Study Title: 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

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1 AMENDMENT HISTORY

Amend-ment No.	Protocol Version No.	Date issued	Author(s) of changes	Section amended	Details of change
1	1.1		Anthony King	3. Glossary of abbreviations	Redundant abbreviations removed.
				5.2 Secondary outcomes	Esterman visual field graded instead of direct question on driving licence retention.
				6.3.1 Overall description of trial participants	Revision of eligible recruiting centres (see also 7.1).
				6.3.2 Inclusion Criteria	Removal of reference to female partners of male participants.
				6.4.3: Recruitment projection	New section added detailing feasibility pilot study. Subsequent section re-numbered.
				6.4.6: Clinical outcomes	Revision to how eligibility determined from VF tests. Esterman visual field at baseline and 24 months replace question about driving licence retention.
				6.4.6 Economic outcomes	Removal of reference to pregnancies in female partners of male participants.
				7.1 Treatment Strategies:	Rephrasing of sentence for clarity.
				8.1.3 Expected	All surgery will be undertaken by senior experienced glaucoma surgeons within 3 months of randomisation. Index eye will be operated

				adverse events. 8.2.3 Reporting AEs and SAEs 9.0 Statistics 9.4 13.1 Research Governance	on first if both eyes eligible. Addition of corneal decompensation. Investigator or a delegate can update missing information following SAE notification. Removal of reference to pregnancies in female partners of male participants. Investigator or a delegate can notify a pregnancy. Paragraph removed and added to new section 6.4.3. Redefinition of restrictions on surgeon involvement. The Statistical Analysis Plan will be available before the second, not first, Trial Steering Committee meeting. Reference to Declaration of Helsinki updated
2	1.2	25.6.14	Anthony King	6.3.1 Overall Description of Trial Participants	Point 5 corrected to refer to under 15dB sensitivity rather than -15dB.
3	1.3	6.8.14	Anthony King	Appendix A	Flow Chart corrected in surgery arm to show surgery within three months of randomisation in line with protocol. Additional box added to surgery arm to highlight requirement for pre-trabeculectomy measures to be conducted in clinic. Additional text added to

				Appendix B	highlight requirement for pre-trabeculectomy participant questionnaire.
4	1.4	26.8.14	Anthony King	8.1.3 Expected adverse events. Appendix B	Addition of cataract formation and retinal detachment to surgery arm. Additional row added to highlight requirement for Esterman Visual Fields at baseline and 24-month clinic visits. Additional text added to highlight Humphrey Visual Field tests required for both eyes at each clinic visit.
5	2.0	22.10.14	Anthony King	7.1	Dissociation of identification of Index Eye from order of surgery.
6	3.0	1.3.16	Anthony King	8.1.3 9.0	Addition of definition for visual acuity adverse event for loss of vision. Updated references in Section 9.0 and reference list.

2 SYNOPSIS

Clinical Phase	Phase IV	
Trial Design	A multicentre RCT of current best medical care in the NHS (a stepped approach of medications) versus primary surgery.	
Trial Participants	Adults presenting with advanced glaucoma in at least one eye	
Sample Size	440	
Follow-up duration	Twenty four months following entry into the study	
Planned Trial Period	Funding: 01/01/2014 - 31/01/2020	
Primary Objectives	Patient-centred Vision specific health profile (NEI-VFQ25) at 24 months	
Secondary Objectives	Patient-centred	Patient reported health status, HUI-3; EQ-5D (5-level), GUI, NEI-VFQ25; patient experience
	Clinical	Visual field mean deviation (MD) at 24 months Intraocular pressure (IOP); LogMAR visual acuity; 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; HUI-3); incremental cost per QALY gained [based on responses to glaucoma utility index (GUI]); incremental costs to NHS, personal social services and patients
Primary Outcome	The primary outcome will be measured at two years, analysed by intention to treat.	
Secondary Outcomes	The profile of secondary outcomes over time will be analysed by repeated measures using a linear mixed model. Subgroup analyses will explore potential effect modification of gender, age, one or both eyes affected and extent of visual field loss at baseline (<-20db, >=20db) on the primary outcomes.	
Surgical Intervention	Standard trabeculectomy augmented with mitomycin-C	
Medical Intervention	Currently licenced glaucoma drops will be used in the trial. These drops will be used in accordance with NICE guidelines. The drops will be used either as monotherapy or in combination therapy as part of an escalating drops regime for IOP control. In situations where maximum tolerated drops therapy is insufficient to control IOP acetazolamide may be administered orally either as 250mg tablet 4 times daily or 250mg SR capsule twice daily.	
Form	Eye drops/oral	
Dose	Various, depending on drug(s) used.	

3 GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CRF	Case Report Form
DCE	Discrete Choice Experiment
dB	Decibels
DMC	Data Monitoring Committee
EQ-5D	EuroQol Group's 5 dimension health status questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
GUI	Glaucoma Utility Index
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
HUI	Health Utility Index
IOP	Intraocular Pressure
ISRCTN	International Standard Randomised Controlled Trial Number
IVR	Interactive Voice Response (randomisation)
logMAR	Logarithm of the mean angle of resolution
MD	Mean Deviation
NEI-VFQ25	National Eye Institute Visual Function Questionnaire 25
NHS	National Health Service
NIHR	National Institute Health Research
PI	Principal Investigator
PIL	Patient Information Leaflet
PMG	Project Management Group
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SOP	Standard Operation Procedure
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TSC	Trial Steering Committee
UK	United Kingdom
UoA	University of Aberdeen
VF	Visual Field

4 BACKGROUND AND RATIONALE

Background and Epidemiology:
Glaucoma is a pressure related optic neuropathy resulting in progressive visual field deterioration. The World Health Organisation estimates that in 2010, 4.5 million people were blind due to glaucoma[1], accounting for 12.3% of global blindness. Glaucoma is estimated to affect around 2% of the UK population over the age of 40 years, increasing with age[2-6], as many as 10% of those in their 80s are affected. Glaucoma is the second commonest cause for registration as visually impaired in the UK accounting for 8.4-11.6% of registrations over the age of 65 years[7 8].This is likely to be an underestimate.[9]

In England in the NHS there are over 1 million glaucoma related visits per year. Management of glaucoma patients constitutes a major part of ophthalmologists' workload accounting for 23% of all follow-up attendances to the UK hospital eye service[10] and 13% of all new referrals[11]. The number of patients with glaucoma is predicted to increase substantially as the result of an ageing population[12]. Currently no effective screening strategy exists in the UK to identify all patients with glaucoma early[13].

Patients are unaware of glaucoma because it is typically asymptomatic in early stages, and as a consequence, in the UK between 10% and 39% of patients with glaucoma present with advanced disease in at least one eye[14-18]. In the most recent study, more than a third of patients presenting to secondary care had severe disease in at least one eye at presentation[16]. Those most at risk include the socially disadvantaged with no family history of glaucoma, those with high intraocular pressure, and those who do not attend an optometrist regularly[16 18-20]. Sight loss from glaucoma is preventable.

Advanced glaucoma at presentation - a risk factor for blindness:
Presentation with advanced visual field loss increases the risk of further progression and blindness[21-26]. Odberg[21] noted in a cohort of patients with advanced glaucoma 70% of the affected eyes had progressed after a mean of 7.6 years despite treatment. Grant and Burke[23] found that eyes with a visual field defect at the beginning of treatment were more likely to progress to blindness than eyes in which treatment was started when there was no field loss. Wilson[24] found that initial field loss was the strongest determinant of the rate of further field loss. The rate of deterioration was 11.7 times faster in eyes with more advanced field loss at presentation. Mikelberg[22] found that when scotoma mass was small (i.e., early glaucoma) the rate of visual field loss was slow, but when large (i.e., severe glaucoma), rapid linear progression of visual field loss occurred. Oliver found that unilateral blindness due to glaucoma more than doubled the risk of bilateral blindness[27].

Current treatment options:
Reducing IOP is currently the only effective treatment for glaucoma[28-31]. 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[32].

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[33]. 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.[28-31 34] 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.[35]

Recently published NICE guidelines suggest patients presenting with advanced disease should be offered augmented trabeculectomy as a primary intervention and only offered medical treatment if surgery is declined[36] but highlighted that the evidence to support this recommendation is of poor quality. By using drops as first line treatment instead of surgery, and operating only on patients who fail this drop therapy, NHS resources could in the short term be saved, however the long term effects on visual outcome are uncertain. Modern glaucoma drops lower IOP significantly better and have fewer side effects than those previously used, this may obviate the need for surgery. Social resources will be saved by avoiding the need to support those becoming blind. A survey of consultant ophthalmologists indicated most do not follow NICE guidance and prefer medical treatment because of the poor evidence base and concern regarding surgery complications[33].

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 QoL in the short-term, however in the long-term insufficient IOP control may produce more visual field loss and poorer health outcomes. A trial of these two primary treatments is therefore required.

Rationale for the study:
There is uncertainty about how best to manage patients diagnosed with advanced glaucoma. Such individuals have a high risk of blindness and effective treatment is needed to minimise the chances of disease progression. At the moment NICE guidelines recommend initial surgery but acknowledge the lack of evidence to support this recommendation. Surgery may be more effective in the long-term but is associated with potential adverse events and increased costs at the time of surgery. Current medical therapies (eye drops) may be able to control the disease in a proportion of patients with advanced glaucoma. The question that we will try to answer is: Is primary medical treatment clinically and cost-effective for the management of newly diagnosed advanced glaucoma compared with the current standard care of trabeculectomy (glaucoma surgery).

A recent Cochrane systematic review[28] comparing primary medical versus surgical treatment for open-angle glaucoma (OAG) identified four relevant studies. Despite methodological weaknesses and non-standard treatments [29 37-39], the authors concluded that "in more severe open-angle glaucoma there is some evidence, from three trials[37-39] that medication was associated with more progressive visual field loss and less intraocular pressure lowering than surgery[37 38]. Risk of treatment failure was greater with medication than trabeculectomy (OR 3.90, 95% CI 1.60 to 9.53; HR 7.27, 95% CI 2.23 to 25.71)". Three of these four trials are now obsolete because of new medical treatments, and the most recent study did not include patients with advanced disease.

The authors concluded that surgery lowers IOP more than medication, however none of these trials specifically addressed the management of those presenting with advanced glaucoma or used modern glaucoma medications which produce better IOP lowering and have fewer side effects than previous generations of drops. The authors recommended that further RCTs comparing current medical treatments and modern glaucoma surgery are required in people with advanced open angle glaucoma[28].

This uncertainty has subsequently been added to the UK Database of Uncertainties about the Effects of Treatments (UK-DUETS) as an important question requiring further investigation:

http://www.library.nhs.uk/DUETS/ViewResource.aspx?resID=327523&tabID=297&catID=14501.

Sight loss from glaucoma is preventable; the Public Health Outcomes Framework for England 2013-2016 has made reducing numbers of people living with preventable sight loss a priority[40]. An advanced glaucoma intervention study (AGIS) has been undertaken but this did not compare primary medical and surgical interventions[41], as all patients had failed maximum medical treatment prior to entry. In addition, it included patients with mild glaucoma. The USA-based collaborative initial glaucoma treatment study (CIGTS), while comparing the outcomes of primary medical and primary surgical treatment in newly diagnosed patients with glaucoma, enrolled patients presenting with mild disease (CIGTS score 4.6 +/-4.2)[29]. A recent update from CIGTS suggests that a subgroup of patients presenting with more advanced disease (MD < -10db) had slower visual field progression if their primary intervention was surgical[42].

This study aims to reduce the uncertainty identified by the Cochrane review[28], UK-DUETS and NICE[36] by undertaking a pragmatic RCT of current best medical care in the NHS (a stepped approach of medications) versus primary surgery. In addition it aims to address the concerns of the Public Health Outcomes Framework for England 2013-2016[40] by identifying the best treatment approach to minimise preventable sight loss in this group of vulnerable patients.

5 OBJECTIVES

5.1 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-VFQ25).

5.2 Secondary Objectives

- To compare generic, visual and glaucoma specific patient reported health and experience in the short and medium term
- To compare the incremental cost per Quality Adjusted Life Year (QALY) gained based on responses to the (1) EQ-5D (2) HUI-3 and (3) GUI of the more effective treatment
- To compare clinical outcomes (visual field mean deviation (MD) changes, LogMAR visual acuity changes, IOP, Esterman visual field for driving vision, registered visual impairment)
- To compare need for additional cataract surgery
- To compare safety by comparing adverse events from both surgical and medical interventions
- To employ an existing Discrete Choice Experiment (DCE) amongst participants with advanced glaucoma to generate a revised scoring system for the GUI that is more sensitive and specific for those with advanced disease.
- To compare long-term costs and benefits through a modeling evaluation

Further funding will be sought to evaluate clinical and patient reported outcomes at 5 and 10 years for this cohort of patients to further explore the lifetime experience, patient reported outcomes and visual loss (visual acuity and visual field survival) of this group of patients. These data would be incorporated into an updated economic model once they become available.

6. TRIAL DESIGN

6.1 Summary of Trial Design

A pragmatic[43 44] multicentre randomised controlled trial (RCT) comparing primary medical treatment with primary augmented trabeculectomy (standard care) (see Appendix A Trial Flow Diagram). Participants will be randomised to medical treatment or augmented trabeculectomy (1:1 allocation minimised by centre and bilateral disease). We will include an internal pilot to confirm the feasibility of recruitment targets.

The perspective of this study is that of the NHS, the patient and society. 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. Both treatment strategies currently in use have been reliably evaluated to assess efficacy and safety. The proposed study will be a prospective RCT to assess relative effectiveness, safety and costs in routine practice. The treatment protocol for the trial will reflect routine care to ensure that the results are representative of NHS practice.

6.2 Primary and Secondary Outcome Measures

6.2.1. Primary outcome

The trial has a primary patient reported outcome, the vision specific health profile (NEI-VFQ25). The primary outcome will be evaluated at 24 months. This is sufficient time to capture the short-term differences in effects and to accurately profile the different patient pathways associated with each intervention.

6.2.2 Secondary outcomes

Patient-centred	Patient reported health status as measured by EQ-5D (5-level), HUI-3, GUI, NEI-VFQ25 (Please see Appendix B for schedule)
	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 costs to NHS, personal social services and patients
	Incremental QALYs (based on responses to EQ-5D, HUI-3 and glaucoma utility index

6.3 Trial Participants

6.3.1. Overall Description of Trial Participants

Four hundred and forty adults presenting with advanced (severe) glaucoma in at least one eye. Advanced disease will be classified according to the "severe" category of visual field loss using the Hodapp classification of glaucoma severity[45] [has **any** of the following]: 1. MD < -12.00dB, 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.

Participants will be recruited in secondary care. Over 20 centres within the UK will be involved. Each recruiting centre has at least one consultant who subspecialises in glaucoma.

6.3.2 Inclusion Criteria

- Severe glaucomatous visual field loss (Hodapp classification) in one or both eyes at presentation.
- Open angle glaucoma including pigment dispersion glaucoma, pseudoexfoliative glaucoma and normal tension glaucoma.
- Willingness to participate in a trial.
- Ability to provide informed consent.
- Adult ≥ 18 years.
- **Female participants of childbearing potential must be willing to ensure that they use effective contraception during the study and for 3 months thereafter. A negative urine pregnancy test for females of childbearing potential is required prior to randomisation.**

6.3.3 Exclusion Criteria

- Inability to undergo incisional surgery due to inability to lie flat or unsuitable for anaesthetic.
- High-risk of trabeculectomy failure such as previous conjunctival surgery, complicated cataract surgery.
- Secondary glaucomas, and primary angle-closure glaucoma.
- Females who are pregnant, nursing, or planning a pregnancy or females of childbearing potential not using a reliable method of contraception. A female is considered to be of childbearing potential unless she is without a uterus or is post-menopausal and has been amenorrheic for at least 12 consecutive months.

6.4 Study Procedures

The intervention will be either primary medical treatment or augmented trabeculectomy. Both interventions are established and well documented approaches to the management of glaucoma[36]. Following randomisation, care for both groups will follow NICE guideline recommendations[36].

6.4.1 Screening and Eligibility Assessment

Patients likely to be eligible for the trial will be identified at the initial consultation for glaucoma by a member of the clinical assessment team. The consultant/research nurse will introduce the study to the patients and, if potential interest is expressed, provide further details of the study by means of the Patient Information Leaflet and information pack. The contact details of all interested patients will be passed on to the study research nurse. If the patient agrees in principle to the study then arrangements will be made for assessment and consenting. This may be done as a separate appointment or at the initial visit if the patient consents to participate at that visit. These arrangements will be individualised for each centre. Eligible participants will be asked for their signed informed consent before being randomised. Both the patient information sheet and the consent form will refer to the possibility of long-term follow-up.

6.4.2 Informed Consent

Informed consent to participate in the trial will be sought and obtained according to Good Clinical Practice (GCP) guidelines. Signed informed consent forms will be obtained from the participants by an appropriately trained individual. Potential participants will be given sufficient time to accept or decline involvement and will be given the opportunity to ask questions. It will be explained that entry into the trial is entirely voluntary and that treatment

and care will not be affected by their decision. It will also be explained that they can withdraw at any time. In the event of their withdrawal, data collected will be retained for inclusion in the final analyses, unless the participant explicitly requests that it is erased.

In centres where it is possible to vet clinic referrals prior to the patient's attendance at clinic, potentially eligible subjects will be identified from their referral letters. In advance of their clinic appointment they will be sent a letter informing them that they may be approached by a member of the clinical team at the clinic visit and asked to participate in a trial.

This letter will be from the local lead clinical investigator who will be the glaucoma specialist in charge of their care. Where vetting of letters is not possible in advance of the clinic appointment, patients likely to be eligible for the trial will be identified at the initial consultation for glaucoma by a member of the clinical assessment team.

Following the provision of the patient information leaflet to the patients and a discussion about the study with the treating ophthalmologist and/or local research nurses/recruitment officers, eligible patients who state that they have had sufficient time and information to make a decision to participate will be invited to complete and sign the consent form at that clinic visit. The consent form will be countersigned by the local clinical team member who has taken the consent (ophthalmologist, local research nurse or recruitment officer).

Patients who take the trial paperwork home and subsequently decide (after further information provision, if requested, by phone from the local clinical team) can return this to the clinical team at their treating hospital by post. If participants return forms by post, the form will be counter-signed and dated on receipt by the local clinical team member (ophthalmologist, local research nurse or recruitment officer). The participant will either be sent a copy of the consent form back through the post or provided with one when they return to hospital.

6.4.3 Recruitment projection

All participating centres have indicated a throughput of least 20 eligible patients annually. The recruitment projection is based on 20 sites recruiting approximately 9-11 patients per year, with a staggered start of recruiting sites. This allows 440 participants to be recruited over 3 years incorporating a reduced rate during the first month of each site set up and 50% reduction during holiday time (August and December).

During the early part of the trial we will conduct a pilot study to demonstrate that recruitment is feasible and that the target of 440 is achievable with the given number of centres. The pilot phase will run until we have aggregated 75 recruiting months (anticipated to be around trial month 20). By that time we expect to have recruited around 55 participants. If less than 34 participants have been recruited in 75 centre months we would consider whether the study is feasible and enter discussions with the funder; between 34 and 41 we would modify our recruitment plan (e.g. whether we needed more sites); 42 recruits or above we would conclude that recruitment is feasible and continue without alteration.

6.4.4 Baseline Assessments

Following consent but prior to randomisation, participants' relevant medical history, IOP, Humphrey visual fields, best corrected LogMar visual acuity will be collected. A general ophthalmic examination including central corneal thickness will be undertaken. Participants will complete a questionnaire including the NEI-VFQ25, EQ-5D, HUI-3, GUI and a question asking about the patient's experience of glaucoma.

6.4.5 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 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 unblinding procedures are necessary as this is an open label trial.

6.4.6 Subsequent assessments

Data Collection and Processing

Patient-centred data will mainly be collected through patient-completed questionnaires. These will be completed either in the participant's home or at clinic, as appropriate. Clinical data will be collected and entered onto the TAGS secure web database at the participating sites.

Patient centred outcomes: NEI-VFQ25 is a vision specific patient reported quality of life tool. This validated questionnaire has been widely used to evaluate visual outcomes in glaucoma[46-49]. In addition to eliciting information about general health and vision it specifically addresses difficulty with near vision, distance vision, driving and the effect of light conditions on vision. We believe this provides a comprehensive evaluation of vision related quality of life. VFQ25 will be completed at baseline and 4, 12, and 24 months post randomisation and immediately prior to trabeculectomy. Generic EQ-5D 5L and HUI-3 and the glaucoma specific GUI will be collected to generate utility outcomes. These questionnaires will be completed at baseline, 1, 3, 6, 12, 18 and 24 months post-randomisation and immediately prior to trabeculectomy.

Clinical outcomes: Visual field (VF) mean deviation (MD) represents the amount of vision loss occurring due to glaucoma during the study period. This outcome measure has been chosen as it represents the severity of disease and will make possible the comparison of the efficacy of the interventions. We have selected a summary VF measure, for which there is data from a clinically similar cohort in the literature to power this study. It is a routinely measured parameter in standard care of glaucoma patients and it is the primary clinical measure on which management decisions in glaucoma are made, according to NICE guidelines.[36] Assessment of VF damage is the major measure of the functional impact of glaucoma with direct relevance to quality of life measures[47 50-52]. Humphrey visual fields (24-

2 SITA- standard) will be performed on all participants, as recommended by NICE guidelines. All VFs tests will be performed by VF technicians. VFs eligible for analysis will have to achieve pre-defined reliability criteria (False positives <15%). If the visual fields are not reliable they will be repeated according to the clinicians' discretion in accordance with local clinical practice. Two baseline VFs (24-2 SITA-Standard) will be performed prior to randomisation to confirm eligibility. Eligibility will be confirmed on the basis of two reliable baseline 24-2 SITA standard VF tests performed. If the second visual field does not fulfil the criteria for "severe defect" by the Hodapp criteria then a third visual field must be undertaken prior to randomisation and the result of this will be deemed to define whether the subject is eligible. These will be performed at the same baseline clinic evaluation or at a separate evaluation but must be completed prior to randomisation. At 24 months two reliable 24-2 SITA standard visual fields will be performed and used to establish the VF outcome MD. In addition a reliable Esterman visual field will be performed and will be used to assess driving eligibility. An independent VF reading centre will assess all the VFs. The reading centre will be masked to the treatment received by the study participant.

Intraocular pressure (IOP) will be measured at baseline, 4, 12 and 24 months. The unit of IOP measurement is millimetres of mercury. Goldman tonometry will be used to measure IOP. The measurement will be undertaken by two observers, the first observer will be interacting directly with the patient. Without looking at the measurement dial the investigator will apply the Goldman tonometer to the eye, and will reach the endpoint for the measurement value of IOP. The second observer will then record the values from the measurement dial. This process will be repeated, and both measures will be recorded. If a difference of more than 3 mmHg exists between first and second measurement a third measurement will be undertaken. Best-corrected LogMAR visual acuity will be measured at baseline, 4, 12 and 24 months post randomisation. Complications of surgery, need for cataract surgery and therapy changes, will be captured from the participants' case records. All clinical outcomes will be recorded on a trial specific CRF.

Retention of ability to drive is one of the most important issues to patients with glaucoma[35]. All patients diagnosed with glaucoma are obliged to inform the DVLA of their diagnosis. Visual standards for driving are assessed on the basis of VF and visual acuity levels. This assessment is arranged at regular intervals by the DVLA. To evaluate visual standard for driving all participants will have an Estermann Visual Field preformed (on the Humphrey Visual Field Analyser) at baseline and final visit at 24 months. Registration as visually impaired is based on visual acuity and visual field criteria. Consultant ophthalmologists are responsible for registering patients as visually disabled on the basis of these criteria. If a participant has been registered as visually impaired or severely visually impaired, this will be recorded along with the date of registration in the study CRF at 24 months.

Economic outcomes: Costs of initial treatments (surgery/medications) including time in hospital and secondary care use will be based on data collected in CRFs. Primary care, personal social service use and patient costs will be collected via questionnaire at 4, 12 and 24 months post-randomisation. Responses to the EQ-5D, HUI-3 and GUI will be combined with relevant tariffs to produce QALYs. Costs and QALYs will be combined in a cost-utility analysis for both 'within trial' and modelled over the patient's lifetime. For the latter, a model will be developed from our previous NIHR HTA funded studies[13 53].

Discrete Choice Experiment: An existing DCE questionnaire will be administered to trial participants to obtain utility scores more applicable to people with advanced glaucoma. The DCE questionnaire will be administered to all trial participants at 27 months. By this time the treatment profiles associated with each randomisation option will be established and patients will be in a position to make experience based judgements. This time point has also been chosen to minimise the burden of patient questionnaires which may occur at other time

points. These data will be used to score the GUI responses and will be incorporated into the economic evaluation.

Pregnancy: Any pregnancy that occurs in a female participant during the study should be followed to outcome. In some circumstances, it may be necessary to monitor the development of the new-born for an appropriate period post- delivery.

Should the female participant not wish for the pregnancy to be followed to outcome or beyond, this should be noted in the CRF and medical notes as appropriate.

6.5 Definition of End of Trial

The end of trial is the date of the last 24-month follow-up of the last participant, although, subject to additional future funding, the intention is to follow-up participants for 10 years. The end of current trial funding is 31 January 2020. Glaucoma is a lifelong disease and patients will need to be monitored and treated for their glaucoma in accordance with NICE guidelines following the end of the study. This will be the responsibility of the clinician overseeing their glaucoma care.

6.6 Discontinuation/ Withdrawal of Participants

Participants can withdraw at any time. The local clinical team would identify what the participant wishes to withdraw from (clinical intervention, completing questionnaires etc). In the event of withdrawal, data collected to that time-point will be used in the final analyses unless the participant explicitly requests that data are deleted. Participants would be advised of any need for continuing clinical follow-up to monitor/treat their advanced glaucoma.

The reason for withdrawal will be recorded in the CRF.

6.7 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF) and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). In this study all clinical data are routinely collected in medical notes and other relevant documents and therefore the CRF will not be the source documents.

Participant completed questionnaires will be source data.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent form, the participant will be referred to by the unique study number, not by name.

7. TREATMENT OF TRIAL PARTICIPANTS

7.1 Treatment Strategies

Arm 1: Primary Medical Treatment – escalating medical therapy
Participants randomised to medical management can be prescribed a variety of currently licenced glaucoma drops. These drops will be used in accordance with NICE guidelines[36]. Definition of escalating medical treatment: study participants may be started on one or more medications at their initial visit depending upon the judgement of the treating clinician. When monotherapy is initiated this should be with a prostaglandin analogue as directed by NICE

guidelines, subsequent addition of medications is based on clinician judgement/preference. When drops fail to control IOP adequately oral carbonic anhydrase inhibitors may be used.

Arm 2: Primary trabeculectomy – standard trabeculectomy augmented with mitomycin-C
Definition of standard trabeculectomy: creation of a "guarded fistula" by making a small hole in the eye which is covered by a flap of partial thickness sclera and which allows aqueous humour to egress from the eye into the subconjunctival space. The operation may be performed under either local or general anaesthetic and normally takes about 40-60 minutes to complete.

All surgery will be undertaken within three months of randomisation by a consultant who subspecialises in glaucoma or a glaucoma fellow who has performed at least 30 trabeculectomies. Where both eyes are eligible for the study a decision will be made locally about which eye will undergo trabeculectomy first.

7.2 Compliance with Study Treatment

This is designed as a pragmatic trial and compliance will be monitored in the study as it would be in routine clinical practice by asking the patient if they are taking their drops. There is currently no practical and effective method for monitoring compliance in patients taking glaucoma medications. In essence the degree of compliance will feed into the outcome measurements as poor compliance in the medical group is likely to lead to further disease progression. There is no requirement for participants to return any unused eye drops.

7.3 Accountability of the Study Treatment

The local clinical team will use a standard hospital prescription form or will ask the patient's GP to prescribe the medications required – whatever is standard practice for that department. This is pragmatic and represents standard NHS practice.

7.4 Concomitant Medication

Medications as required for normal clinical care should be prescribed for the patients. Throughout the study Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care.

8. SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event (AE)

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant that does not necessarily have to have a causal relationship. Adverse events are not:

- Continuous and persistent disease or symptom, present before the trial, which fail to progress;
- Signs or symptoms of the disease being studied

8.1.2 Serious Adverse Event

A serious adverse event (SAE), is any AE that:

- results in death;
- is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- 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.

8.1.3 Expected Adverse Events

In this trial the following events are potentially expected:

Medical Treatment: Redness, stinging, itching, transient blurred vision, eyes watering, ocular discomfort, allergy, eyelash growth, change in skin colour around eye, change in iris colour, shortness of breath, unpleasant taste in mouth, dry mouth, fatigue, kidney stones, skin rash, cataract formation and retinal detachment. In some case these symptoms may be due to preservatives in the drops – if this is the case preservative free drops can be used.

Trabeculectomy with mitomycin C: Discomfort, blurred vision, corneal epithelial defect, conjunctival button-hole, flap dehiscence, IOP too low, transient choroidal effusion, suprachoroidal haemorrhage, hyphema, early bleb leak, shallow anterior chamber (grades 1-3), iris incarceration, persistent uveitis, transient or permanent ptosis, macular oedema, malignant glaucoma, corneal decompensation, cataract formation and retinal detachment, late bleb leak, bleb infection, bleb related endophthalmitis, permanent severe loss of vision at time of surgery (< 1/500), bleeding in the eye.

Visual Acuity Adverse event

Any of the following:

- Irreversible loss of 10 ETDRS letters of logMAR visual acuity,
- loss of 2 or more stages of categorical visual acuity measurement (Count Fingers, Hand Motion, Light Perception, No Light Perception)
- any loss to No Light Perception.

These are based on knowledge of adverse events associated with augmented trabeculectomy and the relevant product information documented in the SmPC. The latest online version of the appropriate SmPC will be considered in the assessment of an adverse event.

8.2 Reporting Procedures for All Adverse Events

8.2.1 Detecting AEs and SAEs

Participants will be asked about any AEs. When an AE occurs, it is the responsibility of the local Principal Investigator (PI) (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event.

Planned hospital visits for conditions other than those associated with glaucoma will not be collected or reported.

8.2.2 Evaluating AEs and SAEs

Assessment of Seriousness

The Principal Investigator (or a delegate) will make an assessment of seriousness as defined in section 8.1.2.

For AEs that meet the criteria for seriousness as defined in section 8.1.2, causality and expectedness will be evaluated.

All deaths for any cause (related or otherwise) will be recorded on the serious adverse event form.

Hospital visits (planned or unplanned) for further treatment of glaucoma will be recorded as outcome measures, but will not be reported as serious adverse events.

Any SAEs related to the treatment for glaucoma (e.g. if a participant is admitted to hospital for treatment of infection) will be recorded on the serious adverse event form.

Assessment of Causality

The Investigator must make an assessment of whether the SAE is likely to be related to treatment according to the following definitions:

An event is defined as related if it occurs as a result of a procedure required by the protocol, whether or not this procedure is the specific intervention under investigation and whether or not it would have been administered outside the study as normal care. This includes the procedure that the participant has been randomised to (e.g. a hospital re-admission due to bleeding after surgery would be a related SAE).

All SAEs judged as related to study procedures are considered to have a causal relationship.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Expectedness

When assessing expectedness refer to the expected events (Section 8.1.3)

8.2.3 Reporting AEs and SAEs

There is no need to report non-serious events to the CI, Sponsor or REC.

Reporting responsibilities

An SAE form is to be uploaded onto the trial website within 24 hours of the investigator's knowledge of the event. The Trial Manager will be automatically notified. If, in the opinion of the local PI and the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager will notify the sponsor within 24 hours of receiving the signed SAE notification.

The CI (or an appropriate delegate) will inform the main REC of these safety issues. Related and unexpected SAEs will be reported no later than 15 calendar days after they are first aware of the event.

If all the required information is not available at the time of reporting, the Investigator (or a delegate) must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

All related SAEs will be summarised and reported to the Ethics Committee, the Funder and the Trial Steering Committee in their regular progress reports.

Pregnancy

Pregnancy is not considered an AE or SAE however the investigator must collect pregnancy information for female trial subjects who become pregnant while participating in the study (TAGS definition is while taking or within three months of ceasing to take study medications). The Investigator (or a delegate) should record the information on a Pregnancy Notification Form and submit this to the Sponsor within 14 days of being made aware of the pregnancy.

Any pregnancy that occurs in a participant during the study should be followed to outcome. In some circumstances, it may be necessary to monitor the development of the new-born for an appropriate period post-delivery.

Should the participant not wish for the pregnancy to be followed to outcome or beyond, this should be noted in the CRF and medical notes as appropriate.

9. STATISTICS

The primary patient reported outcome is the health status measured by the NEI-VFQ25 assessment at 24 months. A study with 190 participants in each group would have 90% power at 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-VFQ25 assuming a common SD of 18 points observed in previous work which is a clinically relevant effect size in patients with advanced glaucoma[54, 55]. Seven points is a likely minimally important difference based on our pilot work on NEI-VFQ scores in patients with glaucoma[55] but there is uncertainty and so we have opted for a more conservative 6 point difference, which is supported by the literature for another chronic eye disease, macular degeneration[56]. Assuming a drop-out rate of 13.5% due to declining further follow-up and death, a total of 440 participants would need to be randomised to be able 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 is derived from a subgroup of patients with advanced glaucoma[28 42] and is a clinically significant difference in the context of advanced glaucoma and predictive further visual disability.

Methods to protect against sources of bias

Selection bias should be minimised and external validity should be maximised as we have used an appropriately sized study sample size, multiple centres and clinicians, and participants are randomised.

To ensure that recognised standard trabeculectomy procedures [57 58] are being followed by all participating glaucoma surgeons all potential surgeons will complete a questionnaire about their surgical technique.

It is impossible to mask the patient or those measuring outcomes to the intervention. All visual field evaluations will be undertaken by an independent reading centre masked to the participant intervention. Intraocular pressure measurement will be undertaken by two observers one taking the reading and the other reading the IOP value to minimise risk of measurement bias.

The expected attrition rate is low based on previous glaucoma treatment RCTs and we have allowed for a potential attrition rate of 13.5% over 24 months to accommodate this.

9.1 Description of Statistical Methods

Baseline characteristics, follow-up measurements and safety data will be described using the appropriate descriptive summary measures. The primary outcomes measured at two years will be analysed using linear regression correcting for baseline measure of the primary outcome and other prognostic variables, for example amount of vision loss and pressure at baseline, one or both eyes affected. 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. The primary analysis strategy will be intention-to-treat. Potentially missing data will be handled using appropriate methods[59] depending on the amount and pattern of missingness with sensitivity analysis to test assumptions[60]. In trials of medical versus surgical management there exists potential for cross-over to the alternative allocation. Therefore, if required, in addition to the "effectiveness" estimate from the intention-to-treat analyses we will explore "efficacy" estimates using causal modelling methods suitable for complex interventions[61]. Secondary outcomes will be analysed using a similar strategy with models suitable for the outcome (i.e. logistic regression for dichotomous outcome need for cataract surgery at two years). 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. All treatment effects will be derived from these models and presented with 95% confidence intervals.

9.2 Planned subgroup analyses

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

9.3 Criteria for the Termination of the Trial.

Due to the staggered nature of recruitment and the primary outcome measurement at two years we do not anticipate that the trial would be terminated early for benefit. We propose one main effectiveness analysis at the end of the trial. During the trial, safety and other data will be monitored by reports prepared for the DMC. The frequency of DMC meetings will be decided with the DMC but we anticipate that these will be at least annually whilst the trial is in recruitment phase

9.4 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

The Statistical Analysis Plan (SAP) will be drafted early in trial, before the second DMC and TSC meetings so that those committees can pass comment on the content of the SAP. Upon agreement of content this will constitute the first version of the SAP. Any changes to the SAP will be documented in accordance with CHaRTs SOPs and the version number incremented. The final version of the SAP will be signed off before the end of the trial recruitment period and before any unbinding takes place. Any post-hoc analyses not outlined in the SAP will be labelled as such in any reports to the funder and publications arising from the trial.

9.5 Inclusion in Analysis

All randomised participants will be included in the analysis.

9.6 Longer term patient outcomes

After completion of the trial, funding will be sought for an evaluation of longer-term patient health and clinical outcomes at 5 and 10 years.

10 ECONOMIC EVALUATION

Within this study both a ‘within trial’ and a model based economic evaluation will be conducted. These analyses will take the form of a cost-utility analysis and a cost-benefit

analysis. 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[62].

Within trial analysis cost-utility analysis*:* For each trial participant the use of health and social care services as well as out of pocket expenses will be recorded. The use of services for the initial treatments (surgery/medications) including time in hospital will be collected on the CRFs. Also collected on the CRFs will be the use of other secondary care services e.g. duration of any hospitalisations, number of outpatient visits, use of tests and changes in medications. Use of primary care (e.g. general practitioner visits, practice and district nurse contacts, etc), personal social services and patient costs (e.g. out of pocket expenses) will be collected via questionnaire (see section 6.4.5 administration information). Further patient costs (time and travel costs for accessing particular types of care) will be based upon a time and travel questionnaire adapted from one developed by the UK working group of patient costs and successfully used in a large number of NIHR HTA programme funded projects previously. This questionnaire will be administered at 18 months post-randomisation.

Costs for healthcare services will be obtained from standard sources such as NHS reference Healthcare Resource Group (HRG) tariffs, the British National Formulary[63] for medications, Unit costs of Health and Social Care[64] 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 will be combined with unit costs to provide a cost for that participant.

As described in section 6.4.5 above 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, HUI-3 and the glaucoma specific GUI. Tariffs are not currently available for the EQ-5D 5L but responses can be crosswalked to scores for the EQ-5D 3L and this scoring will be used unless EQ-5D 5L scoring system becomes available during the lifetime of the trial. GUI responses will be converted into utilities using tariffs developed from the DCE (section 6.7.3). Health state utilities from both the EQ-5D and HUI-3 and the GUI will then be used to estimate QALYs for each participant using the area under the curve approach.

Data on costs and QALYs from both the EQ-5D and HUI-3 and the GUI for each participant will be used to estimate mean cost and QALYs for each intervention group. The cost and QALY data will then be used to estimate incremental costs, QALYs and incremental costs per QALY. These data will be presented as point estimates and bootstrapping techniques will be used to estimate the statistical imprecision surrounding them. The results of this stochastic analysis will be presented as cost and QALY plots and as cost-effectiveness acceptability curves[65].

Model based analysis cost-utility analysis: Drawing upon our existing modelling expertise in this area[13 53] an economic model that describes the progression of disease for those with advanced glaucoma (our earlier work included advanced glaucoma but our revised model will include a finer graduation for disease) will be developed. The model will be constructed following guidelines for best practice in economics modelling[66 67].

The use of services both for the treatment and management of advanced glaucoma will be modelled and the costs of these events will be based upon the estimates for these events derived from within the trial and where necessary by revising the estimates from our existing models. Similarly, the trial based data will be the main source of data for the economic model but it will be supplemented by focused searches of the literature and health economic

data bases (e.g. the Centre for the Evaluation of Value and Risk in Health (CEVR) Cost Effectiveness Analysis (CEA) Registry; https://research.tufts-nemc.org/cear4/; NHS Economic Evaluation Database) to update the estimates used within our existing models.

As already noted both costs and outcomes will be discounted at 3.5% in the base case analyses[62]. Further data required for the model relates to the transition and other probabilities of events occurring over the lifetime of patients. These probabilities include the risk of recurrence and progression as well as probabilities of receiving different types of intervention should progression occur.

The model will be used to produce estimates of costs, QALYs (from the EQ-5D, HUI-3 and the GUI). Cost-effectiveness will be reported as incremental cost per QALY gained (at both 2 years and over the patient's lifetime). The model will be probabilistic and distributions will be attached to all parameters; the shape and type of distribution will depend upon the data available and recommendations for good practice in modelling (http://www.nicedsu.org.uk/TSD%2013%20model%20parameters.pdf). The results will also be presented as point estimates of costs, effects, incremental costs, QALYS, and measures cost-utility. They will also be presented as plots of costs and QALYs derived from the probabilistic analysis and cost-effectiveness acceptability curves. Deterministic sensitivity analyses will be combined with the probabilistic analysis to explore other forms of uncertainty.

11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12 ORGANISATION, TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 Trial office in Aberdeen

The Trial Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. It is responsible for providing and maintaining the randomisation service, trial management, data processing, statistical analysis and communicating with the sites about TAGS specific issues. We will produce newsletters for collaborators to inform everyone of progress and maintain enthusiasm.

The Health Economic Evaluation and analysis will be undertaken by the University of Newcastle.

The TAGS Office Team (Aberdeen-based grant holders and study office members) will meet regularly with the CI during the course of the study to ensure smooth running and trouble-shooting

12.2 Local organisation in sites

12.2.1 Lead Ophthalmologist (Local Principal Investigator)

Each collaborating centre will identify a Lead Ophthalmologist who will be the point of contact for that centre. The responsibilities of this person will be to:

- establish the study locally (for example, by getting agreement from clinical colleagues; facilitate local regulatory approvals; identify, appoint and train a local Research Nurse; and inform all relevant local staff about the study (e.g. other ophthalmologists, junior medical staff, secretaries, ward staff))

- take responsibility for clinical aspects of the study locally (for example if any particular concerns occur)
- identify and/or support colleagues to identify and follow-up participants
- notify the Trial Office of any unexpected clinical events which might be related to study participation
- provide support, training and supervision for the local Research Nurse(s)
- represent the centre at the collaborators' meetings
- report any safety issues to the CI/Trial office.

12.2.2 Local Research Nurse

Each collaborating centre will appoint a local Research Nurse to organise the day to day recruitment of participants to the study. The responsibilities of this person will be to:

- keep regular contact with the local Lead Ophthalmologist, with notification of any problem or unexpected development
- maintain regular contact with the TAGS Office
- keep local staff informed of progress in the trial
- identify any eligible patients at clinics; explain the study and the potential for participation in TAGS if they are eligible
- confirm and record patient's eligibility and obtain written consent
- keep a log of whether patients are recruited or not (with reasons for non-participation)
- collect baseline data describing the participant, log this information in the web-based TAGS database and send paper copies to the Trial Office along with the original signed consent forms
- use this information to randomise the participant
- ensure treatment and post-treatment data are collected and recorded in the web-based TAGS database, and send paper copies (as requested) to the Trial Office
- file relevant study documentation (e.g. consent forms) in the participant's medical records
- organise alternative recruiters in case of holiday or absence
- represent the centre at the collaborators' meetings.

12.3 Project Management Group (PMG)

The trial is supervised by its Project Management Group (PMG). This consists of the grant holders and representatives from the Trial Office. Observers may be invited to attend at the discretion of the PMG. We will meet/teleconference every six months on average.

12.4 Trial Steering Committee (TSC)

The study is overseen by a Trial Steering Committee (TSC). The membership of this Committee is comprised of four independent members along with the Chief Investigator (Anthony King) or a nominated delegate. The trial sponsors, other TAGS grant-holders and key members of the central office (e.g. the trial manager) can participate in TSC meetings but are not members. The funders will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate. CHaRT has adopted the TSC Charter adapted from the DAMOCLES Charter for DMCs and suggests to the independent TSC members that they adopt the Terms of Reference contained within. The TSC will meet approximately yearly.

12.5 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be convened, one of whom is an experienced statistician. The DMC will initially meet to agree its terms of reference, meeting frequency and other procedures. CHaRT has adopted the DAMOCLES Charter for DMCs

and suggests to the independent DMC members that they adopt the Terms of Reference contained within.

The committee will monitor the unmasked trial data, serious adverse events and make recommendations as to any modifications that are required to be made to the protocol or the termination of all or part of the trial.

13 QUALITY ASSURANCE AND ETHICS

13.1 Research Governance

The trial will be conducted in compliance with the Declaration of Helsinki (2008), the principles of GCP and in accordance with all applicable regulatory guidance, including, but not limited to, the Research Governance Framework.

The trial will be run under the auspices of CHaRT based at HSRU, University of Aberdeen. Compliance with Research Governance will be monitored and CHaRT will provide centralised trial administration, database support and statistical analyses. CHaRT is a registered Clinical Trials Unit with particular expertise in running multicentre RCTs of complex and surgical interventions.

The trial will be monitored to ensure that the study is being conducted as per protocol, adhering to Research Governance, GCP. The approach to, and extent of, monitoring (specifying remote, central and any on-site monitoring) will be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of TAGS. All monitoring outcomes will be reported to the sponsor.

13.2 Participant Confidentiality

The trial will comply with the Data Protection Act 1998 and regular checks and monitoring are in place to ensure compliance. Data are stored securely in accordance with the Act and archived to a secure data storage facility. The senior IT manager (in collaboration with the CI) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable international meta-analyses.

13.3 Approvals

The **Derby 1 Research Ethics Committee** has reviewed this study. We believe this study does not pose any specific risks to individual participants beyond those of any treatment for advanced glaucoma, nor does it raise any extraordinary ethical issues. Annual progress reports and a final report at the conclusion of the trial will be submitted to **Derby 1 Research Ethics Committee** within the timelines defined in the regulations.

Local NHS R&D approvals will be obtained prior to commencement of the trial at the participating sites.

14 DATA HANDLING, RECORD KEEPINGS AND ARCHIVING

Clinical data will be entered into the database by the local clinical teams working in each hospital site, together with data from any questionnaires completed at clinic. Patient questionnaires returned by post to the trial office will be entered there. Staff in the trial office will work closely with local research nurses to ensure that the data are as complete and

accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

All study documentation will be kept for at least 15 years after publication of the study data. Copies of consent forms will be forwarded to Aberdeen on a regular basis. At the end of each participant's follow-up, case report forms and site files will be archived at each site. Paper copies of documentation held in Aberdeen will be archived there.

Satellite studies
It is recognised, that the value of the study may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advance with the Project Management Group and ratified by the TSC. REC approval will be sought for any new proposal, if appropriate.

15 FINANCING AND INSURANCE

The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme.

The necessary trial insurance is provided by Nottingham University Hospitals NHS Trust.

16 PUBLICATION POLICY

All RCTs conducted by CHaRT have a commitment to publish the findings of the research. At a minimum this trial will have a results paper published in a peer-reviewed medical/scientific journal. If all grant-holders and researcher staff fulfil authorship rules, group authorship will be used under the collective title of 'the TAGS Group'. If one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to the named individual(s) and the TAGS Group.

For reports which specifically arise from the trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to the named individual(s) for the TAGS Group.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the Project Management Group.

We intend to maintain interest in the study by publication of TAGS newsletters at intervals for staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final TAGS Newsletter to all involved in the trial.

Further details on the publication policy can be found in **Appendix D:**

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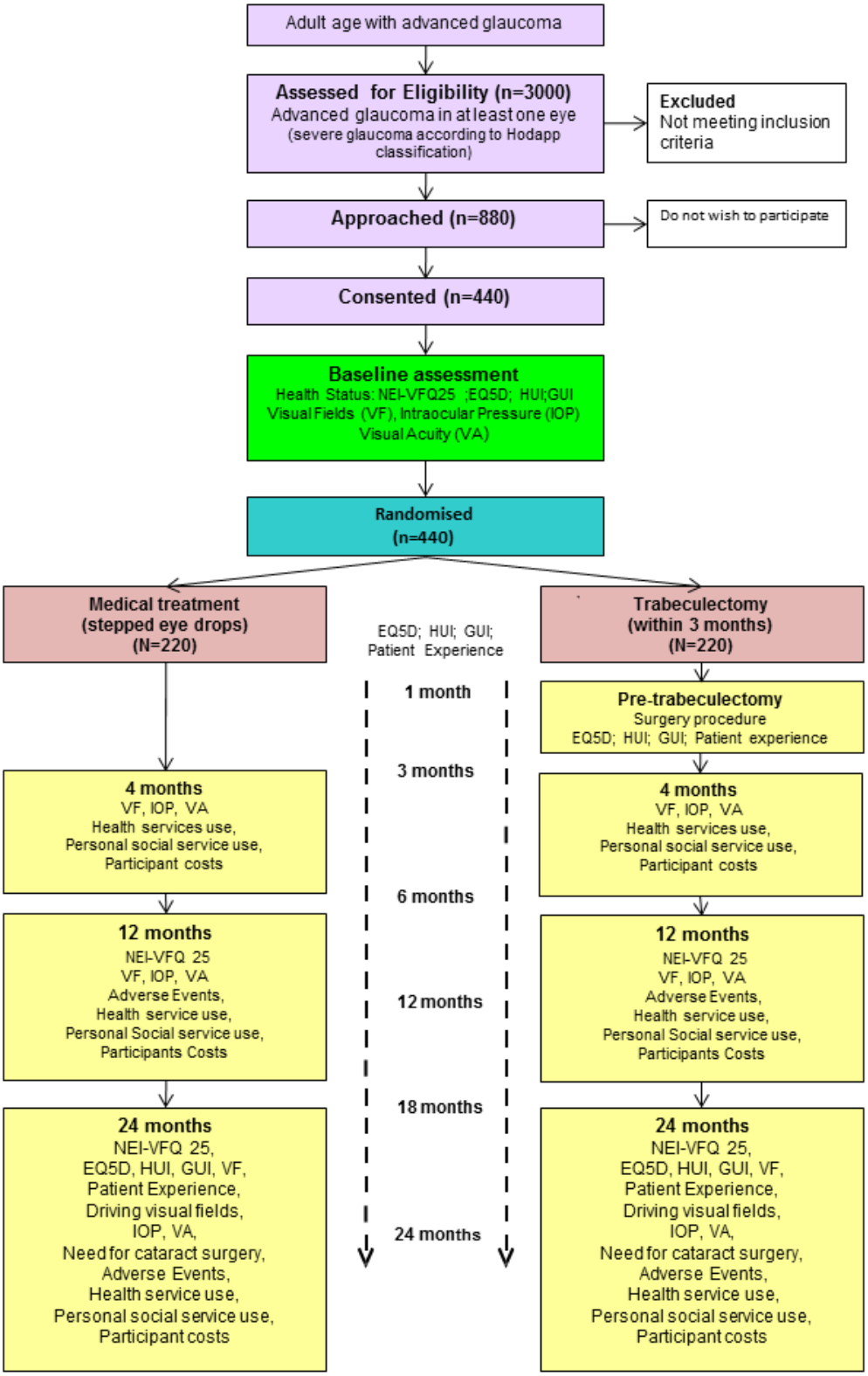
APPENDIX A – Study Flow Diagram

Flow diagram: Treatment of Advanced Glaucoma Study (TAGS): An RCT comparing primary medical treatment with primary augmented trabeculectomy



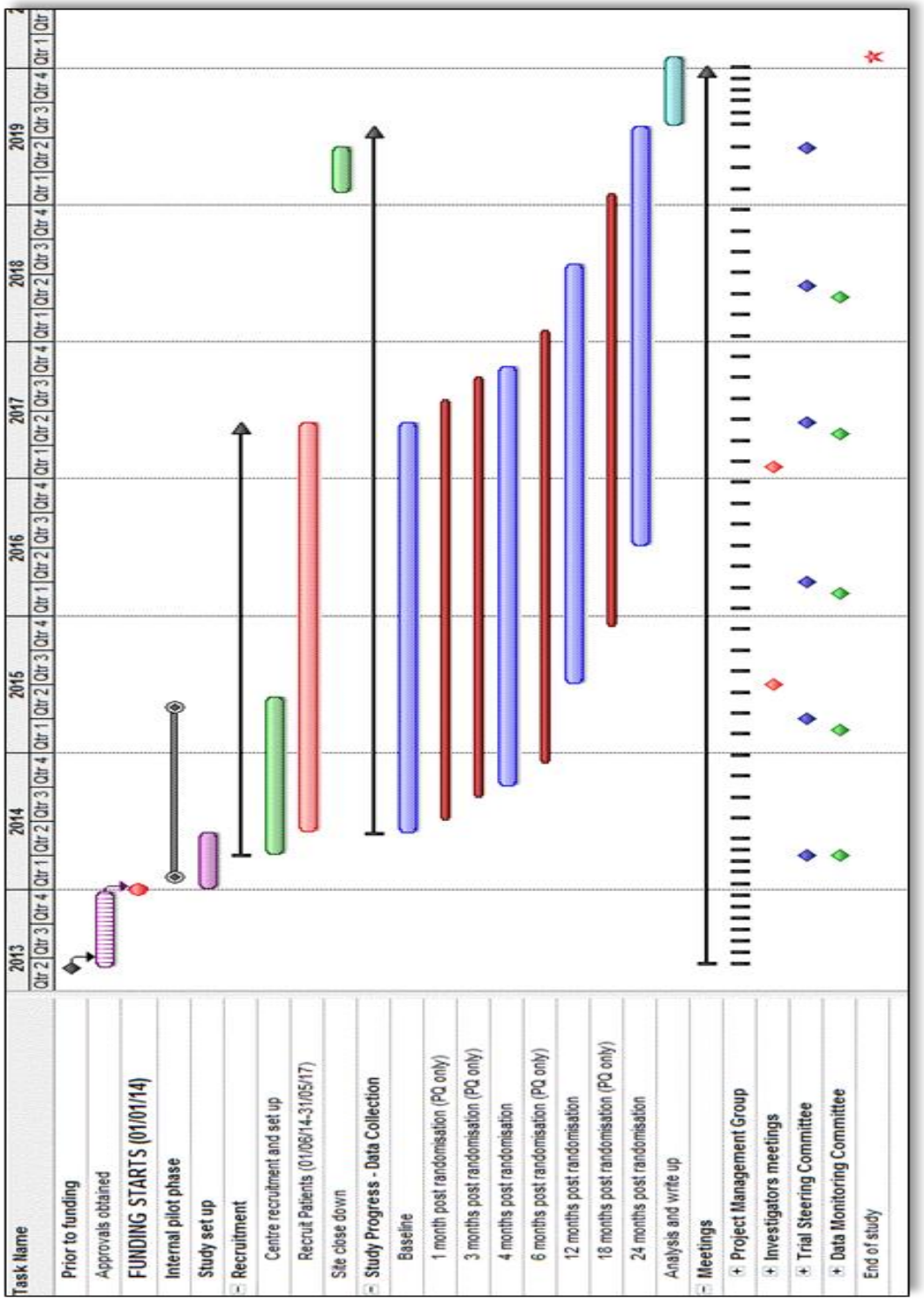
APPENDIX B – Schedule of Outcomes

		Post-randomisation (months)						
	Baseline	1	3	4	6	12	18	24
Medical History	✓							
Consent/Randomisation	✓							
Humphrey Visual Fields (x2)	✓			✓		✓		✓
Esterman Visual Fields	✓							✓
LogMAR Visual Acuity	✓			✓		✓		✓
IOP	✓			✓		✓		✓
Standard clinical examination	✓					✓		✓
NEI - VFQ-25	✓			✓		✓		✓
EQ-5D	✓	✓	✓		✓	✓	✓	✓
HUI-3	✓	✓	✓		✓	✓	✓	✓
GUI	✓	✓	✓		✓	✓	✓	✓
Patient experience questions	✓	✓	✓		✓	✓	✓	✓
Health Care Utilisation				✓		✓		✓
Participant Cost				✓		✓		✓
Participant Time and travel							✓	

* - additional questionnaire undertaken immediately prior to trabeculectomy surgery in surgery group

The DCE will be elicited at 27 months

APPENDIX C – GANTT CHART OF STUDY TIMELINES



APPENDIX D - AUTHORSHIP AND PUBLICATION POLICY FOR THE TAGS STUDY

AUTHORSHIP POLICY

1. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals (see references) and are in accordance with the rules of the International Committee of Medical Journal Editors.

a. Group authorship

Group authorship will be appropriate for some publications, such as main reports. This will apply when the intellectual work underpinning a publication 'has been carried out by a group, and no one person can be identified as having substantially greater responsibility for its contents than others'.[1] In such cases the authorship will be presented by the collective title - The TAGS Trial Group - and the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. In some situations one or more authors may take responsibility for drafting the paper but all group members qualify as members; in this case, this should be recognised using the by-line 'Jane Doe *and* the Trial Group'.[2] Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the by-line would read 'Jane Doe *for* the Trial Group'). [2]

b. Individual authorship

Other papers, such as describing satellite studies, will have individual authorship. In order to qualify for authorship an individual must fulfil the following criteria[1]:

i. each author should have participated sufficiently in the work represented by the article to take public responsibility for the content.
ii. participation must include three steps:
- conception or design of the work represented by the article OR analysis and interpretation of the data OR both; AND
- drafting the article or revising it for critically important content; AND
- final approval of the version to be published.

Participation solely in the collection of data is insufficient by itself and those persons who have contributed intellectually to the article but those contributors do not justify authorship may be acknowledged and their contribution described.[1]

c. Determining authorship

Tentative decisions on authorship should be made as soon as possible[1]. These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Steering Committee.

2. AUTHORSHIP FOR PUBLICATION ARISING FROM TAGS

a. Operationalising authorship rules

We envisage two types of report (including conference presentations) arising from the TAGS trial and its associated projects:

i. *Reports of work arising from the main TAGS trial*

If all grant-holders and research staff fulfil authorship rules, group authorship should be used under the collective title of 'The TAGS Trial Group'; if one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to 'Jane Doe and the TAGS Trial Group'.

ii. *Reports of satellite studies and subsidiary projects*

Authorship should be guided by the authorship rules outlined in Section 1 above. Grant-holders and research staff not directly associated with the specific project should only be included as authors if they fulfil the authorship rules. Grant-holders and research staff who have made a contribution to the project but do not fulfil authorship rules should be recognised in the Acknowledgement section. The role of the TAGS Trial Group in the development and support of the project should be recognised in the Acknowledgement section. The lead researcher should be responsible for ratifying authorship with the Project Management Group.

For reports which specifically arise from the TAGS trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to 'Jane Doe for the TAGS Trial Group'. If individual members of the group are dissatisfied by a decision, they can appeal to the Management Group for reconciliation. If this cannot be achieved, the matter should be referred to the Steering Group.

b. Quality assurance

Ensuring quality assurance is essential to the good name of the trial group. For reports of individual projects, internal peer review among members of the Project Management Group is a requirement prior to submission of papers. All reports of work arising from

the TAGS trial including conference abstracts should be peer reviewed by the Project Management Group.

The internal peer review for reports of work arising from the TAGS project is mandatory and submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. The Project Management Group will be responsible for decisions about submission following internal peer review. If individual members of the group are dissatisfied by decisions, the matter may be referred to the Steering Group.

The Project Management Group undertake to respond to submission of articles for peer review at the Project Management Group Meeting following submission (assuming the report is submitted to the trial secretariat at least two weeks prior to the meeting).

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