TAGS

Treatment of Advanced Glaucoma Study

A multicentre randomised controlled trial comparing primary medical treatment with primary trabeculectomy for people with newly diagnosed advanced glaucoma.

Statistical Analysis Plan

SAP Version:	2
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Approved by:

Anthony King Chief Investigator	(signed)	18-07-19 date
Graeme MacLennan Senior Statistician	(signed)	18/7/19 date

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1 Amendment History

SAP version	Protocol version	Section number changed	Description	Date changed
V2	V4	5	Additional sensitivity analysis has been added, a baseline paper and looking a correlations at baseline.	16/07/2019

2 Introduction

2.1 Study Design

A pragmatic [1] [2] multicentre randomised controlled trial comparing primary medical treatment (a stepped approach of medications) with primary augmented trabeculectomy (primary surgery).

2.2 Primary Objective

The primary objective of this trial is to compare primary medical treatment with primary augmented trabeculectomy (glaucoma surgery) for patients presenting with advanced glaucoma (Hodapp Classification severe) in terms of patient reported health status using the national eye institute visual function questionnaire 25 (NEI VFQ-25[3] [4]).

2.3 Randomisation and Code Breaking

All participants who agree to enter the study will be logged with the central trial office and given a unique Study Number. Randomisation will utilise the existing proven remote automated computer randomisation application at the central trial office in the Centre for Healthcare Randomised Trials (CHaRT, a fully registered UK CRN clinical trials unit) in the Health Services Research Unit, University of Aberdeen. This randomisation application will be available both as a telephone based IVR system and as an internet based service.

Randomisation will be computer-allocated and minimised by centre and bilateral disease status. The unit of randomisation will be the participant (not the eye). Participants with both eyes affected by advanced glaucoma and eligible will undergo the same treatment in both eyes following randomisation. For those participants with both eyes eligible, an index eye will be selected for evaluating clinical outcomes. The eye with better MD value (less severe visual field damage) will be nominated the index eye.

For those randomised to the surgery group with both eyes eligible, a period of 2-3 months would normally be allowed between operations on either eye. Prior to surgery intraoperative pressure (IOP) will be controlled with holding medical treatment.

Masking: As TAGS is investigating medical versus surgical management for patients with advanced glaucoma neither the participants nor the local clinical team can be masked to the randomised treatment allocation. The only masked aspect is the evaluation of visual fields at the end of the study which will be undertaken by an independent reading centre masked to the allocation.

No unmasking procedures are necessary as this is an open label trial.

3 Outcome Measures

3.1 Primary Outcome

The primary patient reported outcome is the vision specific health status measured by the NEI VFQ-25 assessment at 24 months.

3.2 Secondary Outcomes

Patient-centred:

- Patient reported health status as measured by EQ-5D (5-level), HUI-3, GUI, NEI VFQ-25
- Patient experience

Clinical:

- Visual field mean deviation (MD) changes
- Intraocular pressure (IOP)
- LogMAR visual acuity change
- Need for cataract surgery
- Visual standards for driving
- Registered visual impairment
- Safety

3.3 Timing of Outcome Measurements

		Post-randomisation (months)						
	Baseline	1	3	4	6	12	18	24
Medical History	✓							
Consent/Randomisation	✓							
Humphrey Visual Field	✓			✓		✓		✓
LogMAR Visual Acuity	✓			✓		✓		✓
IOP	✓			✓		✓		✓
Standard clinical examination	✓					✓		✓
NEI VFQ-25	✓			✓		✓		✓
EQ-5D	✓	✓	✓		✓	✓	✓	✓
HUI-3	✓	✓	✓		✓	✓	✓	✓
GUI	✓	✓	✓		✓	✓	✓	✓
Patient experience questions	✓	✓	✓		✓	✓	✓	✓

3.4 Adverse Events

Adverse events will be reported in line with National Research Ethics Committee (NREC) guidance. Any of the following events will be reported as an adverse event (AE):

- results in death
- is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is otherwise considered medically significant by the investigator

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs or SAEs as appropriate. Please refer to the Protocol for more detail on AE.

4 Sample Size and Power Calculation

The primary patient reported outcome is health status measured by the NEI VFQ-25 assessment at 24 months. A study with 190 participants in each group would have 90% power at a 5% significance level to detect a difference in means of 0.33 of a standard deviation (SD); this translates to 6 points on the NEI VFQ-25 assuming a common SD of 18 points observed in previous work which is a clinically relevant effect size in patients with advanced glaucoma [5] [6]. Seven points is a likely minimally important difference based on our pilot work on NEI VFQ-25 scores in patients with glaucoma, due to uncertainty around this we have opted for a more conservative 6 point difference, which is supported by the literature for another chronic eye disease, macular degeneration [3]. Assuming a drop-out rate of 13.5% due to declining further follow-up and death, a total of 440 participants need to be randomised to detect this difference.

For the secondary clinical outcome (visual field score, mean deviation [MD]) the study will have 90% power at a 5% level of significance to detect a 1.3db difference in mean deviation. This was derived from a subgroup of patients with advanced glaucoma [7] [8] and is a clinically significant difference in the context of advanced glaucoma and predictive further visual disability.

5 Statistical Methods

Baseline characteristics, follow-up measurements and safety data will be described using appropriate descriptive statistics. The primary analysis strategy will be intention-to-treat, so that all randomised patients will be included in the analysis and analysed as allocated.

Outcomes measured at the eye-level will be analysed initially using data from the index eye only (excluding the other eye in participants with bilateral disease). Sensitivity analysis using data from all eligible eyes will be analysed by including a random effect at the participant level to reflect the lack of independence of eyes within participants. A further sensitivity analysis will look at the effect of when SITA - standard has not been used and if only one eligible baseline visual field has been done - either due to only one visual field being performed or 1 or 2 of the visual fields not fulfilling the false positive standard of $< 15\%$.

All treatment effects will be derived from these models and presented with 95% confidence intervals.

A baseline paper will be published summarising the baseline characteristics at the cohort level.

We will also look at the correlations at baseline between Index of Multiple Deprivation and VFQ-25, HUI, EQ5D, GUI, VA (LogMAR, better and worse eye and combined), VF - MD better and worse eye, IOP index eye, age, sex, family history of glaucoma, ethnicity, number of visits to the optician in the last 10 years.

5.1 Primary Outcome

The primary outcome measured at 24 months will be analysed using linear regression correcting for baseline measure of the primary outcome and bilateral disease. We will also explore the profile of primary outcomes over time by analysing repeated measures using a linear mixed model. All models will include a random effect for surgeon.

In trials of medical versus surgical management there exists potential for cross-over to the alternative allocation. Therefore we will explore the influence of compliance on the treatment effect for the primary outcome by doing a per-protocol analysis and complier adjusted causal estimation (CACE) using instrumental variable regression [9].

5.2 Secondary Outcomes

Secondary outcomes will be analysed using a similar strategy with models suitable for the outcome.

5.3 Subgroup Analysis

Planned subgroup analyses are intended to explore potential effect modifications of gender, age ($<$65 years, $\geq$ 65 years), one or both eyes affected, Index of Multiple Deprivation (Quintile), and extent of visual field loss at baseline ($<$-20db, $\geq$ -20db) on the primary outcomes. Subgroup by treatment interaction will be assessed by including interaction terms in the models outlined above.

5.4 Missing Data

The sensitivities of treatment effect estimates to missing outcome data will be explored; these models will explore the robustness of the treatment estimate to whatever small amount of missing data there is. We will follow the strategy outlined in White et al [10]. The analysis will use all available data that we believe are valid under the assumption of missing at random. We will then use a suite of sensitivity analysis to explore the robustness of the primary analysis to departures from assumptions, including all randomised participants. If required, sensitivity analyses will include multiple imputation, and imputing a range of values for missing data under missing not at random assumptions e.g. using rctmiss in Stata.

Data missing at baseline will reported as such. If required for models for primary or secondary outcomes continuous data will be imputed with the centre specific mean of that variable, missing binary/categorical data will include a missing indicator.

6 Dummy Tables

Table 1. Baseline characteristics

	Surgery N=	Medication N=
Age - mean (sd)		
Gender - n (%)		
Male		
Female		
Ethnicity - n (%)		
Caucasian		
Asian - Oriental		
Asian - Indian/Pakistan/Bangladesh		
Afro-Caribbean		
Mixed heritage		
Other		
Eyes affected - n (%)		
One		
Both		
Eligible to be registered as sight impaired - n (%)		
No		
SI		
Severe SI		
Glaucoma diagnosis - n (%)		
Primary Open Angel glaucoma (including NTG)		
Pigment Dispersion Syndrome		
Pseudoexfoliation Syndrome		
Other		
Lens status - n(%)		
Phakic		
Pseudophakic		
Central corneal thickness - mean(sd)		
Number of drops - median (IRQ)		
Family history of glaucoma - n (%)		
Number of times visited the optician in the last 10 years - median (IRQ)		
Co-morbidity - n (%)		
AMD - n (%)		
Vascular occlusion - n (%)		
Diabetic Retinopathy - n (%)		
Cataract - n (%)		
Other - n (%)		

Table 2. Baseline outcome characteristics

	Surgery N=	Medication N=
NEI-VFQ-25 - mean(sd)		
NEI-VFQ-25 subscales - mean(sd)		
Near vision		
Distance vision		
Dependency		
Driving		
General health		
Role difficulties		
Mental health		
General vision		
Social functioning		
Colour vision		
Peripheral vision		
Ocular pain		
Visual Fields Mean Deviation (dB) - mean (sd)		
LogMAR Visual Acuity - mean (sd)		
IOP (mmHg) - mean (sd)		
at diagnosis		
at baseline		
EQ-5D - mean (sd)		
HUI-3 - mean (sd)		
GUI - mean (sd)		
Patient experience (glaucoma is getting worse) - n (%)		
Yes		
No		

Table 3. Surgical procedure

	Surgery N =	Medication N=
Pre-operation drops - n (%)		
PG analogue		
B-blocker		
CA inhibitor		
A-agonist		
Parasympathomimetic		
Diamox		
Pre-operation IOP - mean (sd)		
Surgeon Grade - n (%)		
Consultant		
Fellow		
Other		
Anaesthetist Grade - n (%)		
Consultant		
Fellow		
Other		
Type of anaesthesia - n (%)		
Regional block		
General		
Traction suture - n (%)		
Corneal		
Superior rectus		
Conjunctival flap - n (%)		
Fornix based		
Limbal based		
MMC dose - n (%)		
0.2 mg/ml		
0.4 mg/ml		
Other		
MMC duration - n (%)		
3 minutes		
other		
Scleral flap sutures - n (%)		
Interrupted		
Releasable		
Adjustable		
A/C maintainer - n (%)		
Pre-operative lopidine - n (%)		
Peri-operative miochol - n (%)		
Peri-operative viscoelastic - n (%)		
Subconjunctival antibiotic - n (%)		
Subconjunctival steriod - n (%)		

Table 4. Reason for surgery - n (%)

	Surgery N =	Medication N=
Study allocation		
Uncontrolled IOP		
Visual Field progression		
Drop intolerance/allergy		
Patient preference		
Other		

Table 5. Primary outcome - NEI-VFQ-25

	Surgery N =	Medication N=	Estimate	95% CI	p-value
NEI-VFQ-25 - mean (sd)					
Baseline					
4 months					
12 months					
24 months					

Table 6. Secondary outcomes - Patient-centred

	Surgery N =	Medication N=	Estimate	95% CI	p-value
EQ-5D - mean (sd)					
Baseline					
1 month					
3 months					
6 months					
12 months					
18 months					
24 months					
HUI-3 - mean (sd)					
Baseline					
1 month					
3 months					
6 months					
12 months					
18 months					
24 months					
GUI - mean (sd)					
Baseline					
1 month					
3 months					
6 months					
12 months					
18 months					
24 months					
Patient experience (glaucoma is getting worse) - n (%)					

Table 7. Secondary outcomes - clinical

	Surgery N =	Medication N=	Estimate	95% CI	p-value
Visual field - mean (sd)					
Baseline					
4 months					
12 months					
24 months					
Intraocular pressure - mean (sd)					
Baseline					
4 months					
12 months					
24 months					
LogMAR Visual Acuity - mean (sd)					
Baseline					
4 months					
12 months					
24 months					
Need for cataract surgery - n (%)					
Baseline					
4 months					
12 months					
24 months					
Visual standards for driving					
Baseline					
4 months					
12 months					
24 months					
Registered visual impairment - n (%)					
Baseline					
4 months					
12 months					
24 months					
Safety - n (%)					
Baseline					
4 months					
12 months					
24 months					

Table 8. Trabeculectomy interventions (4, 12, and 24 months)

Intervention	Surgery N =	Medication N =
Massage		
Releasable release		
Adjustment		
Suturelysis		
Releasable		
5-FU injection		
Steroid injection		
Needing + 5-FU injection		
Bleb resuturing		
AC reformation		
Bleb revision		
Phaco + IOL		
Other		

values are n(%)

Table 9. Number of drops

Intervention	Surgery N =	Medication N =
Baseline		
4 months		
12 months		
24 months		

values are mean (sd)

Table 10. Subgroup analysis - NEI-VFQ-25 - mean (sd)

	Surgery N =	Medication N=	Estimate	95% CI	p-value
Gender					
Male					
Female					
Age					
< 65 years					
≥ 65 years					
Eyes affected					
One					
Both					
Visual field loss at baseline					
$<$ -20db					
$\geq$ 20bd months					
Deprivation Index Quintile (20%)					
1					
2					
3					
4					
5					

Table 11. Serious adverse Events

	Surgery N =	Medication N =
Death		
Life-threatening		
Required hospitalisation		
Resulted in persistent or significant disability		
Medically significant		
Total		

values are n(%)

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Treatment of Advanced Glaucoma Study (TAGS): A multicentre randomised controlled trial comparing primary medical treatment with primary trabeculectomy for people with newly diagnosed advanced glaucoma

HEALTH ECONOMICS ANALYSIS PLAN

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Tables and figures

Summary of the Economic Analysis Plan

A single main analysis will be performed at the end of the trial. The primary analysis is based on the two-year follow-up of the trial and following outcomes have been specified: Incremental cost per Quality adjusted Life year (QALY) gained (based on responses to the EQ-5D-5L; Health Utilities Index Mark 3 (HUI3) and to the glaucoma utility index (GUI)); Incremental QALYs (based on responses to the EQ-5D-5L; HUI3 and the GUI) and Incremental costs to NHS, personal social services and patients. The economic analyses will be conducted at the level of the participant, with minimisation factors included as covariates. All NHS costs associated with the use of both secondary and primary health care services by the participants, as well as participant cost, will be estimated. All health economic analyses within the RCT will be based on the intention-to-treat principle.

All health economic outcomes will be described with the appropriate descriptive statistics. The continuous and count outcomes will be expressed as mean ± standard deviation or medians and inter-quartile range if required and dichotomous and categorical outcomes will be presented as absolute numbers and percentages. Analysis of costs to the health services and outcomes (QALYs) will estimate the mean differences (and bootstrapped 95% confidence intervals) between the intervention and control groups using a standard general linear model adjusting for minimisation and the appropriate prognostic covariates at baseline (e.g. Baseline EQ-5D-5L score). Statistical modelling techniques will be used to account for missing data and methods for imputation will be explored depending on the pattern of data missingness.

The joint estimates of costs and effects will be combined in an incremental analysis between two strategies and will be presented as point estimates of the mean incremental cost-effectiveness ratio (ICER), calculated as difference in costs over the difference in effects (QALYs). Bootstrapping estimates of incremental costs and QALYs gained will be obtained to characterise the uncertainty surrounding these outcomes as well as the ICER. Other forms of uncertainty, e.g. concerning the unit cost of a resource, will be addressed using standard deterministic sensitivity analysis. The ICER for intervention versus control group will be compared with accepted threshold values (£20-30,000 per QALY) to help inform judgements on cost-effectiveness. Key subgroup analyses will be conducted to reflect heterogeneity.

Although the within trial analysis will prove useful for informing short to medium term cost-effectiveness, due to chronic nature of glaucoma the effects of treatment on costs and outcomes may persist into the future. Therefore a further modelling analysis (anticipated to be used a Markov model) will be undertaken to extrapolate results beyond the trial follow-up period. The primary source of data for the model will be the within trial dataset, but this will be supplemented with data from the literature where necessary. The uncertainty surrounding the model findings will be assessed using probabilistic sensitivity analysis (PSA) and deterministic analysis.

1. Background on the Trial

The World Health Organization has ranked glaucoma as the second most common cause of blindness after cataract, and as the leading cause of irreversible blindness (1). A recent study has shown that the global prevalence of glaucoma, for the population aged 40–80 years, is 3.54% (2). It has been estimated that in 2013 the number of people (aged 40–80 years) with glaucoma worldwide was 64.3 million, and it will increase to 76.0 million in 2020 and 111.8 million in 2040 (2).

Reducing intraocular pressure (IOP) is currently the only effective treatment for glaucoma (3-6). Better IOP control at an early stage reduces the risk of progression to blindness. The Advanced Glaucoma Intervention Study (AGIS) demonstrated that the extent of IOP lowering was related to the progression of visual fields over an 8 year period showing that progression was least when IOPs were maintained below 18 mmHg at all follow-up visits (7).

Primary treatment options in the UK for advanced glaucoma are mainly medical or surgical interventions. Currently most ophthalmologists treat patients medically starting with topical drop monotherapy followed by escalating the number of drop therapies until maximum tolerated combination therapy is achieved(8). The most frequently used drops (latanoprost, timolol, brimonidine) are now available in generic form and therefore cost less. In patients who continue to progress or in whom target IOP is not achieved, clinicians may opt for surgical intervention, most frequently trabeculectomy.(3-6, 9). Patients have indicated that they are not concerned about the treatment they receive as long as it is effective in prevention of further visual loss.(10)

Compared with surgery, primary drop treatment could save up-front surgery costs and other NHS costs in the short-term such as intensive follow-up and reduce the number of patients requiring cataract surgery to restore visual function. Avoiding surgery could improve patient health and quality of life (QoL) in the short-term, however in the long-term insufficient IOP control may lead to more visual field loss and poorer health outcomes. A trial of these two primary treatments is therefore required. We have conducted this pragmatic RCT to reduce the uncertainty regarding comparative effectiveness of current best medical care in the NHS (a stepped approach of medications) versus primary surgery (trabeculectomy).

1.1 Study Design

A pragmatic multicentre randomised controlled trial comparing primary medical treatment (a stepped approach of medications) with primary augmented trabeculectomy (primary surgery).

1.2 Outcome Measures

Primary Outcome

The primary objective of this trial is to compare primary medical treatment with primary augmented trabeculectomy (glaucoma surgery) for patients presenting with advanced glaucoma (Hodapp Classification severe) in terms of patient reported health status using the National Eye Institute visual function questionnaire 25 (NEI-VFQ25) at 24 months.

Secondary Outcomes

Patient-centred	Patient reported health status as measured by EQ-5D-5L (5-level), Health Utilities Index Mark 3 (HUI3), GUI Patient experience
Clinical	Visual field mean deviation (MD) changes Intraocular pressure (IOP) LogMAR visual acuity change Need for cataract surgery Visual standards for driving Registered visual impairment Safety
Economic	Incremental cost per Quality adjusted Life year (QALY) gained (based on responses to the EQ-5D-5L; HUI3) Incremental cost per QALY gained (based on responses to glaucoma utility index (GUI)) Incremental costs to NHS, personal social services and patients

1.3 Timing of Outcome Measurements

Outcomes		Post-randomisation (months)						
	Baseline	1	3	4	6	12	18	24
Medical History	✓							
Humphrey Visual Fields (x2)	✓			✓		✓		✓
Esterman Visual Fields	✓							✓
LogMAR Visual Acuity	✓			✓		✓		✓
IOP	✓			✓		✓		✓
Standard clinical examination	✓					✓		✓
NEI - VFQ-25	✓			✓		✓		✓
EQ-5D-5L	✓	✓	✓		✓	✓	✓	✓
HUI3	✓	✓	✓		✓	✓	✓	✓
GUI	✓	✓	✓		✓	✓	✓	✓

Patient experience questions	✓	✓	✓		✓	✓	✓	✓
Health Care Utilisation				✓		✓		✓
Participant Cost				✓		✓		✓
Participant Time and travel							✓	

1.4 Participants

TAGS is being conducted in over 20 centres within the UK. Each recruiting centre has at least one consultant who subspecialises in glaucoma. Participants have been randomised to medical treatment or augmented trabeculectomy (1:1 allocation minimised by centre and bilateral disease). The estimated sample size is 440 participants (n=220 in each arm). Participants are adult ≥ 18 years or over, diagnosed with severe open angle glaucoma (Hodapp classification (11) [has **any** of the following: 1. MD ≥ -12.dB, 2. More than 50% of points depressed below the 5% level on the pattern deviation probability plot, 3. More than 20 points depressed below the 1% level on the pattern deviation probability plot, 4. A point in the central 5 degrees has a sensitivity of 0-dB, 5. Points within 5 degrees of fixation under 15 dB sensitivity in both upper and lower hemi-fields] in one or both eyes at presentation including pigment dispersion glaucoma, pseudoexfoliative glaucoma and normal tension glaucoma.

2 Methods

Within this study both a 'within trial' and a model based economic evaluation will be conducted. The framework of the study is an integrated clinical and economic evaluation of the costs and patient outcomes associated with two alternative methods of management of patients presenting with advanced glaucoma. The 'within trial' analyses will take the perspective of the NHS and personal and social services, but we will also take a wider perspective by including costs borne by the participants and their families. The model based analysis will take the perspective of the NHS and personal and social services. As the duration of follow-up in both the within trial and the model based analyses is greater than one year both costs and benefits will be discounted at 3.5%, the UK recommended rate (12).

2.1 Within Trial Analysis

2.1.1 Health Care Cost Estimation

Costs of initial treatments (surgery/medications) including time in hospital and secondary care use will be based on data collected in Case Report Forms (CRFs). Unit costs for healthcare services will be obtained from standard sources such as NHS reference Healthcare Resource Group (HRG) tariffs, the

British National Formulary (BNF) (13) for medications, Unit costs of Health and Social Care (14) for contacts with primary care. Further data will come from the study centres themselves e.g. for the costs of consumable and other equipment used in the surgery. The price year adopted for the base case analysis will be the year when the final analysis is conducted. For each participant measures of use of resources (i.e. different types of surgical and non-surgical procedures such as trabeculoplasty, iridotomy, drainage implant surgery and etc.) will be combined with unit costs to provide a cost for that participant. These unit costs are reasonably specific to the individual procedures and are available by treatment location: inpatient, day case, and outpatient. Thus, the CRFs will be used to determine the procedure undertaken, the treatment setting and the durations of stay, and the appropriate reference cost will be used to cost each episode of care.

The number of outpatient visits, hospitalisations and interventions per patient for each relevant specialty will be obtained from the case report forms. Other health service costs incurred as the consequence of each intervention will be estimated prospectively for every participant in the study via questionnaire at 4, 12 and 24 months post-randomisation. For example, number of general practice contacts e.g. GP office or home visits or phone consultations will be obtained from the Health Service Utilization Questionnaire.

Unit costs for outpatient visits, hospitalisations and interventions will be obtained from the National Reference Costs. Unit costs for GP visits will be obtained from the Personal Social Services Research Unit (PSSRU) unit costs of health and social care (15). A potential list of unit costs and associated sources are presented in Table 1.

A list of medications that patients are taking at the moment of completing the questionnaire will be sought at each follow-up period. Length of medical treatment will be estimated based on the data in the CRFs and supplemented with data from clinical advice and information contained within the BNF. The unit costs for medications will also be obtained from the BNF (16). The duration of any relevant admissions (without intervention) during the follow-up period will also be estimated from the CRFs and costed using the methods described above. These costs will be summed to produce a total cost per patient. Once a cost for each patient has been estimated, the mean costs will be estimated by treatment allocation group.

Table 1 Preliminary list of unit costs that will be used in the analysis

Input variables	Unit cost (£)	Source	Details
Interventions			
Trabeculectomy		National schedule of reference costs year 2018-19	Intermediate glaucoma procedures implemented as day case (BZ18)
Subsequent procedures			
Laser iridotomy implemented as outpatient		National schedule of reference costs year 2018-19	Laser iridotomy (Minor glaucoma procedures implemented as outpatient
Lens capsulotomy		National schedule of reference costs year 2018-19	Lens capsulotomy (BZ04) implemented as outpatient
Iridoplasty		National schedule of reference costs year 2018-19	Major glaucoma procedures implemented as outpatient (BZ17)
Trabeculectomy		National schedule of reference costs year 2018-19	Intermediate glaucoma procedures implemented as day case (BZ18)
Cataract surgery		National schedule of reference costs year 2018-19	Phacoemulsification cataract extraction and lens implant implemented as day case
Primary health care			
General practitioner visit		PSSRU 2018	Community-based health care staff
General practitioner visit at home		PSSRU 2018	Community-based health care staff
General practitioner telephone conversation		PSSRU 2018	Community-based health care staff
Community optician & optometrist		National schedule of reference costs year 2018-19	Follow-up attendance- non consultant led outpatient attendances
District nurse		PSSRU 2018	Community-based health care staff
Practice nurse		PSSRU 2018	Community-based health care staff
Clinical support worker nursing (community)		PSSRU 2018	Community-based health care staff
Secondary health care			
Ophthalmologist visit		National schedule of reference costs year 2018-19	Consultant led outpatient attendances, follow-up

Finally, all of the health care cost in each intervention arm will be presented for each treatment group separately. The cost will be categorized in four groups including; Cost of intervention, cost of subsequent procedure, medication and primary care costs. For each cost category mean resource used and cost and the way they have been estimated will be presented as showed in Table 2.

Table 2 Dummy table of cost of health care utilization

Row	Intervention	Unit cost	Surgery		Medical therapy	
	Cost Category		**Mean (SD) resource use**	**Mean (SD) costs**	**Mean (SD) resource use**	**Mean (SD) costs**
1	**Cost of intervention**					
2	Trabeculectomy	Cost per case †	From trial data	=Unit cost*mean resource use	NA	NA
3	Medications	Cost per case ††	NA	NA	From trial data	=Unit cost*mean resource use
4	**Cost of subsequent procedure**					
5	cost of cataract surgery	Cost per case †	From trial data	=Unit cost*mean resource use	From trial data	=Unit cost*mean resource use
6	Cost of iridotomy	Cost per case †	From trial data	=Unit cost*mean resource use	From trial data	=Unit cost*mean resource use
7	Other procedures	Cost per case †	From trial data	=Unit cost*mean resource use	From trial data	=Unit cost*mean resource use
8	**Medication Cost**	Average participant cost (BNF) ††	From trial data	=Unit cost*mean resource use	From trial data	=Unit cost*mean resource use
	Primary care costs					
9	GP visits	Cost per consultation	From trial data	=Unit cost*mean resource use	From trial data	=Unit cost*mean resource use
10	GP calls	Cost per consultation	From trial data	=Unit cost*mean resource use	From trial data	=Unit cost*mean resource use
11	GP home visits	Cost per consultation	From trial data	=Unit cost*mean resource use	From trial data	=Unit cost*mean resource use
12	Practice nurse consultations	Cost per consultation	From trial data	=Unit cost*mean resource use	From trial data	=Unit cost*mean resource use
13	District nurse consultations	Cost per consultation	From trial data	=Unit cost*mean resource use	From trial data	=Unit cost*mean resource use
14	Community optician/optometrist	Cost per consultation	From trial data	=Unit cost*mean resource use	From trial data	=Unit cost*mean resource use
15	Other specialist	Cost per consultation	From trial data	=Unit cost*mean resource use	From trial data	=Unit cost*mean resource use
	Total costs	NA	NA	Sum rows	NA	Sum rows

† Average cost will be take account if the procedures has been done as a day case or inpatients/outpatients as well as existence of complication and comorbidity

†† since some drug can be prescribed in joint dose, estimations will be based on the medication price in joint dose where it is appropriate

2.1.2 Participant Costs

Participant costs which includes: self-purchased health care; travel costs for making return visit(s) to NHS health care; and time costs of travelling and attending NHS health care, will also be calculated. The participants travel and time questionnaire will be administered at 18 months post-randomisation.

- Self-purchased health care include items such as prescription costs and over the counter medications and costs associated with spectacle wear. Information about these is being collected through the health care utilisation questionnaire at 4, 12 and 24 months.
- Estimation of travel costs will be based upon the number of visits to GP, optometrists/community optician etc. (obtained from the health care utilisation questionnaire) and will be multiplied by the unit cost of making a return journey to each type of health care provider.
- The cost of participant time will be estimated in a similar manner. The participants will be asked how long they spent travelling to and attending their visits and what activity they would have been undertaking (e.g. paid work, leisure, housework) if they had not attended the health care provider. This data will be combined with appropriate unit costs, e.g. gross age/sex specific wage rates from the Department of Work and Pensions will be used to cost work time, to estimate the cost of participant's time.
- The estimated participant costs per healthcare visit will be combined with the estimates of number of health care contacts made to estimate total patient costs.
- Data on wage rates will be taken from the Department of Work and Pensions and used to value time lost from paid or unpaid employment (17), inferred rates for housework and leisure time were obtained from other published sources (18).

Table 3 Dummy table of Participant cost

Row	Cost category	Surgery	Medical therapy
		Mean (SD) Cost	**Mean (SD) Cost**
1	Cost of spectacle	From health care utilisation questionnaire	From health care utilisation questionnaire
2	Cost of other private care	From health care utilisation questionnaire	From health care utilisation questionnaire
3	**Total self-purchased costs**	**= sum of rows 1, 2**	**= sum of rows 1, 2**
4	Cost of return journey to GP	Cost of each return journey * the number of journeys	Cost of each return journey * the number of journeys
5	Cost of return journey to optometrists /optician	Cost of each return journey * the number of journeys	Cost of each return journey * the number of journeys
6	Cost of return journey to hospital	Cost of each return journey * the number of journeys	Cost of each return journey * the number of journeys
7	Cost of return journey to other outpatients attending	Cost of each return journey * the number of journeys	Cost of each return journey * the number of journeys

8	**Total travel costs**	**Sum of rows 4-7**	**Sum of rows 4-7**
9	Cost of time for return journey to GP/nurse	Time * unit cost of time at X activity	Time * unit cost of time at X activity
10	Cost of time for return journey to optometrists /optician	Time * unit cost of time at X activity	Time * unit cost of time at X activity
11	Cost of time for return journey to hospital	Time * unit cost of time at X activity	Time * unit cost of time at X activity
12	Cost of time for return journey to other outpatients visit	Time * unit cost of time at X activity	Time * unit cost of time at X activity
13	**Total Cost of time for return journey**	**=sum rows 9-12**	**=sum rows 9-12**
14	Cost of time off work	Time * unit cost of time at X activity	Time * unit cost of time at X activity
15	**Total patients cost**	**=sum rows 3, 8, 14**	**=sum rows 3, 8, 14**

2.1.3 Effectiveness Measures

Effectiveness will be measured in terms of quality adjusted life years (QALYs). The relative changes in health related quality of life resulting from the physical and psychological benefit together with any harms associated with each treatment strategy and with subsequent treatments will be captured by the EQ-5D-5L, HUI3 and the glaucoma specific GUI. QALYs will be estimated using the EQ-5D-5L questionnaire completed by participants at baseline, 1, 3, 6, 12, 18 and 24 months follow up. We will use value set developed by Devlin et al., (2016) to convert responses into utility values (19). QALY will be also estimated based on the responses to HUI3. HUI3 is a multi-attribute health status classification system providing an aggregated score on eight variables, i.e. vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. Scoring will be achieved through the HUI3 Multi-Attribute Utility Function on the Dead-Healthy Scale (20) as shown in Table 4. Here xn is the attribute level and bn is the attribute utility score. Then a patient's HUI3 score on the Dead-Healthy scale is defined by the formula on the Dead–Perfect Health scale:

$$u=1.371(b1\times b2\times b3\times b4\times b5\times b6\times b7\times b8)-0.371$$

Where u is the utility of a chronic health state on a utility scale where 'dead' has a utility of 0.00 and 'healthy' has a utility of 1.00. The range of the score is between –0.371 to +1.000.

Table 4 HUI3 Multi-Attribute Utility Function on the Dead-Healthy Scale

Vision	Hearing	Speech	Ambulation	Dexterity	Emotion	Cognition	Pain
x1 b1	x2 b2	x3 b3	x4 b4	x5 b5	x6 b6	x7 b7	x8 b8
1 1.00	1 1.00	1 1.00	1 1.00	1 1.00	1 1.00	1 1.00	1 1.00
2 0.98	2 0.95	2 0.94	2 0.93	2 0.95	2 0.95	2 0.92	2 0.96
3 0.89	3 0.89	3 0.89	3 0.86	3 0.88	3 0.85	3 0.95	3 0.90
4 0.84	4 0.80	4 0.81	4 0.73	4 0.76	4 0.64	4 0.83	4 0.77
5 0.75	5 0.74	5 0.68	5 0.65	5 0.65	5 0.46	5 0.60	5 0.55
6 0.61	6 0.61		6 0.58	6 0.56		6 0.42	

The QALYs for each participant will be calculated by estimating the area under the curve, assuming a linear change of utility values between time points. We will assign a zero utility weight for those participants who die within the study follow-up from their death until the end of the study. As we are collecting health utility data from each participant at baseline, we will perform an adjusted analysis to account for any imbalance in the health status of the two groups at baseline.

In addition, QALY will be estimated by Glaucoma Utility Index (GUI) as well. The GUI is a disease specific questionnaire that can be transformed using a standard algorithm (21) to produce a health state utility at each time point for each patient. The GUI dimensions include central and near vision; lighting and glare; activities of daily living; mobility, eye discomfort and other effects. This instrument has been scored using a discrete choice experiment conducted on a sample of individuals with glaucoma, providing a preference based index value on a scale where 0 is equal to the worst state and 1 is equal to the best state described by the instrument. The current scoring system for the GUI was developed using a sample where less than a third of participants has advanced disease. This means that the utility weights estimated in the current algorithm may not be representative of the trial population. Therefore in this study we will develop a revised algorithm. This will be accomplished by administering a discrete choice experiment (DCE) questionnaire to the trial population. The DCE has the same attributes and levels as the one used to derive the original algorithm but using an updated statistical design to reflect improvements in methodology. This DCE will be administered to trial participants at the end of study follow-up and analysed according to best practice methods.

EQ-5D-5L will be the main utility measure for the economic evaluation, as it has several advantages over HUI3. First, the EQ-5D-5L tariff is based on 'time trade-off' valuations by around 996 members of the UK general population (19). By contrast, the HUI3 value set is based on a mixture of visual analogue and 'standard gamble' valuations by 256 members of the Canadian general population (22, 23). The HUI3 tariff is, therefore, less precise and less relevant to a UK setting than EQ-5D-5L. Second, the EQ-5D-5L is recommended by NICE (12) and is used more widely than HUI3 (24). Also ICERs calculated using the EQ-5D-5L can, therefore, be directly compared with ICERs calculated in a large number of other UK economic evaluations to help decision-makers ensure that the most cost-effective treatments are provided. However, HUI3 will be used in sensitivity analyses, as it includes questions specifically relating to vision and may be more sensitive or responsive to changes in eye disease than EQ-5D-5L. We will not use GUI to estimate base-case QALYs. Although GUI is a disease specific utility measure, it is not anchored between 0-1 where 0 is equal to death. Therefore estimated QALY using GUI will not be comparable to QALY estimated using EQ-5D-5L scores.

As indicated in Table 5 all estimated utility scores for each follow-up time points and total QALY estimated using three different measures will be summarized for each intervention arm.

Table 5 Dummy table for effectiveness measures

Treatment	Trabeculectomy group		Medication therapy group	
Effectiveness	**Mean**	**SD**	**Mean**	**SD**
EQ-5D-5L Baseline				
EQ-5D-5L 1 months				
EQ-5D-5L 3 months				
EQ-5D-5L 6 months				
EQ-5D-5L 12 months				
EQ-5D-5L 18 months				
EQ-5D-5L 24 months				
QLAYs over 2 years using EQ-5D-5L				
HUI3 Baseline				
HUI3 1 month				
HUI3 3 months				
HUI3 6 months				
HUI3 12 months				
HUI3 18 months				
HUI3 24 months				
QLAYs over 2 years using HUI3				
GUI Baseline				
GUI 1 month				
GUI 3 months				
GUI 6 months				
GUI 12 months				
GUI 18 months				
GUI 24 months				
QLAYs over 2 years using GUI				

2.1.4 Statistical Analysis

All health economic outcomes will be described with the appropriate descriptive statistics. The continuous and count outcomes will be expressed as mean ± standard deviation or medians and inter-quartile range if required and dichotomous and categorical outcomes will be presented as absolute numbers and percentages. Analysis of costs to the health services and outcomes (QALYs) will estimate the mean differences (and bootstrapped 95% confidence interval) between the intervention and control groups.

All data will be analysed on an intention-to-treat basis using StataTM software. Healthcare cost and utility data often have several characteristics that must be addressed through the careful selection of appropriate statistical analysis methods. Within a defined period (e.g.1 year) significant proportions of

patients have no contact with healthcare provider's therefore no costs incur. However, amongst those individuals who have received a health services, the cost data are typically right-skewed because a relatively small proportion of patients incur extremely high costs. Although linear regression models can provide an unbiased estimate of parameters, it can be unstable given the skewness and kurtosis of the data distribution and inefficient due to heteroskedasticity. In this study general linear models (GLM) with appropriate variance functions (e.g. gamma, Poisson, etc) and link will be used to identify the relationship between treatment allocation and costs after adjusting for minimisation and the appropriate prognostic covariates at baseline (e.g. Baseline EQ-5D-5L score). To estimate the incremental effect of the treatment indicator variable, recycled predictions will be used.

2.1.5 Missing Data

Economic evaluations alongside RCTs are very likely to encounter problems with missing data. Total estimated cost is the sum of numerous components like inpatient care, primary care, and medications; if one component is missing then the total cost will also be missing. Complete case analysis may introduce biases if those with complete data differ from those with incomplete data. There are several methods that can be employed to account for such missing data. All analyses will also be repeated using a multiple imputation dataset (n=20) generated using chained equations to deal with missing cost and utility data (25).

2.1.6 Incremental Cost-Effectiveness Analysis

The joint estimates of costs and effects will be combined in an incremental analysis between two strategies, and will be presented as the point estimate of mean incremental cost-effectiveness ratio (ICER) for trabeculectomy versus medication therapy. The ICER is calculated as difference in costs divided by difference in effects (QALYs) between two treatment options. The Incremental cost per QALY gained will be estimated. Measures of variance for the joint incremental costs and effects will be obtained using non-parametric bootstrapping, and presented graphically using the cost-effectiveness plane and cost-effectiveness acceptability curves.

To help identify the optimal approach to treatment, the net monetary benefit (NMB) framework will be used, where the NMB for a given strategy is equal to the accrued QALYs multiplied by the ceiling ratio (CR) of willingness to pay (WTP) per QALY, minus the strategy costs.

NMB = (QALYs * CR) - Costs

The value of £20,000-30,000, which is typically used by NICE to inform judgements on cost-effectiveness, will be placed on Rc (12). The probability of each strategy generating the greatest NMB at this value of Rc will be reported (Table 6).

Table 6 Incremental cost effectiveness measures (within trial analysis)

Data	Intervention	Cost (£)	ΔCost (£)	QALY	ΔQALY	ICER (ΔCost/ ΔQALY) (£)	Probability cost-effective at Rc	
							£20,000	£30,000
Complete case data	Surgery							
	Medication							
Imputation data	Surgery							
	Medication							

2.1.7 Sensitivity Analysis

Bootstrapping estimates of incremental costs and QALYs gained will be obtained to characterise the uncertainty surrounding these outcomes as well as the ICER. Other forms of uncertainty, e.g. concerning the unit cost of a resource, will be addressed using standard deterministic sensitivity analysis. The ICER for intervention versus control group with be compared with accepted threshold values (£20-30,000 per QALY) to help inform judgements on cost-effectiveness. Key subgroup analyses will be conducted to reflect heterogeneity.

2.2 Model Based Analysis

2.2.1 Model Overview

Although the within trial results will prove useful, due to the chronic nature of glaucoma the effects of treatments on costs and outcomes may persist into the future. Therefore a further modelling analysis (expected to be a Markov model) will be undertaken to extrapolate the results of the trial beyond the two year follow up, which will help to inform likely longer-term cost-effectiveness.

The anticipated Markov model will be developed using in-house experience of previous evaluations of glaucoma treatment, the literature and advice from clinical colleagues. A preliminary version of the model structure is presented in Figure 1. The model will be used to simulate patient pathways from randomisation until death. The clinical trial outcomes will be used to define relative disease progression. These data will be combined with the best available UK relevant data to define transition probabilities for the model. All parameter estimates beyond two years will be informed by the data from the trial,

other existing data sources (routine databases and the literature) and expert opinion. Survival analysis methods will be used to generate transition probabilities for cataract surgery and disease progression (i.e. transiting to unilateral or bilateral blindness).

Based on the trial inclusion and exclusion criteria and given that participants could have one or two eyes eligible for the study (i.e. advanced glaucoma (stage 4 or 5 in either eye based on Hodapp Classification system) following combination of health statues, with regard to patients' eyes health, are possible within the Markov model (Table 7). However some of these health states may be rare or non-existent in the real world (e.g. being blind due to glaucoma in one eye and no glaucoma in the other eye). We have suggested this model structure as it will allow us to estimate the chance of unilateral and bilateral blindness more precisely even via a cohort Markov model.

Table 7 Theoretically possible health states with regard to glaucoma in either eye among participants within the trial

	condition	Non-index eye					
		No glaucoma	Stage 1	Stage 2	Stage 3	Stage 4 & 5	Blindness
Index eye	No glaucoma	NA	NA	NA	NA	NA	NA
	Stage 1	NA	NA	NA	NA	NA	NA
	Stage 2	NA	NA	NA	NA	NA	NA
	Stage 3	NA	NA	NA	NA	NA	NA
	Stage 4	NA	NA	NA	NA	NA	NA
	Stage 4 & 5	1	2	3	4	5	6
	Blindness	7	8	9	10	11	12

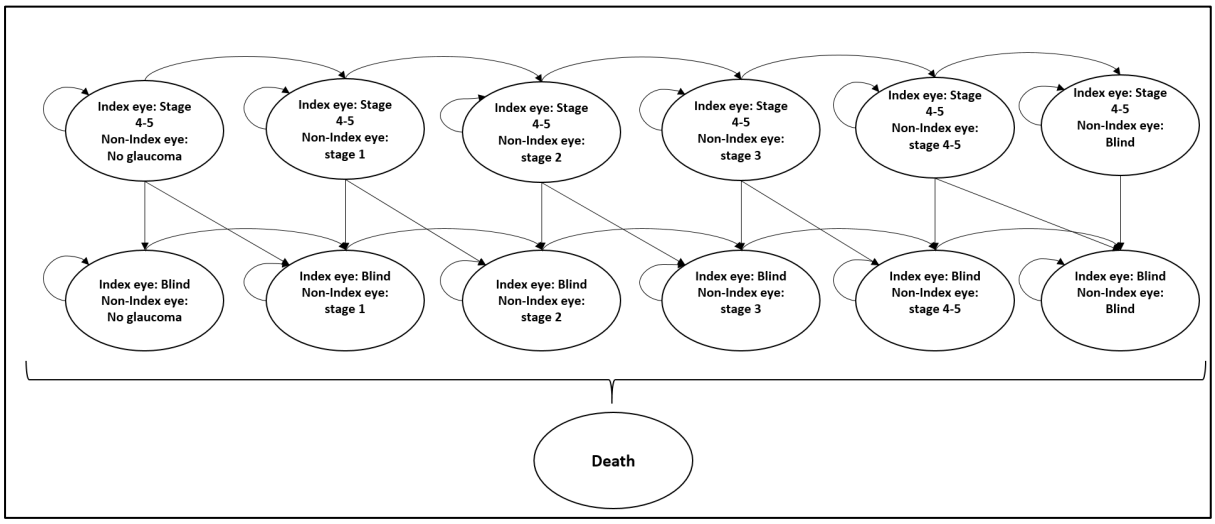

Figure 1 Model structure

The model structure will allow a cohort of patients with advanced glaucoma to enter into the model and then follow the disease progression to unilateral or bilateral blindness and death. The model will be updated iteratively on a constant six-month time interval known as the Markov cycle. Although it will take long time for disease progression for glaucoma, we have chosen 6 months cycle length because health utility data are being collected with 6 months interval after the first 6 months and we believe this will help to estimate QALY more precisely. The mean age and sex distribution of the modelled cohort will be matched that of the trial participants at baseline. During each model cycle, a portion of the cohort progresses based on the probabilities of progression derived from the analysis of the trial data. For those with binocular disease, the risk of visual loss in each eye will be modelled independently. Within each model cycle, a proportion of the cohort could have cataract surgery. This will be based on time dependent transition probabilities derived from a parametric survival model with appropriate distribution (e.g. Weibull, lognormal…) of the observed time to surgery up to 24 months follow-up. The distributions will be selected based on the Bayesian information criterion (BIC) and Akaike information criterion (AIC). Finally, death from all causes will be included in the model as an absorbing state. Transition probabilities to this state will be assumed to be independent of severity and treatment history and are derived from age/sex specific UK life-tables (26).

Costs will be assigned to each state in the model, reflecting the mean monitoring and medication costs per 6-month cycle by glaucoma severity and treatment allocation. To populate the model total monitoring and medication costs incurred within the trial follow-up period will be disaggregated to those incurred between each follow-up time point. This will be done to best reflect the trend in health services utilisation over time following initial intervention. Costs associated with cataract surgery will be incorporated as transition costs for those modelled to experience this event. Utility values will also be attached to the modelled severity states by treatment allocation group, allowing cumulative model based QALYs to be estimated. We will assign a zero utility weight for death health state. The mean QALYs for each intervention will be calculated by multiplying amount of time patients spend in each health state by associated health state utility values (HSUV). HSUVs will also be adjusted to account for the effect of ageing on patient's HRQoL using information provided by Kind et al. (27).

The model will be developed using TreeAge Pro 2017 (28) or R. Beyond 24 months in the model we will assume that the mean cost and utility values (by clinical severity state and treatment allocation) are the same as those incurred between 18 and 24 months. Alternative scenarios will be explored using sensitivity analysis. All parameters including costs and utilities will be defined as statistical distributions in the model, allowing probabilistic analysis to be conducted. Ranges and distributional assumptions for input parameters will be based on the trial data and literature. We will assign gamma distributions for costs and beta distributions for utility data. We will also calculate correlations between the estimated

coefficients for the variables included in the time-to-event and logistic regression analyses using Cholesky decomposition, and will assign multi-normal distributions to these parameters in the model to account uncertainty in the estimated transition probabilities. The analysis will be conducted using second order Monte Carlo simulation, whereby the model will be analysed 1000 times with a value randomly drawn for each input parameter from its assigned distribution. By estimating the NMB for each strategy on each iteration of the probabilistic analysis, cost-effectiveness acceptability curves will be generated. These present the probability of each strategy being cost-effective across plausible ranges for Rc. All future costs and QALYs will discounted using a discount rate of 3·5 percent per annum (12). All estimated final cost effectiveness measure including; QALYs, total cost; average cost effectiveness ratio, ICER and NMB for two time horizon will be presented in a table as below (Table 8).

Table 8 Dummy table of incremental cost effectiveness

Outcome Measure	**Short-term Time Horizon**		**Life-time Time Horizon**	
	Surgery	**Medication**	**Surgery**	**Medication**
	Mean SD	Mean SD	Mean SD	Mean SD
QALYs				
ΔQALY				
Total costs				
ACER (cost/QALY)				
ICER (Δcost/ΔQALY)				
NMB (ΔQALY * ceiling ratio - Δcost)				
Probability of cost effectiveness at 20k, 30k				

2.2.2 Sensitivity Analysis

Both probabilistic and deterministic sensitivity analysis will be used to explore parameter and other forms of uncertainty surrounding model based estimates of cost-effectiveness. The deterministic sensitivity analyses will be conducted to investigate the impact of varying key assumptions and/or parameter values used in the base case analysis. We will explore the robustness of our base case cost-effectiveness estimates using a best and worst case scenario analysis.

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