatment and followed the Medicine-1st algorithms. If the participant subsequently underwent drainage surgery which failed in the course of the trial, the step-wise medical intervention algorithm was initiated again and further SLT was not permitted.

Appendix 5 Questionnaire: sample patient response

LIGHT Trial
Questionnaire booklet- version 4.3, 8th January 2014

Moorfields Eye Hospital NHS
NHS Foundation Trust

Patient ID [M][E][H][7][3][1] DOB [ ][ ][ ]

LiGHT Trial- Laser in Glaucoma and Ocular Hypertension

QUESTIONNAIRE BOOKLET- Thirty month

In the UK glaucoma affects over half a million individuals. The LiGHT trial is one of the largest studies in this country assessing effective ways of treating Glaucoma and its effects on individuals. For this study to be successful and to give us valuable information about Glaucoma and how to improve people's lives, we need your help.

We would be grateful if you could take the time to fill in this booklet as part of the LiGHT trial. You may think some of the questions do not seem related to you, but they have all been specially chosen because they measure significant and important effects of Glaucoma and its treatment. Your answers will help us to find which treatment pathway used in the LiGHT trial leads to a better health related quality of life.

Each of the sections covers a different area and there is an explanation at the beginning of each of the sections.

As you will see there are quite a lot of questions, but please do not be put off as most of them are very straightforward. Some of the questions do overlap or ask similar things. We know about this, but would ask you to fill them all in as the questions are very important to the outcome of the trial.

You do not have to fill in the booklet in one go. If you want you can take a break and come back to it later. It is easier to complete the booklet in a quiet place, and at a time of day when you are not too busy.

All of the information you provide is confidential and Anonymous.
Please send the completed booklet back to us in the stamped addressed envelope provided.

NIHR National Institute for Health Research

LIGHT

Please turn over 1

M30

Appendix 6 Patient and public involvement survey sent to patients

If you have been diagnosed with either glaucoma or ocular hypertension, we need your feedback on research!

How can you help?

We would be grateful if you could take the time to fill in this brief survey, focusing on your experience with glaucoma or ocular hypertension and your treatment. The survey should take no more than 5 minutes. Your feedback will be used to shape our research in this area.

If you have any questions regarding this survey please contact Richard Cable on XXXX or by email at XXXX.

Please complete the questionnaire below and email/post this back to Richard Cable.

Email: XXXX

Address:
NIHR Moorfields BRC
RDCEC 2nd floor
Moorfields Eye Hospital NHS Foundation Trust
162 City Road
London EC1V 2PD

If you have been diagnosed with either glaucoma or ocular hypertension, please read the information below before completing the survey:

Selective laser trabeculoplasty (SLT) is an option for lowering intra-ocular pressure (IOP) for patients with glaucoma or ocular hypertension. It is a treatment that can be repeated if necessary, depending on the individual patient response.

SLT is a non-thermal laser which uses low energy light to Target specific, melanin rich cells in the drainage channel of the eye. During the procedure, which lasts around 15 minutes, approximately 100 shots are applied along the drainage angle, whilst the surrounding structures remain unaffected.

After the procedure vision might be blurred for a few hours and driving is not advised for the same day. It is possible for the pressure of the eye to rise immediately after the procedure and for some inflammation to develop. To prevent this special drops are used immediately before and after the treatment; drops to control the inflammation are also prescribed for the first 2-3 days. Rarely the pressure of the eye might rise significantly and surgery might be needed to lower the pressure; this is a very unusual event.

SLT has been shown to have a success rate of approximately 78%. Some patients respond better than others but it is not possible to predict who will respond to the treatment. It can take up to 8 weeks for the pressure of the eye to drop after SLT. The effects of the laser might wear off with time; approximately half of the treatments wear off after 5 years, but the treatment can be repeated.

Question 1: What is your age group?

☐ <30 years old
☐ 31-40 years old
☐ 41-50 years old
☐ 51-60 year sold
☐ 61-70 year sold
☐ >70 years old

Question 2: Are you male or female?

☐ Male
☐ Female

Question 3: Have you ever been prescribed eye drop medication for glaucoma or ocular hypertension?

☐ Yes
☐ No

Question 4: If you answered 'Yes' to Question 1, what are your thoughts and experiences of eye drop medication as a treatment?

Question 5: Having read the attached information about SLT, if offered SLT as a supplement (or even replacement for a limited time) to eye drop medication, would you take up the offer to have it?

☐ Yes

☐ No

☐ Don't know enough information to make a decision

Please explain your answer:

Question 6: If you have already undergone SLT for your eye condition, what are your thoughts and experiences of the treatment?

Question 7: Have you had treatment for glaucoma or ocular hypertension other than SLT or eye drop medication? If so, please specify and give your thoughts on the treatment in question.

Appendix 7 Frequency of data monitoring across sites

TABLE 23 Frequency of data monitoring across sites

Site	Patients (*n*)	Monitored (*n*)	Monitored (%)	Notes
Guy's and St Thomas' Hospital	106	106	100.0	January 2015–February 2016
Guy's and St Thomas' Hospital (repeat)	106	30	28.3	April 2016–October 2017
Hinchingbrooke Hospital	82	38	46.3	
York Hospital	37	19	51.4	
Royal Victoria Hospital, Belfast	30	11	36.7	
Norfolk and Norwich University Hospitals NHS Foundation Trust	89	40	44.9	

Appendix 8 Recruitment

TABLE 24 Recruited patients by month and by site

Date	Monthly target	Cumulative overall target	Actual recruitment	Cumulative actual recruitment
October 2012	10	10	7	7
November 2012	17	27	24	31
December 2012	17	44	10	41
January 2013	17	61	19	60
February 2013	17	78	13	73
March 2013	17	95	11	84
April 2013	17	112	12	96
May 2013	17	129	16	112
June 2013	17	146	7	119
July 2013	26	172	33	151
August 2013	39	211	22	173
September 2013	39	250	27	200
October 2013	39	289	39	239
November 2013	39	328	39	278
December 2013	39	367	40	318
January 2014	39	406	47	365
February 2014	39	445	36	401
March 2014	39	484	45	446
April 2014	39	523	47	493
May 2014	39	562	23	516
June 2014	39	601	37	553
July 2014	39	640	53	606
August 2014	39	679	26	632
September 2014	39	718	38	670
October 2014	39	718	49	719

Appendix 9 Protocol deviations and violations

TABLE 25 Protocol deviations and violations over the 36 months of the trial

Patient ID	Site	Date of event	Violation/deviation	Preventative action
MEH-070	MEH	27 February 2013	Violation: ineligible patient randomised	Any patient who is judged to have angles < 10°, or where there is a conflict of diagnosis, should be checked by the chief investigator/PI prior to randomisation
YOR-246 YOR-265 YOR-286 YOR-287 YOR-319	York	8 January 2014	Deviation: health-care assistants have been performing SITA fast visual fields instead of SITA standard	Research manager has sent an e-mail to all centres (PIs and co-ordinators) to ensure that patients are tested using SITA standard and not SITA fast. VF are now being done by the research team in York rather than health-care assistants
HIN-340	Hinchingbrooke	15 January 2014	Deviation: after the patient was randomised they decided to withdraw as they wanted to have only one of the two treatments	E-mailed the site explaining that patients who are adamant about receiving a particular treatment should not be consented to participate as this is a randomised trial. Site is happy to continue with this guidance. Mr Bourne confirmed that the patient did not express a preference to a treatment prior to randomisation, but once randomised they had made a preference. Patient has been withdrawn and will have their preferred treatment on the NHS
GST-472	Guy's and St' Thomas'	14 April 2014	Violation: ineligible patient randomised	VF MD more than the eligibility criteria
YOR-265	York	17 December 2013; 14 January 2014	Deviation: patient previously randomised to SLT. Patient did not attend 2-week IOP check and York hospital rescheduled the appointment. At this appointment, the algorithm was updated which should not have been Violation: HRT test was not done and data not entered on to the algorithm on the day of the appointment. Data were also entered for the wrong follow-up visit as a result of data being entered at the IOP check visit when this should not have been entered. The patient was then prescribed eyedrops as an increase in treatment as a clinical decision over-riding the algorithm	Provided intense training for all team members on 28 January 2014

continued

TABLE 25 Protocol deviations and violations over the 36 months of the trial (*continued*)

Patient ID	Site	Date of event	Violation/deviation	Preventative action
BEL-613	Belfast	8 August 2104	Deviation: patient was recruited and randomised to laser. As the patient's IOP increased, Ms Wilson decided to start eyedrops and not go ahead with the laser	
GST-486	Guy's and St' Thomas'	28 April 2014	Violations: ineligible patient randomised owing to VF MD criteria	
GST-512	Guy's and St' Thomas'	20 November 14	Violations: appointment schedule had not been followed	Has been noted and corrected. Centre retrained on protocol
GST-156				
GST-261				
GST-541				
GST-531				
GST-552				
GST-585				
GST-598				
GST-596				
GST-430				
GST-570				
GST-544				
GST-561				
GST-571				
GST-530				
GST-358				
GST-239				
NOR-349	Norfolk and Norwich	20 January 2014	Violation: patient not eligible owing to PDS	
GST-178	Guy's and St' Thomas'	11 January 2016	Deviation: third SLT done in the left eye	
GST	Guy's and St' Thomas'		Violation: Mr Lim had advised all patients to take Acular (ketorolac) for 3/7 t.i.d. following SLT. However, the protocol and SOP for SLT states 'Acular as required only' for everyone is indeed at variance with the agreed protocol	Acular for everyone is indeed at variance with the agreed protocol, but consistency with what has already been done within a unit is important. It was proposed that repeat lasers get the same as what Mr Lim has already done

ID, identification; PDS, pigment dispersion syndrome; SITA, Swedish Interactive Threshold Algorithm; t.i.d., ter in die (three times a day).

Appendix 10 Results of sensitivity analyses

TABLE 26 Results of sensitivity analyses

Approach	Adjusted mean difference[a] (Laser-1st – Medicine-1st)	95% CI
1. Using exact dates	0.007	–0.009 to 0.022
2. Adjusted for variables associated with missingness	0.011	–0.008 to 0.030
3. Multiple imputation	0.016	–0.004 to 0.035
4. Mapping algorithm	0.019	–0.005 to 0.042
5. Data recorded within 3 months of 36 months	0.012	–0.007 to 0.031
6. Robust SEs	0.012	–0.007 to 0.031
7. Beta regression	0.002	–0.010 to 0.013

a Mean difference is adjusted for baseline score, severity, centre, baseline IOP and number of eyes affected at baseline.

Appendix 11 Details of ophthalmic- and laser-related adverse events

TABLE 27 Details of ophthalmic- and laser-related AEs

	Medicine-1st		Laser-1st		Total	
	n of events	*n* (%) of patients	*n* of events	*n* (%) of patients	*n* of events	*n* (%) of patients
Other ophthalmic-related AEs	744	118 (32.6)	459	117 (33.0)	1041	235 (32.8)
Conjunctival injection	109	61 (16.9)	33	25 (7.0)	142	86 (12.0)
Ocular irritation, discomfort or dry eye	239	125 (34.5)	147	97 (27.3)	386	222 (31.0)
Itching	103	51 (14.1)	73	44 (12.4)	176	95 (13.2)
Stinging on instillation	89	53 (14.6)	18	11 (3.1)	107	64 (8.9)
Optic disc haemorrhage	4	4 (1.1)	8	7 (2.0)	12	11 (1.5)
Macular haemorrhage	0	0 (0)	0	0 (0)	0	0 (0)
Subconjunctival haemorrhage	9	8 (2.2)	2	2 (0.6)	11	10 (1.4)
Cataract	14	13 (3.6)	19	17 (4.8)	33	30 (4.2)
Blurred vision	19	18 (5.0)	12	12 (3.4)	31	30 (4.2)
Change in vision	16	14 (3.9)	9	9 (2.5)	25	23 (3.2)
Floater(s)	5	5 (1.4)	11	8 (2.3)	16	13 (1.8)
Flashes	4	4 (1.1)	8	7 (2.0)	12	11 (1.5)
Conjunctivitis	8	8 (2.2)	6	5 (1.4)	14	13 (1.8)
Watery eye	8	7 (1.9)	13	11 (3.1)	21	18 (2.5)
Glare	4	4 (1.1)	6	5 (1.4)	10	9 (1.3)
Pain/sore eye	10	10 (2.8)	8	8 (2.3)	18	18 (2.5)
Blepharitis	6	6 (1.7)	0	0 (0)	6	6 (0.8)
Swollen eye(s)	3	3 (0.8)	1	1 (0.3)	4	4 (0.6)
Photophobia	4	4 (1.1)	4	3 (0.8)	8	7 (1.0)
CRVO	2	1 (0.3)	0	0 (0)	2	1 (0.1)
BRVO	1	1 (0.3)	2	1 (0.3)	3	2 (0.3)
Diabetic retinopathy	0	0 (0)	1	1 (0.3)	1	1 (0.1)
Diabetic macular oedema	0	0 (0)	3	2 (0.6)	3	2 (0.3)
Other laser-related AEs	1	1 (0.3)	51	47 (13.2)	52	48 (6.7)
Photophobia	0	0 (0)	21	20 (5.6)	21	20 (2.8)
Hyperaemia	0	0 (0)	3	3 (0.8)	3	3 (0.4)
Discomfort	0		6		6	
Breaks taken during procedure	0		0		0	
Fewer laser shots	0		3		3	
Visualisation of angle/other angle issues	0		5		5	

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

Appendix 12 Medical contacts

TABLE 28 Clinic visits and medical contacts over 36 months (data for the previous 6 months for each follow-up point)

	Baseline		6 months		12 months		18 months		24 months		30 months		36 months	
	Medicine-1st ($n = 362$)	Laser-1st ($n = 356$)	Medicine-1st ($n = 326$)	Laser-1st ($n = 329$)	Medicine-1st ($n = 317$)	Laser-1st ($n = 317$)	Medicine-1st ($n = 302$)	Laser-1st ($n = 302$)	Medicine-1st	Laser-1st	Medicine-1st	Laser-1st	Medicine-1st	Laser-1st
Eye related, mean (SD)														
Optician	0.898 (0.691)	0.874 (0.729)	0.336 (0.600)	0.464 (0.789)	0.364 (0.569)	0.422 (0.660)	0.397 (0.611)	0.412 (0.714)	0.409 (0.546)	0.456 (0.597)	0.394 (0.637)	0.399 (0.631)	0.497 (0.718)	0.492 (0.721)
General practitioner[a]	0.192 (0.477)	0.186 (0.493)	0.095 (0.408)	0.116 (0.630)	0.073 (0.363)	0.050 (0.314)	0.05 (0.273)	0.053 (0.412)	0.112 (0.493)	0.076 (0.387)	0.081 (0.378)	0.1 (0.539)	0.125 (0.729)	0.122 (0.631)
General practitioner nurse	0.045 (0.363)	0.074 (0.371)	0.074 (0.378)	0.068 (0.317)	0.064 (0.304)	0.065 (0.517)	0.086 (0.384)	0.034 (0.246)	0.090 (0.407)	0.026 (0.229)	0.121 (0.817)	0.053 (0.254)	0.063 (0.319)	0.072 (0.339)
Social worker	0.003 (0.053)	0.003 (0.053)	0.003 (0.055)	0.003 (0.055)	0.003 (0.056)	0	0	0	0.003 (0.058)	0.003 (0.057)	0	0	0	0.003 (0.058)
Home care worker	0.003 (0.053)	0.008 (0.092)	0.006 (0.078)	0	0	0	0.003 (0.058)	0	0	0	0	0	0	0
Other community services	0	0	0.003 (0.056)	0.003 (0.056)	0	0	0.007 (0.083)	0.010 (0.175)	0	0	0	0	0	0.007 (0.081)
Non-eye related, mean (SD)														
General practitioner[a]	1.346 (1.909)	1.427 (2.446)	1.356 (2.039)	1.405 (2.097)	1.070 (1.550)	1.196 (2.081)	1.174 (1.711)	1.296 (2.004)	1.150 (2.122)	1.079 (1.814)	1.182 (2.060)	1.073 (1.725)	0.979 (1.664)	1.132 (1.924)
General practitioner nurse	0.415 (0.999)	0.394 (1.046)	0.439 (1.023)	0.480 (1.096)	0.316 (0.666)	0.549 (1.371)	0.424 (0.840)	0.529 (1.211)	0.406 (1.374)	0.365 (0.811)	0.435 (1.003)	0.356 (0.827)	0.378 (0.786)	0.493 (0.991)
Social worker	0.006 (0.075)	0.011 (0.106)	0.009 (0.096)	0.003 (0.055)	0.003 (0.056)	0.010 (0.126)	0	0.003 (0.058)	0.017 (0.174)	0.026 (0.354)	0.007 (0.083)	0.003 (0.059)	0.024 (0.266)	0.003 (0.058)
Home care worker	0	0.008 (0.092)	0.003 (0.056)	0.006 (0.078)	0.044 (0.733)	0.010 (0.126)	0.068 (1.16)	0	0.010 (0.175)	0	0.007 (0.083)	0	0.003 (0.058)	0
Other community services	0.073 (0.705)	0.025 (0.231)	0.157 (1.269)	0.142 (1.093)	0.039 (0.312)	0.089 (1.168)	0.084 (1.024)	0.127 (1.113)	0.032 (0.243)	0.010 (0.101)	0.101 (0.860)	0.042 (0.311)	0.048 (0.421)	0.154 (1.473)

	Baseline		6 months		12 months		18 months		24 months		30 months		36 months	
	Medicine-1st ($n = 362$)	Laser-1st ($n = 356$)	Medicine-1st ($n = 326$)	Laser-1st ($n = 329$)	Medicine-1st ($n = 317$)	Laser-1st ($n = 317$)	Medicine-1st ($n = 302$)	Laser-1st ($n = 302$)	Medicine-1st	Laser-1st	Medicine-1st	Laser-1st	Medicine-1st	Laser-1st
Acute hospital services[b]														
Outpatient, mean (SD)	0.838 (1.331)	0.707 (1.259)	0.808 (1.826)	0.911 (1.948)	0.551 (1.350)	0.543 (1.230)	0.620 (1.489)	0.568 (1.283)	0.562 (1.193)	0.685 (1.602)	0.553 (1.431)	0.582 (1.491)	0.642 (1.378)	0.5 (1.092)
A&E attendance, mean (SD)	0.062 (0.252)	0.085 (0.343)	0.049 (0.256)	0.085 (0.447)	0.061 (0.299)	0.098 (0.472)	0.077 (0.313)	0.06 (0.370)	0.048 (0.244)	0.093 (0.641)	0.075 (0.381)	0.070 (0.294)	0.083 (0.416)	0.067 (0.288)
Day case, mean (SD)	0.352 (0.839)	0.316 (0.828)	0.297 (1.091)	0.287 (0.826)	0.244 (0.690)	0.220 (0.688)	0.306 (0.950)	0.194 (0.584)	0.199 (0.771)	0.276 (0.837)	0.264 (0.890)	0.345 (1.275)	0.315 (1.022)	0.248 (0.759)
Planned inpatient admission, *n* (%)	11 (3)	6 (2)	6 (2)	8 (2)	5 (2)	8 (3)	10 (3)	10 (3)	2 (1)	8 (3)	6 (2)	8 (3)	5 (2)	5 (2)
LOS planned inpatient admissions, mean (SD)[c]	1.091 (0.302)	1 (0)	1.333 (0.516)	1.125 (0.354)	1 (0)	1.125 (0.354)	1.1 (0.316)	1.1 (0.316)	1 (0)	1.125 (0.354)	1.667 (0.516)	1.5 (1.414)	1.4 (0.548)	1 (0)
Emergency inpatient admission, *n* (%)	5 (1)	3 (1)	5 (2)	9 (3)	8 (3)	10 (3)	9 (3)	8 (3)	3 (1)	5 (2)	8 (3)	11 (4)	10 (3)	6 (2)
LOS emergency inpatient admissions, mean (SD)[c]	1.2 (0.447)	1 (0)	1 (0)	1.889 (2.315)	1.25 (0.463)	1 (0)	1 (0)	1.125 (0.354)	1 (0)	1 (0)	1 (0)	1.545 (0.688)	1.7 (1.337)	1.5 (1.224)

A&E, accident and emergency; LOS, length of stay.
a Visit, telephone call, home visit.
b Excluding ophthalmology.
c For LOS, mean and SD is reported for patients with an admission only.

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library