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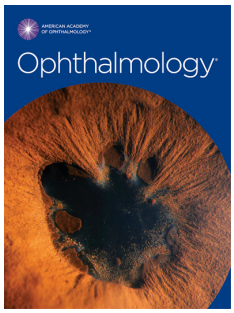

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Evaluating primary treatment for people presenting with advanced glaucoma: 5-year results of the Treatment of Advanced Glaucoma Study

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Abstract

Purpose: to determine whether primary trabeculectomy or medical treatment produces better outcomes in term of quality of life (QoL), clinical effectiveness and safety in patients presenting with advanced glaucoma.

Design: multicentre randomised controlled trial

Participants: between June 3, 2014 and May 31, 2017, 453 adults presenting with newly diagnosed advanced open angle glaucoma in at least one eye (Hodapp Classification) were recruited from 27 secondary care glaucoma departments in the UK, 227 were allocated to trabeculectomy and 226 to medical management.

Methods: participants were randomised on a 1:1 basis to have either mitomycin C augmented trabeculectomy or escalating medical management with intraocular pressure reducing drops as their primary intervention and followed up for 5 years. ISRCTN registry: ISRCTN56878850.

Main Outcome Measures: The primary outcome was vision-specific quality of life measured with Visual Function Questionnaire-25 (VFQ-25) at 5-years. Secondary outcomes: general health status, glaucoma related QoL, clinical effectiveness [intraocular pressure (IOP), visual field (VF), visual acuity (VA)] and safety.

Results: At 5 years the mean VFQ-25 in the trabeculectomy and medication arms were 83.3 (SD 15.5) and 81.3 (SD 17.5) respectively, mean difference 1.01, (95% CI -1.99 to 4.00); p=0.51. Mean IOPs were 12.07 (5.18) mmHg and 14.76 (4.14) mmHg respectively, mean difference -2.56 (95% CI -3.80 to -1.32); p<0.001. Glaucoma severity measured with visual field mean deviation were -14.30 (7.14) and -16.74 (6.78) dB respectively, mean difference 1.87 (95% CI 0.87 to 2.87) dB, p<0.001. Safety events occurred in 115 (52.2%) in the trabeculectomy arm and 124 (57.9%) in the medication arm, relative risk 0.92 (95% CI 0.72 to 1.19); p=0.54. Serious adverse events were rare.

Conclusion:

At 5 years TAGS has demonstrated that primary trabeculectomy surgery is more effective in lowering IOP and preventing disease progression than primary medical treatment in patients presenting with advanced disease and has a similar safety profile

Trial registration: Health Technology Assessment (NIHR-HTA) Programme (Project number: 12/35/38). ISRCTN registry: ISRCTN56878850.

Keywords: open angle glaucoma, randomised controlled trial, quality of life, intraocular pressure, visual field loss.

Introduction

Sight loss from glaucoma is often preventable with early diagnosis and treatment. However, as glaucoma is asymptomatic in its early phases, people are often unaware of its onset leading to presentation with more advanced disease. In the UK around 25% of patients with glaucoma present with advanced disease in at least one eye(1, 2). Presentation with advanced glaucoma is associated with socio-economic deprivation(3) and is the main risk factor for progression to blindness(4).

Reducing IOP is the only proven effective treatment for glaucoma. Better IOP control at an early stage reduces the risk of further progression(5). Primary treatment options for advanced glaucoma are mainly medical or surgical interventions. The Preferred Practice Patterns of the American Academy of Ophthalmology (6) do not recommend a specific treatment approach for those presenting with advanced disease whereas the European Glaucoma Society (EGS) Guidelines(7) suggests trabeculectomy can be considered in cases presenting with advanced glaucoma. In the UK, the National Institute for Health and Care Excellence (NICE) guidelines suggest patients presenting with advanced disease should consider trabeculectomy as a primary intervention(8) but cite poor evidence to support this recommendation. Most UK ophthalmologists do not follow this guidance and choose to treat patients medically with escalating topical medication therapy(9), only offering trabeculectomy if medical management is not successful. This approach is due to the poor evidence base supporting trabeculectomy as a primary intervention and concern regarding surgical complications. However, clinicians indicated high quality evidence would change their practice(9).

In a Cochrane systematic review(10) comparing primary medical versus surgical treatment for open-angle glaucoma (OAG), the authors concluded that trabeculectomy lowers IOP more than medication but also that trials excluded patients with advanced disease and did not reflect current medical and surgical practice. Comparison of current medical options and modern trabeculectomy in people with advanced OAG was identified as a research priority(10).

We carried out a multi-centre randomised controlled trial (RCT) to compare primary medical management against primary trabeculectomy for people presenting with advanced OAG evaluating patient reported outcomes, clinical effectiveness and safety.

Patients recruited to the Treatment of Advanced Glaucoma Study (TAGS) were on average 67 years at diagnosis and were representative of the eligible patient population(11). A previous report at 24 months showed a lower IOP in the trabeculectomy arm, but no evidence of a difference in disease progression or in any other clinical or QoL measurement(12, 13). In this report we compared long term outcomes.

Methods

Study design and participants

TAGS is a multi-centre, parallel group, open label, pragmatic RCT in 27 hospitals in the UK. The study was approved by the East Midlands – Derby Research Ethics Committee (reference number 13/EM/0395). The study was conducted in accordance with good clinical practice guidelines and adhered to the tenets of the Declaration of Helsinki. All patients provided written informed consent before participation.

Two independent committees oversaw the trial. An independent data and safety monitoring committee appraised adverse events and reported to an independent trial steering committee. This study was registered with the ISRCTN registry, ISRCTN56878850.

The protocol(14) was previously published and the methods are summarised below.

Participants

Adults with severe glaucoma according to the extent of visual field loss (Hodapp-Parrish-Anderson classification)(15) in one or both eyes at presentation. Inclusion criteria included diagnosis of OAG (including pigment dispersion glaucoma, pseudoexfoliative glaucoma and normal tension glaucoma), being willing to participate in a trial, able to provide informed consent and over 18 years of age. Patients were excluded if they were unable to undergo incisional surgery, had a high-risk of trabeculectomy failure such as previous conjunctival surgery or complicated cataract surgery, had secondary glaucoma or primary angle-closure glaucoma, were pregnant, nursing, or planning a pregnancy or were females and of childbearing potential not using a reliable method of contraception.

Advanced glaucoma

Severe glaucomatous visual field loss (Hodapp-Parrish-Anderson classification)(15) was defined according to the following criteria:

a. Mean deviation <−12.00 dB.
b. >50% of points defective in the pattern deviation probability plot at the 5% level (>27 points on 24-2 HVF).
c. >20 points defective at the 1% level.
d. A point in the central 5 degrees has a sensitivity of 0 dB.

e. Points within 5 degrees of fixation<15 dB sensitivity in both upper and lower hemifields.

Randomisation and masking

Participants were randomly assigned (1:1) to trabeculectomy or medical management with a minimisation algorithm based on centre and presence of bilateral disease. The unit of randomisation was the participant (not the eye). For participants with both eyes eligible, an index eye was selected based on less severe disease according to the mean deviation (MD) value of the visual field (VF) but both eyes would receive the same allocated treatment. For those in the trabeculectomy arm of the study it was planned that the index eye would undergo surgery first.

Participants were enrolled by trained centre staff (local principal investigator (PI), research nurse, or proxy) who used a remote web-based application or an Interactive Voice Response telephone system located at the Centre for Healthcare Randomised Trials (CHaRT; University of Aberdeen, Aberdeen, UK) for group allocation.

IOP measurement was undertaken with Goldman tonometry and was masked to the intervention according to the two-observer technique(14) to avoid bias. VF assessment was undertaken using the Humphrey Visual Field (HVF) analyser 24-2 Sita Standard algorithm and evaluation of VF progression was undertaken by an independent reading centre which was not aware of allocation assignment of participants (Central Administrative Research Facility (CARF), Queens University, Belfast). The reading centre assessed progression on the basis of HVF MD change. Surgeons and participants could not be masked to the allocated procedure because of the nature of the interventions.

Procedures

After the diagnosis of advanced glaucoma was made, potential participants were placed on holding medical treatment. Following randomisation, participants allocated to trabeculectomy were placed on the National Health Service (NHS) surgical waiting list and continued holding medication to lower their IOP until trabeculectomy was undertaken. We anticipated that surgery would occur within three months of randomisation. Each operating surgeon was a fellowship trained glaucoma specialist experienced in undertaking standard trabeculectomies. A surgical technique questionnaire was completed by all potential surgeons to ensure that

recognised standard trabeculectomy procedures(16) were followed. These questionnaires were reviewed and signed off by the Chief Investigator; no feedback was given as all surgeons were essentially conducting the same operation. The technique used was not modified for the purposes of the trial. All other aspects of care were left to the discretion of the responsible surgeon.

The definition of standard trabeculectomy included the fashioning of a 'guarded fistula' and augmentation with mitomycin C. The exposure time and concentration of mitomycin C was left to the discretion of the operating surgeon. A small hole into the anterior chamber was created which was covered by a flap of partial thickness sclera allowing aqueous humour to filter into the subconjunctival space. The operation could be performed under either local or general anaesthetic. For participants with bilateral advanced glaucoma allocated to the trabeculectomy arm, it was expected that the index eye would undergo surgery first, however the final decision was made by the treating surgeon, in discussion with the patient, about which eye would undergo trabeculectomy first.

Participants randomised to the medical treatment arm underwent an escalating medical management regimen and were prescribed a variety of topical glaucoma medications in accordance with accepted standard of care (NICE(8), EGS(7), and AAO-PPP guidelines(6)). Escalation of medical management was based upon the judgement of the treating clinician. When topical medications failed to control IOP adequately, oral carbonic anhydrase inhibitors could be used. If IOP control was deemed inadequate on maximum medical therapy, trabeculectomy was offered.

IOP targets were guided by the Canadian perspectives in glaucoma management: setting target IOP range Consensus(17).

Outcomes

The primary outcome was vision-related quality of life (HRQOL) measured with the Visual Function Questionnaire-25 (VFQ-25)(18). The secondary outcomes included other patient reported outcomes measured with the EQ-5D-5L(19), Health Utility Index-mark 3 (HUI-3)(20), Glaucoma Utility Index (GUI)(21), VFQ-25 and patient experience. The VFQ-25 was measured at baseline, 4, 12, 24, 36, 48 and 60 months, while the remainder were measured at baseline, 1, 3, 6, 12, 18, 24, 36, 48 and 60 months post-randomisation.

Patient reported outcomes were assessed with self-completed questionnaires at baseline (before randomisation) and at follow-up clinic visits. Additionally, postal questionnaires were sent to participants at 1, 3, 6 18, 36 and 48 months post-randomisation.

The clinical effectiveness outcomes were IOP, LogMAR Visual Acuity (VA), glaucoma severity according to VF MD measured with the HVF Analyzer, need for cataract surgery, accordance with visual standards for driving (based on Esterman visual field), eligibility for sight impairment certification(22) and safety of interventions. These were measured at baseline, 4, 12, 24 and 60 months. Adverse events (AEs) were recorded by the local research team and through follow-up questionnaires completed by the participants. Events related to participating in the trial or related to glaucoma were considered as AEs.

The local research team at each centre collected data at baseline and at scheduled follow-up visits at 4, 12, 24 and 60 months post randomisation. Data collected at follow-up visits included post-operative interventions, related hospital readmissions and medication changes.

Statistical Analysis

The sample size was constrained by the initial 2-year TAGS follow-up: we planned to randomise 440 patients, allowing for a 13.5% attrition rate, to get 90% power for two-sided 5% significance level to detect a 6-point difference on the VFQ-25, assuming a common standard deviation of 18 points(23). We summarised outcome data using mean (SD) for continuous data and frequencies and percentages for categorical variables, and line plots to visualise outcomes over time. Outcomes were analysed with a heteroscedastic partially nested repeated measures mixed effects linear model(24) correcting for the baseline measure of the outcome and bilateral disease severity, and including a random effect for surgeon by using restricted maximum likelihood. For visual standards for driving and need for drops at 60 months, we used a Poisson model adjusting for bilateral disease and including a random effect for surgeon to estimate relative risk. For amount of cataract surgery, safety, and further surgery, as there were varying follow-up times for participants, data were presented as n (probability) and analysed using cox regression adjusting for bilateral disease and presented as risk ratios(25). For certification as sight impaired, we used Fisher's exact test to compare groups. All estimates were presented with 95% confidence intervals. Subgroup analysis for the primary outcome is reported on variables shown in supplementary Figure 1, using a stricter level of

statistical significance (two-sided 1% significance level) and 99% confidence intervals. Sensitivity analysis of the primary outcome, VFQ-25 and clinical outcomes IOP and VF explored missing data using multiple imputation using chained equations. We used Stata version 17 software(26) for all analyses.

Results

Between June 3, 2014 and May 31, 2017, 453 participants from 27 hospitals were allocated to either trabeculectomy (227) or medical management (226) (Figure 1). In the trabeculectomy arm, 201 (88.5%) participants received trabeculectomy on their index eye. All participants received their allocated treatment in the medical management arm. In total 401 (88.5%) participants agreed to extended follow-up beyond 2 years.

At baseline both arms were evenly matched for all clinical, demographic and quality of life variables (12). There were 44 participants (19.4%) in the trabeculectomy arm and 40 (19.5%) in the medical management arm who had advanced glaucoma in both eyes.

At 5-years, the mean VFQ-25 was 83.3 (SD 15.5) and 81.3 (SD 17.5) in the trabeculectomy and the medical management arms, respectively. The groups' mean difference was 1.01, 95% CI (-1.99 to 4.00), p=0.51; (Table 1). Supplementary Table 2 shows the results for VFQ-25 subscales at 5-years which did not reveal treatment effect differences apart from the driving subscale, which suggested that those in the medical arm were less likely to be driving at 5-years [78.3 (29.8) and 67.9 (37.2); mean difference = 8.93, for trabeculectomy and medical arms, respectively; P< 0.04].

There was also no evidence of any differences between the prespecified, subgroups (Supplementary Figure 2). Sensitivity analysis of multiple imputation showed similar results (Supplementary Table 3).

For the EQ-5D-5L at 5-years, the mean score was 0.787 (0.191) and 0.765 (0.187) in the trabeculectomy arm and medical management arm, respectively; the mean difference was 0.016 95% CI (-0.025 to 0.057), p=0.44; (Table 1, Figure 3). Similarly, for the HUI-3 and GUI the mean score was higher in the trabeculectomy arm but the differences were not statistically significant (Table 1, Figure 3). There was a reduction in the number of participants in the trabeculectomy arm who thought their glaucoma was getting worse at 5-years compared to baseline, but not in the medical management arm [RR = 0.64 95% CI (0.40 to 1.01); p=0.06]

The mean IOP at 5-years was 12.07 (SD 5.18) for the trabeculectomy arm and 14.76 (SD

4.14) for the medical management arm: mean difference -2.56, 95% CI (-3.80 to -1.32); p<0.001, (Table 4, Figure 3). Sensitivity analysis of multiple imputation were consistent with the main analysis (Supplementary Table 3).

There was a significant and clinically meaningful difference in disease (VF) progression between arms at 5-years. The MD for the trabeculectomy arm was -14.30 (7.14) dB and -16.74 (6.78) dB for the medical management arm with a mean difference of 1.87dB, 95% CI (0.87 to 2.87); p<0.001; (Table 4, Figure 4). Sensitivity analysis of multiple imputation were consistent with the main analysis (Supplementary Table 3).

There was no difference in LogMAR visual acuity between arms (mean difference 0.02 95% CI (-0.04 to 0.08); p=0.48; (Table 4, Figure 4)).

The need for cataract surgery, accordance with visual standards for driving and certification as sight impaired were similar for both arms (Table 4).

The concentration of MMC used for surgery was left to the discretion of the operating surgeon. MMC concentration was recorded for 225 of the trabeculectomies undertaken, 74% of cases used the lower 0.2mg/ml dosage for surgery. In total, 115 (52.2%) participants in the trabeculectomy arm and 124 (57.9%) in the medical management arm had a safety event during the 5-year follow-up: relative risk 0.92, 95% CI (0.72 to 1.19), p-value 0.54 (Table 5). There were 20 participants in both arms who experienced a serious AE. There were 29 deaths, all unrelated to the trial. Two participants developed endophthalmitis, one in each arm of the study, and four participants lost more than 10 letters of LogMAR VA, three in the trabeculectomy arm (two due to progressive glaucoma and one due to central serous retinopathy) and one in the medical arm (due to progressive glaucoma). There was no difference between groups for these AEs. Hypotony and shallow anterior chamber (AC) requiring intervention were not common; the need for additional interventions are shown in Table 6. Although in total 249 participants underwent trabeculectomy (173 had split fixation using the definition of "the presence at least one paracentral quadrant test location with a retinal sensitivity of "0" dB and 78 had VF loss < -22dB) there were no episodes of " wipeout" reported.

The additional glaucoma surgery required in both arms is shown in Table 6. In the medical management arm, 48 participants (21%) required a trabeculectomy for IOP control. The frequency of additional interventions following trabeculectomy, such as bleb revision, AC reformation and bleb re-suturing was higher in the trabeculectomy arm, but proportionate to the number of trabeculectomies undertaken in each arm. In the trabeculectomy arm, trabeculectomy failure required further surgery in the form of Glaucoma Drainage Devices in four participants.

At 5-years, 62/175 (35.4%) participants were using IOP lowering drops in the trabeculectomy arm and 124/171 (72.5%) in the medical management arm [RR 0.48 95% CI (0.34 to 0.67); p-value <0.001]. The mean number of drops was 0.64 (1.01) and 1.54 (1.21) in the trabeculectomy and medical management arms, respectively (Supplementary Table 7).

Discussion

Principal Findings

At 5-years, initial surgery was associated with less disease progression compared with medical treatment. There was no evidence of a difference in the primary outcome measure vision-related QoL between treatment arms. This is also true for the general health status and glaucoma QoL measurements undertaken. Trabeculectomy was more effective in lowering IOP. In addition, the trabeculectomy arm required far fewer topical medications for IOP control. Adverse events including serious adverse events between arms were similar.

Comparison with other studies

A sustained reduction in IOP is recognised to be the most effective method of preventing further VF loss in glaucoma(5, 27, 28). There was a reduction to 12.07 (5.18) mmHg in the trabeculectomy arm and 14.8 (4.1) mmHg in the medical arm at 5-years. This is a clinically important difference and is consistent with clinicians' interpretation of a clinically important difference between interventions(29).

The IOP-lowering achieved in the trabeculectomy arm is consistent with current results reported from the NHS by Kirwan(30) in his multi-centre service evaluation of trabeculectomies and by Stead(31) and Filippopoulos(32) who specifically reported IOP lowering in eyes with advanced VF loss. It is also consistent with trabeculectomy-related IOP achieved in other recent glaucoma treatment RCTs undertaken in a variety of health care systems(33, 34).

The superior efficacy of trabeculectomy is further reflected in the reduced need for topical medications. at 5-years, the number of participants receiving topical medications was 62/175 (35.4%) in the trabeculectomy arm and 124/171 (72.5%) in the medical management arm.

Clinicians consider the VF to be the most important outcome as this is a measure of functional vision loss(35) and the main indicator of disease severity. There was a clinically important and statistically significant difference in disease progression with those in the initial trabeculectomy group having almost 2dB less visual field loss compared with initial medicine after 5-years. TAGS is the first trial to report a beneficial effect of primary surgery compared with medication regarding disease progression in patients presenting with advanced disease.

Reduced VF progression is particularly important in people with severe disease as they have less visual field reserve. Differences in disease progression are most likely a consequence of the sustained lower IOP(5) in the trabeculectomy arm and possibly less reliance on drops, eliminating the potential for poor adherence to contribute to VF progression(36). In TAGS the mean age of glaucoma diagnosis was 67 years and their the expected mean survival is about 18 years(37). A sustained differential in IOP reduction between treatment arms is likely to result if further lifetime divergence in visual field preservation.

For patients, the most important outcome of glaucoma management is their ability to continue to live an independent life and maintain their QoL(38, 39). For all generic, vision and glaucoma specific QoL measures, there was no statistical difference between the interventions at 5-years suggesting neither intervention had a greater effect on participants' QoL, which will help inform patients when considering their treatment options.

Recent publications suggest that measurements of QoL have low power to discriminate between treatment arms in trials of disease-modifying treatments for glaucoma and probably have greater importance to capture the impact of side-effects and adverse effects(35, 40). However, glaucoma is typically a slowly progressive disease and we would argue that the lack of evidence of a difference tells us that the difference in QoL between treatments is not large rather than some degree of failure in the tools themselves. With respect to the EQ-5D and HUI these are tools of proven value over a range of conditions including numerous eye conditions. More interestingly, the GUI is a condition specific tool and its scoring was developed using best practice methods and provides utilities specific to this study(41). As such if there were a substantial difference in QoL between groups with respect to glaucoma specific quality of life then we would have expected to detect this. Having said this we cannot infer that there is no difference in QoL, that is not what our study was designed to do, rather our inference is that changes in clinical measures have not translated into a difference in QoL. It is possible that this may occur in the future, should measures of clinical effect continue to diverge between the randomised arms.

A major concern for clinicians was the perceived 'high risk' of complications associated with trabeculectomy(9). Specifically the risk of unexplained catastrophic vision loss immediately after surgery (termed 'wipeout') which was believed to be a significant risk in patients with

advanced VF loss and the risk of long-term complications and sight loss associated with trabeculectomy(9). At 5 years there was no evidence to support these concerns. Additional surgery was required in both arms. In the medical management arm 48 (21.4%) participants had undergone trabeculectomy by 5 years for uncontrolled glaucoma. There was additional surgery in both arms to deal with consequences of trabeculectomy, such as hypotony, these were proportional between the arms in the context of trabeculectomy surgeries undertaken. However, 8% of the trabeculectomy group did require an intervention to manage clinically significant hypotony and the need for the possibility of this and other potential additional interventions should be highlighted to patients when considering trabeculectomy as a primary intervention.

Strengths

TAGS strengths include its pragmatic design to replicate, as closely as possible, current practice and the reality of outcomes in a publicly funded health care system, the large sample size with low attrition rate over a 5-year follow-up, the involvement of multiple centres in the UK, the randomisation process, and masking of the clinical assessments for IOP and visual fields, which kept the potential risk of bias to a minimum.

Limitations

The surgical treatments could not be masked from participants, nor could some of the clinical outcome assessments such as evaluation of complications. Some of the 5 year data were collected during the restrictions of the COVID pandemic and consequently, to minimize patient and clinician contact time, the two observers technique for IOP measurement was not done for some IOP measurements and for visual field assessment a shorter testing algorithm (24-2 Sita Fast) was used. Some data collection was also incomplete. However, sensitivity analyses demonstrate there was no evidence that attrition or missing data affected the validity of the results at 60 months. The majority of participants were caucasian, which reflects the population of the UK, this may however, limit generalisability of our findings to non-caucasian populations”

Conclusion

At 5 years TAGS has demonstrated that primary trabeculectomy surgery is more effective in lowering IOP and preventing disease progression than primary medical treatment in patients presenting with advanced disease and has a similar safety profile. Trabeculectomy should be offered as a primary intervention in patients presenting with advanced glaucoma.

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Table 1: Quality of life outcomes

	Trabeculectomy N=227	Medical management N=226	ES[1]	95% CI	p-value
VFQ-25*					
Baseline	87.1 (13.6); 226	87.1 (13.4); 224			
4 months	85.1 (14.9); 212	86.5 (13.6); 216	-1.13	(-3.85 to 1.59)	0.42
12 months	85.4 (14.3); 214	86.3 (13.1); 209	-0.49	(-3.23 to 2.24)	0.72
24 months	85.4 (13.8); 207	84.5 (16.3); 205	1.15	(-1.60 to 3.91)	0.41
36 months	84.1 (15.8); 159	83.6 (16.2); 152	-0.01	(-3.03 to 3.00)	0.99
48 months	84.6 (14.7); 138	81.9 (17.0); 142	1.94	(-1.17 to 5.04)	0.22
60 months	83.3 (15.5); 157	81.3 (17.5); 159	1.01	(-1.99 to 4.00)	0.51
EQ-5D-5L					
Baseline	0.844 (0.185); 222	0.837 (0.176); 222			
1 months	0.838 (0.185); 194	0.808 (0.203); 203	0.024	(-0.013 to 0.062)	0.21
3 months	0.836 (0.167); 186	0.814 (0.195); 179	0.014	(-0.024 to 0.053)	0.47
6 months	0.850 (0.184); 186	0.822 (0.204); 195	0.016	(-0.022 to 0.055)	0.40
12 months	0.837 (0.177); 211	0.823 (0.164); 209	0.014	(-0.023 to 0.051)	0.45
16 months	0.828 (0.185); 181	0.791 (0.219); 184	0.022	(-0.017 to 0.061)	0.26
24 months	0.810 (0.179); 206	0.796 (0.191); 203	0.015	(-0.022 to 0.053)	0.43
36 months	0.806 (0.186); 156	0.787 (0.207); 151	0.017	(-0.024 to 0.058)	0.43
48 months	0.820 (0.160); 135	0.769 (0.192); 140	0.042	(-0.001 to 0.084)	0.05
60 months	0.787 (0.191); 151	0.765 (0.187); 152	0.016	(-0.025 to 0.057)	0.44
HUI-3					
Baseline	0.814 (0.202); 214	0.809 (0.208); 214			
1 months	0.791 (0.232); 184	0.786 (0.230); 193	-0.003	(-0.048 to 0.042)	0.89
3 months	0.796 (0.223); 180	0.779 (0.222); 179	0.004	(-0.042 to 0.050)	0.87
6 months	0.805 (0.216); 180	0.782 (0.224); 182	0.017	(-0.029 to 0.063)	0.47
12 months	0.829 (0.193); 204	0.798 (0.199); 196	0.021	(-0.023 to 0.066)	0.35
16 months	0.802 (0.212); 169	0.749 (0.258); 174	0.019	(-0.028 tp 0.066)	0.42
24 months	0.786 (0.227); 198	0.751 (0.246); 193	0.033	(-0.012 to 0.077)	0.15
36 months	0.769 (0.229); 154	0.747 (0.220); 145	0.011	(-0.038 to 0.060)	0.66

48 months	0.756 (0.239); 132	0.709 (0.247); 138	0.026	(-0.024 to 0.076)	0.31
60 months	0.726 (0.262); 150	0.706 (0.239); 147	0.001	(-0.048 to 0.050)	0.97
GUI					
Baseline	0.897 (0.127); 219	0.886 (0.120); 222			
1 months	0.876 (0.142); 194	0.870 (0.151); 205	0.004	(-0.025 to 0.032)	0.81
3 months	0.864 (0.129); 187	0.861 (0.152); 190	-0.003	(-0.032 to 0.026)	0.82
6 months	0.856 (0.154); 186	0.868 (0.130); 191	-0.015	(-0.044 to 0.014)	0.30
12 months	0.875 (0.132); 209	0.875 (0.135); 204	-0.002	(-0.030 to 0.026)	0.88
16 months	0.866 (0.142); 181	0.853 (0.148); 184	0.003	(-0.026 to 0.033)	0.82
24 months	0.861 (0.151); 205	0.845 (0.175); 202	0.016	(-0.012 to 0.044)	0.26
36 months	0.849 (0.143); 158	0.827 (0.162); 150	0.008	(-0.023 to 0.039)	0.61
48 months	0.855 (0.141); 135	0.828 (0.167); 139	0.018	(-0.014 to 0.050)	0.28
60 months	0.858 (0.127); 155	0.826 (0.161); 151	0.023	(-0.009 to 0.054)	0.16
Patient experience (glaucoma getting worse), n/N (%)					
Baseline	95/208 (45.7)	76/209 (36.4)			
1 months	60/188 (31.9)	50/201 (24.9)	1.12	(0.73 to 1.71)	0.60
3 months	37/182 (20.3)	40/185 (21.6)	0.82	(0.51 to 1.34)	0.44
6 months	30/182 (16.5)	40/189 (21.2)	0.69	(0.41 to 1.16)	0.16
12 months	38/207 (18.4)	57/199 (28.6)	0.55	(0.35 to 0.87)	0.01
18 months	40/180 (22.2)	38/181 (21.0)	0.94	(0.58 to 1.53)	0.80
24 months	44/196 (22.4)	57/194 (29.4)	0.66	(0.42 to 1.02)	0.06
36 months	39/153 (25.5)	43/143 (30.1)	0.77	(0.48 to 1.24)	0.29
48 months	42/135 (31.1)	45/140 (32.1)	0.86	(0.54 to 1.37)	0.53
60 months	39/147 (26.5)	53/145 (36.6)	0.64	(0.40 to 1.01)	0.06

Values are n; mean (standard deviation) for continuous outcomes and n/N (%) for dichotomous outcomes. CI Confidence Interval. * = Primary Outcome; [1] mean difference for continuous outcomes and risk ratios for dichotomous outcomes.

Table 4: Clinical outcomes

	Trabeculectomy N=227	Medical management N=226	ES[1]	95% CI	p-value
Intraocular pressure (mmHg)					
	26.9 (9.1); 226	25.9 (8.4); 223			
Diagnosis*					
Baseline	19.40 (6.15); 222	19.05 (5.73); 221			
4 months	12.39 (5.73); 217	16.40 (4.12); 220	-4.04	(-5.17 to -2.91)	<0.001
12 months	11.94 (4.48); 215	16.12 (4.54); 209	-4.19	(-5.33 to -3.05)	<0.001
24 months	12.40 (4.71); 206	15.07 (4.80); 202	-2.67	(-3.82 to -1.51)	<0.001
60 months	12.07 (5.18); 166	14.76 (4.14); 162	-2.56	(-3.80 to -1.32)	<0.001
LogMAR visual acuity					
Baseline	0.15 (0.25); 227	0.17 (0.26); 223			
4 months	0.25 (0.31); 210	0.16 (0.24); 217	0.09	(0.04 to 0.14)	<0.001
12 months	0.18 (0.23); 212	0.16 (0.26); 209	0.03	(-0.02 to 0.08)	0.26
24 months	0.21 (0.28); 199	0.16 (0.26); 201	0.06	(0.01 to 0.12)	0.014
60 months	0.19 (0.23); 138	0.20 (0.32); 136	0.02	(-0.04 to 0.08)	0.48
Visual fields mean deviation (dB)					
Baseline	-14.91 (6.36); 227	-15.26 (6.34); 226			
4 months	-14.35 (6.78); 211	-14.84 (6.52); 217	0.05	(-0.85 to 0.95)	0.92
12 months	-14.76 (6.92); 214	-14.95 (6.53); 209	0.13	(-0.77 to 1.03)	0.77
24 months	-15.15 (6.63); 202	-15.42 (6.39); 200	0.29	(-0.63 to 1.20)	0.54
60 months	-14.30 (7.14); 144	-16.74 (6.78); 145	1.87	(0.87 to 2.87)	<0.001
Need for cataract surgery					
Yes, n (Probability)	57 (26.9)	56 (27.5)	0.99	(0.69 to 1.43)	0.97
Visual standards for driving at 60 months (pass), n/N (%)					
Yes	161/178 (90.4)	162/182 (89.0)	1.02	(0.82 to 1.27)	0.84
Certified as sight impaired at 60 months, n/N (%)					
No	168/175 (96.0)	171/177 (96.6)			0.91
SI	5/175 (2.9)	5/177 (2.8)			
Severe SI	2/175 (1.1)	1/177 (0.6)			
Eligible to be certified as sight impaired at 60 months, n/N (%)					
No	170/184 (92.4)	173/187 (92.5)			
SI	10/184 (5.4)	9/187 (4.8)			
Severe SI	4/184 (2.2)	5/187 (2.7)			

Values are mean (standard deviation); n for continuous outcomes unless otherwise stated. [1] Mean Difference for continuous outcomes and risk ratios for dichotomous outcomes. CI Confidence Interval.

* At diagnosis a total of 134 participants had an IOP < 22mmHg [62 (27.3%0) and 72 (31.9%) in the trabeculectomy and medicine arms respectively

Table 5: Safety events, as allocated, ocular events for index eye

	Trabeculectomy N=227	**Medical management N=226**
Number of participants with a safety event	115 (52.2) RR 0.92	124 (57.9) 95% CI (0.72, 1.19); p=0.54
SAE		
Number of participants	20	20
Number of events	22	24
Details		
Death	14	15
Life-threatening	-	1
Hospitalisation	3	8
Significant disability	2	-
Important condition	3	2
Expected event		
Yes	3	3
No	18	20
Unknown	1	1
Classification		
General medical (death)	9	15
Unclassified (death)	5	1
General medical	3	7
Related to glaucoma surgery	2	-
General ophthalmology	1	-
Non-glaucoma vision loss	1	1
Glaucoma progression despite treatment	1	-
AE's		
Number of participants	106	110
Number of events	206	225
Details		
Drop related	28	97
Ocular surface related	48	55
Non-specific	35	29
Potential AE related to surgery	13	8
Glaucoma progression	3	12
Hypotony requiring intervention	15	5
Early bleb leak	13	3
Choroidal effusion	9	4
Shallow anterior chamber	8	3
Ptosis	7	3
Irreversible loss of ≥ 10 ETDRS letters	3	1
Corneal epithelial defect	4	-
Hyphaema	4	-
Late bleb leak	4	-
Cataract	1	2
Conjunctival buttonhole	3	-

Macular oedema	1	1
Suprachoroidal haemorrhage	2	-
Blebitis	2	-
Endophthalmitis – endogenous	1	-
Endophthalmitis – bled related	-	1
Persistent uveitis	1	-
Retinal detachment	-	1
Non-specific unrelated uveitis	1	-

Values are n (probability); RR risk ratio; CI Confidence interval

Table 6: Further Surgery

	Trabeculectomy N=227	**Medical management N=226**
Number of participants, n (probability)	75 (0.35) RR 0.68	96 (0.46) 95% CI (0.50 to 0.92); p-value 0.011
Number of interventions for those that had at least one, mean (SD)	1.24 (0.46)	1.33 (0.63)
Details of intervention, n		
Cataract surgery	57	56
Surgery related to previous glaucoma surgery		
Bleb revision	11	2
AC reformation	5	3
Bleb re-suturing	6	1
Further glaucoma surgery		
Trabeculectomy	-	48
Deep Sclerectomy with spacer	-	1
Deep Sclerectomy	1	-
Late Bleb needling +/- Mitomycin C	3	-
Selective laser trabeculoplasty	3	11
Cypass	-	1
iStent	-	1
Glaucoma Drainage device*	4	1
Supramid removal	1	1
Tube revision	1	-
Cyclodiode laser	2	2

*Tube types - Paul x 2, Ahmed x1, Baerveldt x 1, Not stated x 1
RR risk ratio; CI Confidence interval

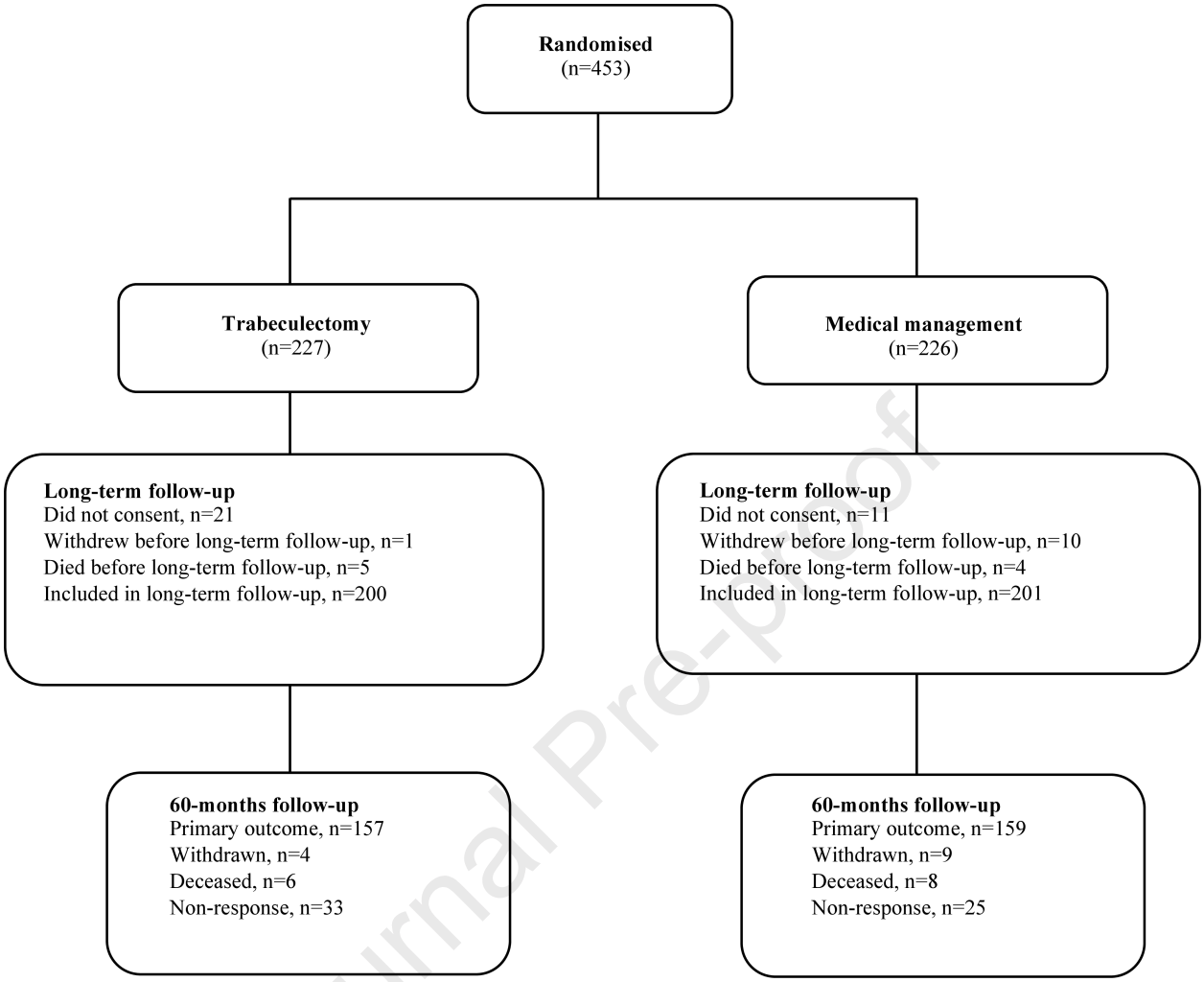

Figure 1: CONSORT diagram

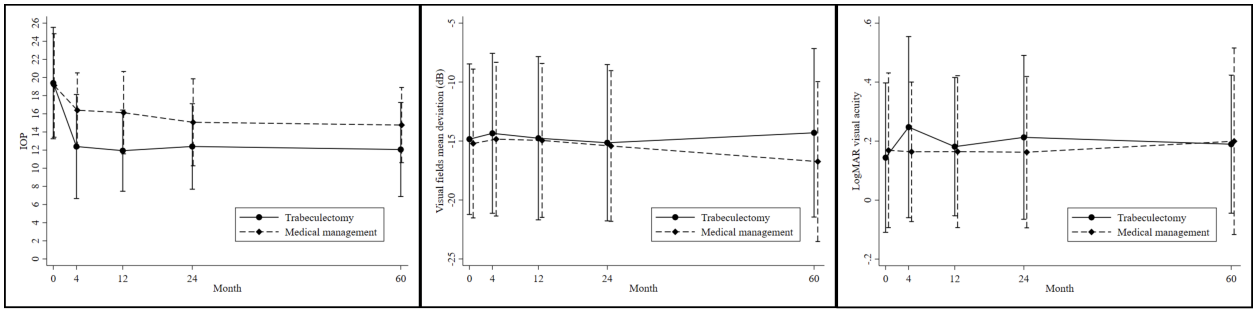

Figure 4: Clinical outcomes up to 5-years for IOP, VF and LOGMAR VA

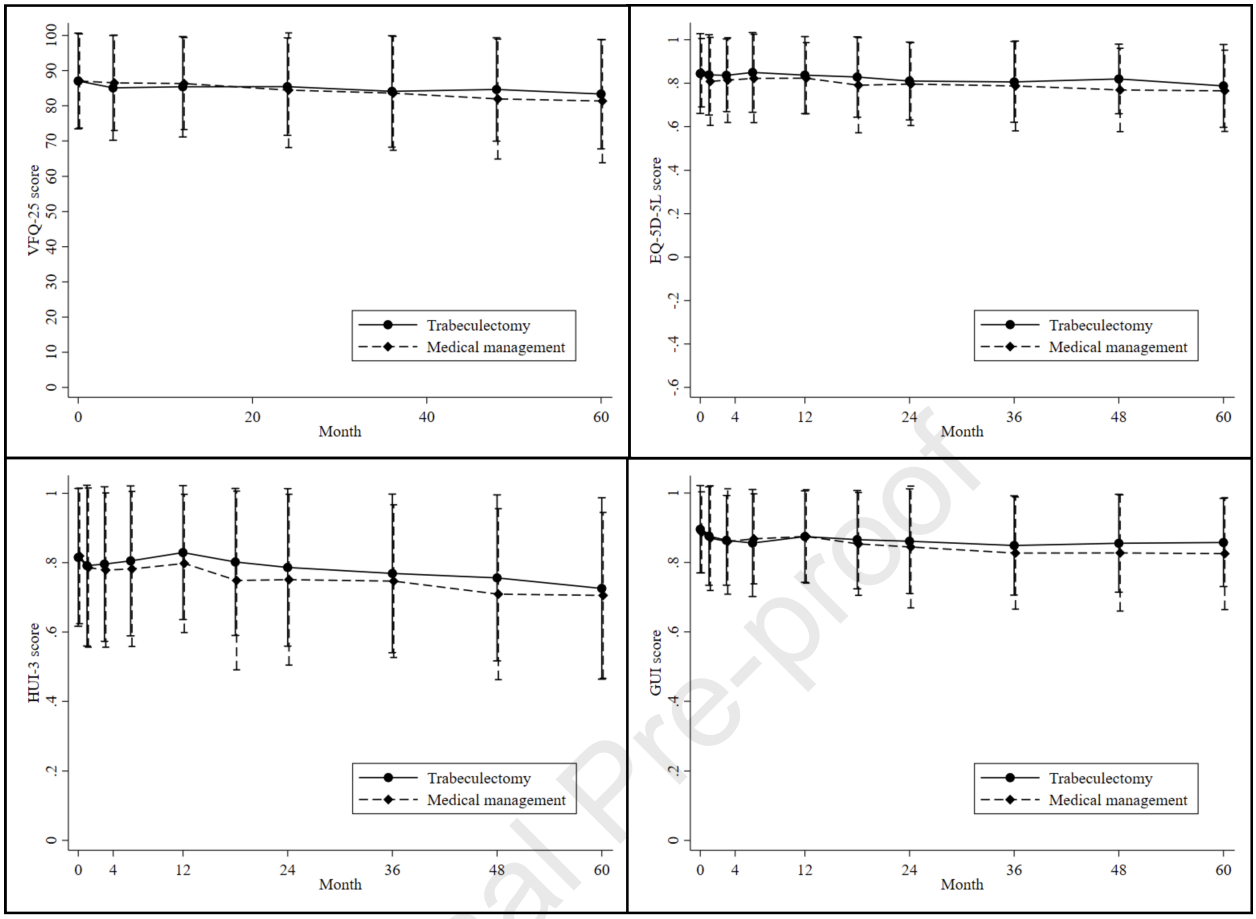

Figure 3: Quality of Life outcomes up to 5-years for VFQ-25, EQ5D, HUI-3 and GUI

Precis

At 5 years primary trabeculectomy surgery is more effective in lowering IOP and preventing disease progression than primary medical treatment in patients presenting with advanced open angle glaucoma.