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
Protocol Version:	4
Protocol Date:	4th August 2016
ISRCTN:	56878850

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					
$\geq$ 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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