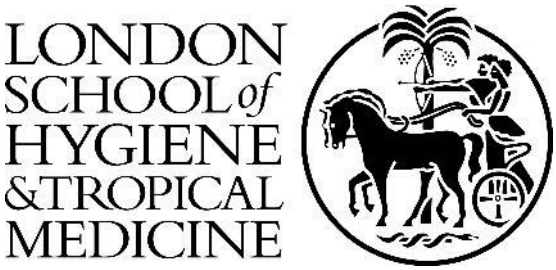


# SELECTIVE LASER TRABECULOPLASTY VERSUS 0.5% TIMOLOL EYE DROPS FOR THE TREATMENT OF GLAUCOMA IN TANZANIA: A RANDOMISED CONTROLLED TRIAL

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Thesis submitted in accordance with the requirements for the degree of Doctor of Philosophy of the University of London

**April 2022**

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Funded by CBM and Seeing is Believing

# Declaration

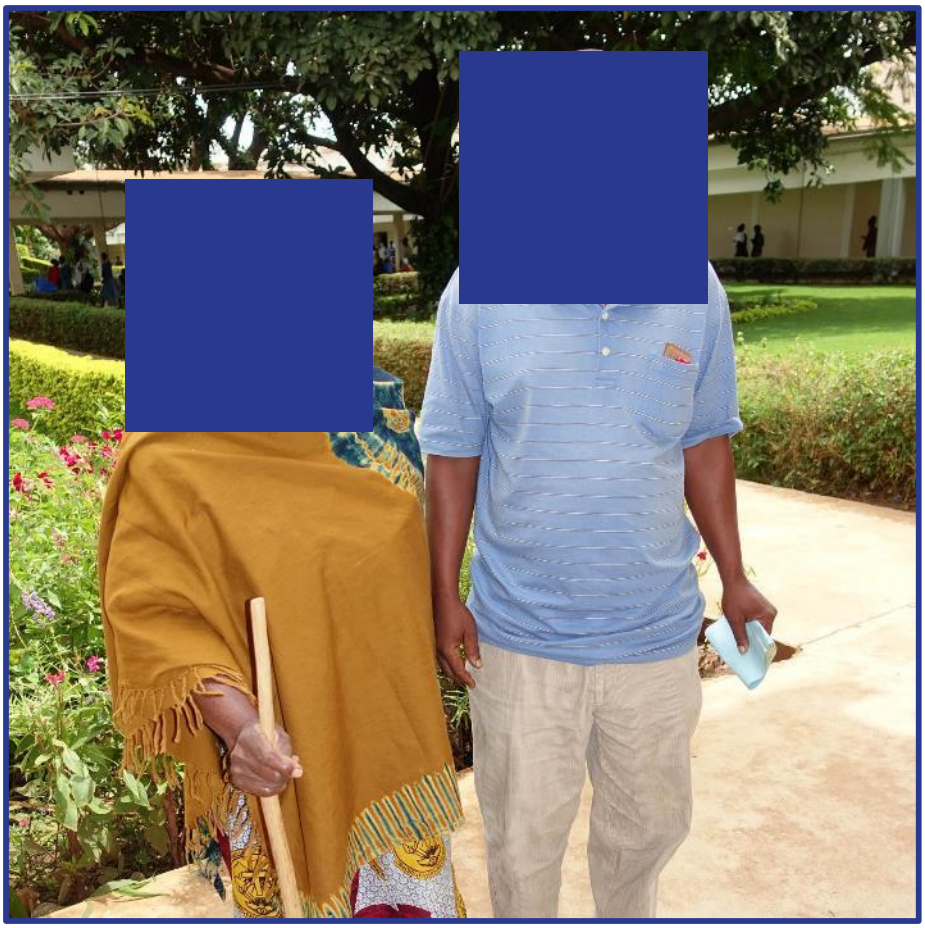
I, Heiko Philippin, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

[redacted]

Signature

28th April 2022

Date



*Two participants of the trial, mother and son, in front of the main entrance of Kilimanjaro Christian Medical Centre, Moshi, Tanzania*

# Abstract

**BACKGROUND:** Glaucoma is a major cause of sight-loss worldwide, with the highest regional prevalence and incidence reported from Africa. The most common low-cost treatment used in this region to control glaucoma is long-term timolol eye drops. However, side effects, low adherence, limited availability, and high long-term costs are a challenge. Selective laser trabeculoplasty (SLT) is a short outpatient procedure to lower eye pressure but was not formally compared with standard treatment in Africa. We tested the hypothesis that SLT is superior to timolol 0·5% eye drops for the treatment of open-angle glaucoma.

**METHODOLOGY:** A randomised, controlled, parallel group, single-masked clinical trial was conducted at KCMC Eye Department, Moshi, Tanzania. Participants (aged ≥18 years) had open-angle glaucoma, intraocular pressure (IOP) >21mmHg and neither previous glaucoma surgery nor asthma. They were randomly allocated to receive timolol 0.5% eye drops twice daily or SLT. The primary outcome was the proportion of success after one year defined as an IOP ≤18mmHg for eyes with advanced glaucoma (disc damage likelihood scale (DDLS) 8-10) and IOP ≤21mmHg for moderate glaucoma (DDLS 5-7). Re-explaining the application of eye drops or a repeat SLT was permitted once. Further outcomes included safety, acceptance, vision-related quality of life (VRQoL) using the WHO/PBD VF20 questionnaire, preservation of visual acuity, and cost. Results were analysed by intention to treat using logistic regression; generalised estimating equations were used to adjust for the correlation between eyes.

**RESULTS:** 201 participants (382 eligible eyes) were enrolled; 100 people (191 eyes) were randomly assigned to timolol and 101 (191 eyes) to SLT. At baseline, mean IOP was 26.7mmHg (SD 6.9mmHg), 162 eyes had moderate glaucoma and 220 eyes advanced glaucoma. DDLS yielded an area under the receiver operating characteristics curve (AROC) of 0.90 (95% CI 0.87-0.93), compared to AROC for vertical CDR of 0.88 (95% CI 0.85-0.91), p=0.048, for identifying severe/end-stage disease. After one year, 339 eyes were analysed (89%). Treatment was successful in 55/176 eyes (31.3%) in the timolol arm (39 eyes without repeat counselling) and in 99/163 eyes (60.7%) in the SLT arm (66 eyes without repeat SLT); odds ratio 3.37 (95% CI 1.96-5.80, p<0.0001). The multivariable analysis identified baseline IOP <25mmHg, moderate glaucoma and no exfoliation material as predictors of success. Safety, acceptance, VRQoL, preservation of vision after one year were similar in both groups. Depending on the number of eyes treated annually, SLT can be an affordable and cost-covering intervention. A post hoc analysis of the SLT group showed a response (IOP reduction of 2mmHg or more) in 81% of eyes after SLT and 19% had no response after primary SLT. Among non-responders, 70% responded and 30% showed no response after repeat SLT (p=0.872). SLT treatment response was correlated between eyes: primary SLT in 85 pairs, chi-squared=18.07 (p<0.001), after repeat SLT in 47

pairs 3.68 (p=0.055). The most parsimonious model of absolute IOP reduction after primary SLT included age <70 years, no timolol eye drops before enrolment, IOP ≥25mmHg and a minimum height of the trabecular meshwork of >1/2 of the laser spot size as predictors, and only IOP ≥25mmHg for the model after repeat SLT.

**CONCLUSIONS:** SLT was superior to timolol for managing open-angle glaucoma in this East African setting. It has potential to transform the management of glaucoma in Africa, even where the prevalence of advanced stages of this blinding disease is high.

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*Philippin family, TPC sugar cane plantation, Moshi, Tanzania*

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tsc = trial steering committee

# Format and structure of the thesis

The format of this PhD thesis follows the “research papers format” of the London School of Hygiene & Tropical Medicine. It includes a number of manuscripts which are either published, accepted or prepared for submission in peer reviewed journals. Chapters listed in italics in the table of contents refer to such manuscripts also indicated by a structured cover sheet. Other chapters are a synthesis of background information and additional material which link the research manuscripts. Each chapter starts with a picture reflecting the contribution of different people or other aspects of the work. All patients shown in this document gave their written consent.

# Abbreviations

| | |
|---|---|
| AGIS | Advanced Glaucoma Intervention Study |
| ALT | Argon Laser Trabeculoplasty |
| CBM | Christian Blind Mission |
| CCT | Central Corneal Thickness |
| CIGTS | Collaborative Initial Glaucoma Treatment Study |
| CONSORT | Consolidated standards of reporting trials |
| DDLS | Disc Damage Likelihood Scale |
| DSMB | Data safety and monitoring board |
| EQ-5D | EuroQoL questionnaire |
| GLT | Glaucoma Laser Trial |
| HRQoL | Health-related quality of life |
| HRT | Heidelberg Retina Tomograph |
| IAPB | International Agency for the Prevention of Blindness |
| IOP | Intraocular pressure |
| KCMC | Kilimanjaro Christian Medical Centre |
| KCMUC | Kilimanjaro Christian Medical University College |
| KiGIP | Kilimanjaro Glaucoma Intervention Programme |
| LSHTM | London School of Hygiene and Tropical Medicine |
| NIMR | National Institute of Medical Research |
| OAG | Open angle glaucoma |
| OCT | Optical coherence tomography |
| OHT | Ocular Hypertension |
| OHTS | Ocular Hypertension Treatment Study |
| PBD | Prevention of Blindness and Deafness |
| POEM | Patient reported outcome and experience measure |
| QoL | Quality of life |
| RCT | Randomized controlled trial |
| RNFL | Retinal nerve fibre layer |
| SiB | Seeing is Believing |
| SLT | Selective laser trabeculoplasty |
| SSA | Sub-Saharan Africa |
| TM | Trabecular meshwork |
| TSC | Trial steering committee |
| VA | Visual acuity |
| VRQoL | Vision-related quality of life |
| WHO | World Health Organisation |

# 1 Background

*A participant of the trial is led by her son after a follow-up examination at the Eye Department of Kilimanjaro Christian Medical Centre*

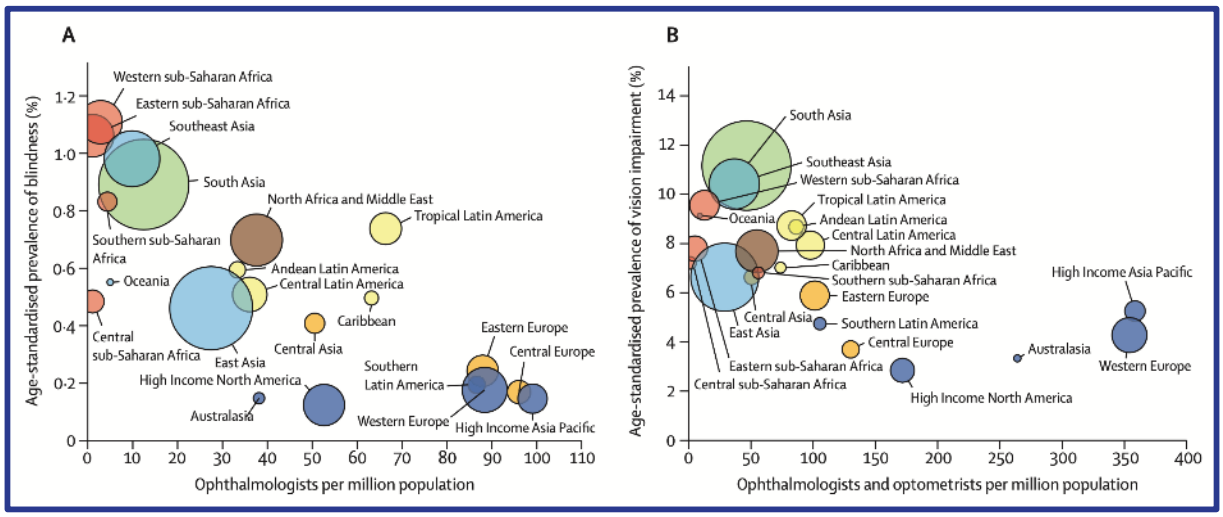
## 1.1 Overview

People suffering from loss of vision caused by early glaucoma may report missing or blurry patches in their visual fields or do not even notice any change which hampers an early detection of the disease.[1] Late stages of the irreversible condition are characterised by small remnants of visual field and end in absolute blindness. The glaucomas are a group of diseases affecting the optic nerve which causes these visual field damages. The main modifiable risk factor for developing glaucomatous optic nerve damage is a painless elevated intraocular pressure (IOP). Therefore, lifelong treatment to reduce IOP can halt progression, but not restore lost sight.

The glaucomas are the most frequent cause of irreversible blindness globally.[2] The highest prevalence of glaucoma exists in Africa with 4.79 % and it is probably underreported because prevalence studies in this region might not always have had the diagnostic capabilities to detect glaucoma.[3,4] African populations are expected to experience nearly a doubling in the number of people with glaucoma from 10.31 to 19.14 million between 2020 and 2040, which represents the highest estimated incidence rate for all world regions.[4] This is probably mainly due to the expected increase in life expectancy and population growth. The African region is not only affected by the highest prevalence and incidence of glaucoma, but also by the highest proportion of advanced disease (see also Figure 3, page 22). The prevalence of glaucoma-specific blindness in all ages is highest in Africa at 1.5/1000, which is twice the global figure of a prevalence of blindness in all ages due to glaucoma of 0.7/1000.[5]

In the African region the battle to prevent sight loss from glaucoma is fought with very limited resources such as diagnostic technology, treatment options and trained personnel. The four African sub-regions have the lowest per capita number of ophthalmologists and highest rates of vision impairment of any world region – averaging around 2.7 ophthalmologists per million population (Figure 1).[6,7] Key areas to address are developing strategies for the earlier detection of people at risk of developing glaucoma blindness and more effective, timely interventions to slow down progression. including capacity building and strengthening eye care systems. Where possible, the treatment approaches would ideally be suitable for task sharing / shifting with other cadres.

***Figure 1: Vision impairment and eye health workforce*.**




*Shown for the Global Burden of Disease regions. (A) Age-standardised prevalence of blindness (all ages) by the number of ophthalmologists per million population. The circle area is proportional to the number of people who are blind. (B) Age-standardised prevalence of vision impairment (mild, moderate, severe, and blind; all ages) by the number of ophthalmologists and optometrists per million population. The circle area is proportional to the number of people who have vision impairment. From Burton MJ, Ramke J, Marques AP, et al. The Lancet Global Health Commission on Global Eye Health: vision beyond 2020. Lancet Glob Health 2021; 9: e489–551.(with permission).*

This work explores the potential role of selective laser trabeculoplasty (SLT) in Tanzania. SLT is an efficacious, safe, 5-minute outpatient procedure which has a short learning curve.[8] However, apart from promising pilot studies, it has not yet been formally tested and compared with a standard treatment in a randomised controlled trial in an African setting.

## 1.2 Introduction to glaucoma

### 1.2.1 Definition

The glaucomas are a group of diseases defined as a characteristic glaucomatous optic neuropathy with an associated visual field defect. Higher intraocular pressure is the main risk factor but not part of the definition.[9]

### 1.2.2 Glaucoma related anatomy and physiology

Glaucoma is typically caused by an elevated intraocular pressure due to compromised aqueous humour dynamics. Aqueous humour is secreted into the posterior chamber, flows across the vitreous cavity or directly through the pupil into the anterior chamber (AC). After circulating in the AC, it drains out through the anterior chamber angle. From there it drains via the two known routes of trabecular meshwork or uveoscleral outflow.

Intraocular pressure (IOP) is determined by the balance between the production, circulation, and drainage of ocular aqueous humour (aqueous humour dynamics, AHD). Parameters of AHD are the rate of aqueous humour formation ($F_a$), the facility of trabecular outflow (C), the rate of drainage through the uveoscleral outflow pathway ($F_u$), and the pressure in the episcleral veins ($P_e$). The Goldmann equation describes the relationship between these factors:[10]

$$IOP = (F_a - F_u)/C + P_e$$

The rate of aqueous formation (F) is normally 2-3 µL/min; the uveoscleral outflow is typically 1.4-1.5 µL/min; the facility of outflow (C) is normally 0.2-0.3 µL/min/mmHg; and the episcleral venous pressure ($P_e$) is normally 8–10 mmHg. Elevated IOP is most commonly caused by a low outflow facility (high in outflow resistance).

### 1.2.3 Types of glaucoma

#### Overview

The different types of glaucoma can be classified using different classification systems (table 1). Usually a mixed system is used, which loosely follows the aetiology, anatomical features and other risk factors of glaucoma phenotypes. The nomenclature doesn't follow a hierarchical system. But specifying the type or phenotypes of glaucoma is relevant for a specific treatment planning.

***Table 1: Different classification systems to describe the glaucomas.***

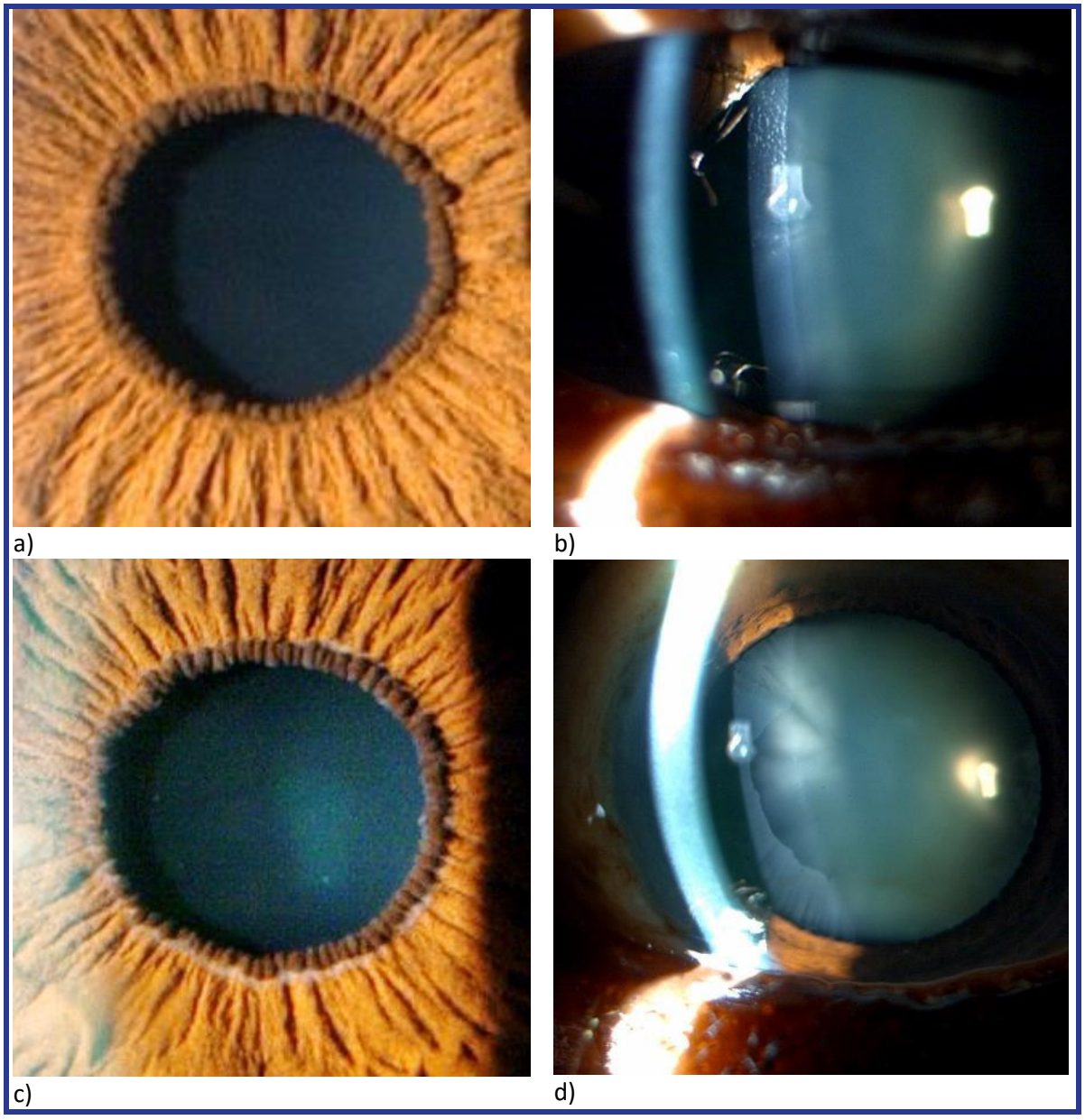
| **Criterion** | **Examples** |
|---|---|
| Time of onset | Childhood glaucoma, juvenile glaucoma, adult-onset glaucoma |
| Cause | Primary glaucoma (normal looking trabecular meshwork, pathology unknown), Secondary glaucoma (known pathology causes high IOP) |
| Aetiology | Angle dysgenesis, exfoliation glaucoma, pigment dispersion, traumatic, uveitic, high-pressure, normal tension, neovascularisation, post-surgical |
| Chamber angle | Open-angle, narrow angle, occludable angle, closed angle |
| Chronology | Acute angle closure, chronic glaucoma |
| Risk | Ocular hypertension, angle closure suspect ('occludable angle') |
| Genetic composition | Variations in different genes, e.g. the myocilin (MYOC) gene or lysyl oxidase-like 1 gene (LOXL1) |

The distribution of different types across Africa is not very well understood but is probably heterogeneous, with a dominance of open-angle glaucoma and relatively high proportions of secondary glaucomas. A population-based survey in Nigeria screened 13,591 people aged ≥40 years in 305 clusters and identified 682 persons with glaucoma (5.02%, 95% CI 4.60-5.47%) based on the ISGEO criteria.[11,12] Out of the 682 participants with glaucoma, 386 were not phenotyped further (56.6%) and 296 (43.4%) were classified with gonioscopy, out of which 243 (82.1%) were identified as primary glaucoma and 53 (17.9%) as secondary glaucoma. The participants with primary glaucoma were further classified - 208 (86%) had primary open-angle glaucoma (POAG) and 35 (14%) had primary angle-closure glaucoma (PACG).[11]

### Exfoliation syndrome and exfoliation glaucoma

An example of a type of glaucoma with a high relevance for Africa is exfoliation glaucoma (XFG) which is caused by exfoliation syndrome (XFS). XFG is typically associated with high intraocular pressure, a relatively fast progression of glaucomatous optic nerve damage and subsequently a worse prognosis of vision impairment.[13,14] While the clinical presentation is often asymmetric (Figure 2), the underlying pathology can be detected in both eyes. Electron microscopic observations have revealed exfoliation fibres in the conjunctiva of the clinically uninvolved fellow eye almost invariably.[13]

***Figure 2: Exfoliation glaucoma***




*Images of one participant of the KiGIP SLT trial with asymmetric Exfoliation glaucoma. Right eye: a) normal appearance of the pupillary border. b) regular anterior lens surface. DDLS 5, baseline IOP 26mmHg. Left eye: c) fine deposits of exfoliation material at the pupillary border e.g. at 2h00 and 3h30 and deposits of pigment on the anterior lens surface. d) deposits of white exfoliation material on the anterior lens surface. DDLS 8, baseline IOP 43 mmHg*

### 1.2.4 Severity of glaucoma

The impact of glaucoma on the quality of life of an affected person, its treatment and its economic impact on the livelihood of the person and society depend on the severity or stage of the disease. The vigour of treatment can be less for early glaucoma, whereas patients with advanced disease are thought to need more aggressive therapy.[15] Staging of glaucoma usually relies on measuring structural changes, functional changes or both. However, there is no consensus on definitions of different stages of glaucoma and different trials have used different approaches (see chapter Structural changes, page 46 and chapter Functional changes, page 48).

### 1.2.5 Diagnosing and detecting glaucoma

Preventing blindness from glaucoma is a challenging task. In the African region, patients often present with late stages of the irreversible disease (Figure 3).[16,17] Many people with glaucoma in SSA only become aware of their problem after they have already lost a significant proportion of their vision.[18,19] There may be several contributory factors such as limited access to eye care services, higher presenting intraocular pressure (IOP) and more rapid progression.[20] Therefore, earlier detection and diagnosis of glaucoma is an essential component of a strategic approach to reduce blindness and visual impairment from glaucoma (Figure 14, page 143).

### 1.2.6 Management and treatment of glaucoma

Once glaucoma is detected and the diagnosis is known to the patient and his eye care provider, a lifelong patient - eye care provider relationship starts. Management of glaucoma includes a regular follow-up and review of the glaucomatous damage and adjustment of treatment. The main modifiable risk factor is elevated intraocular pressure (IOP); lifelong IOP control can halt disease progression.[21,22] Treatment options for glaucoma consist of medical treatment (mainly eye-drops), surgery and laser. More details on management and treatment with a focus on Africa are provided in the following chapters.

## 1.3 Epidemiology of glaucoma in Africa and worldwide

The limited epidemiological data on glaucoma in Africa mainly comes from a few population-based studies, most of which are summarised in Table 2. This limited evidence on the epidemiology of glaucoma suggests that the prevalence of glaucoma varies across Africa.

***Table 2: Prevalence of glaucoma in different population-based studies across Africa.***

| Location | Ethnic group | Study period | Age yrs. | Exam./sample (response rate %) | All glaucomas | Types of glaucoma | | | | Blind (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | POAG | PACG | Sec-ondary | Non-classified | |
| Kongwa, Tanzania[23] | Bantu (Wagogo) | 1996 | >40 | 3247/3641 (89%) | 135 (4.2%) | 74.1% | 14.1% | 3.7% | 8.1% | 14 |
| Temba, South Africa[24] | Bantu (Sotho, Nguni) | 2003 | >40 | 839/1120 (75%) | 55 (5.3%) | 54.6% | 9.1% | 36.3% | - | - |
| Tema, Ghana[25] | Ethnically diverse | 2006-2008 | ≥40 | 5603/6806 (82%) | 362 (6.5%) | 94.5% | 2.5% | 3.0% | - | 3 |
| Nigeria, national[11] | Ethnically diverse | 2005-2007 | ≥40 | 13,591/15027 (90%) | 682 (5.0%) | 30.5% | 5.1% | 7.8% | 56.6% | 20 |
| Nakuru, Kenia[26] | Bantu 63% (Kikuyu), Nilotic 23% (Kalenjin) | 2007-2008 | ≥50 | 2111/2171* (97%) | 88 (4.3%) | 94.3% | 5.7%* | NA | | 6 |

*- = no data. *2111 right eyes and 2107 left eyes had gonioscopy, 5 right and 5 left eyes considered to have occludable angles (based on visualization of Schwalbe's line and the anterior meshwork or less)*

Worldwide, the leading causes of blindness in those aged 50 years and older in 2020 were cataract (15.2 million cases [95% uncertainty interval 12.7–18.0]), followed by glaucoma (3·6 million cases [2.8–4.4]), uncorrected refractive error (2.3 million cases [1.8–2.8]), age-related macular degeneration (1.8 million cases [1.3–2.4]), and diabetic retinopathy (0.86 million cases [0.59–1.23]).[27] Leading causes of moderate and severe vision impairment were uncorrected refractive error (86.1 million cases [74.2–101.0]) and cataract (78.8 million cases [67.2–91.4]).[27]

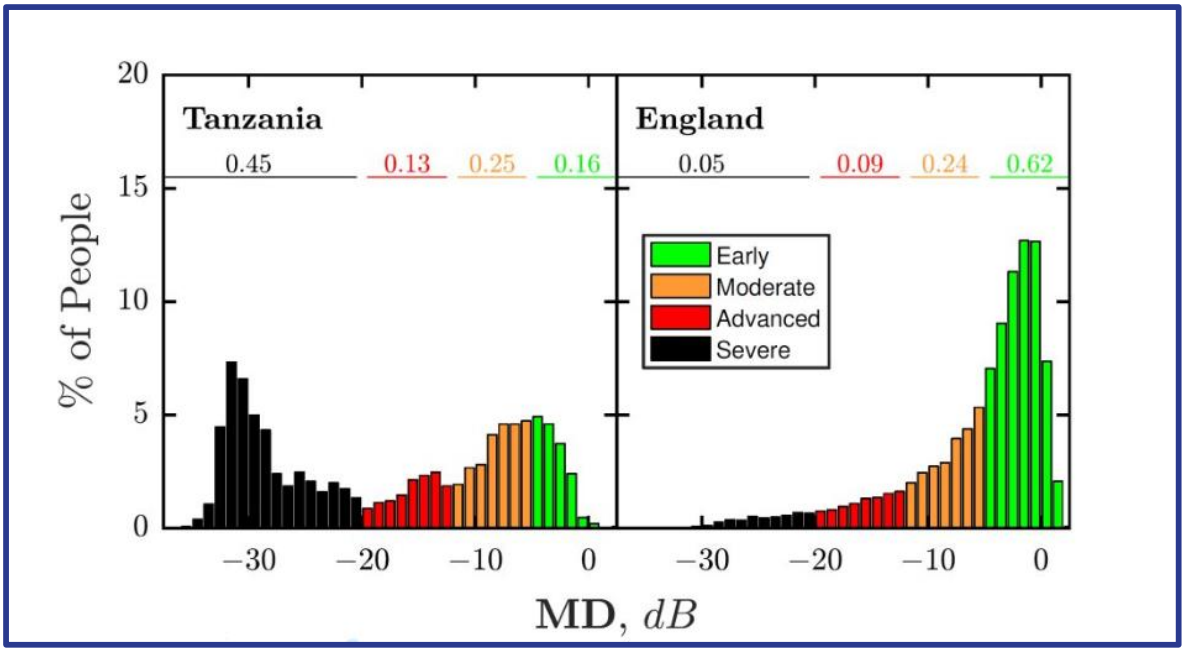
***Table 3: Number and prevalence of glaucoma in different world regions***

| World region | Cases (thousands) | Age-standardised prevalence (per 1000) |
|---|---|---|
| Global | 3600 (2800 to 4410) | 2·04 (1·59 to 2·49) |
| Central Europe, eastern Europe, central Asia | 178 (139 to 219) | 1·25 (0·972 to 1·53) |
| High income | 785 (622 to 964) | 1·41 (1·12 to 1·74) |
| Latin America and Caribbean | 334 (256 to 411) | 2·63 (2·01 to 3·23) |
| North Africa and Middle East | 463 (354 to 578) | 5·69 (4·37 to 7·10) |
| South Asia | 577 (439 to 726) | 2·26 (1·71 to 2·83) |
| Southeast Asia, east Asia, and Oceania | 754 (575 to 957) | 1·34 (1·02 to 1·67) |
| Sub-Saharan Africa | 510 (398 to 628) | 6·64 (5·20 to 8·09) |

*Number of cases (thousands) and age-standardised prevalence in 2020 for blindness due to glaucoma in adults aged 50 years and older. Adapted from Bourne RRA, Steinmetz JD, Saylan M, et al. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: The Right to Sight: An analysis for the Global Burden of Disease Study. Lancet Glob Heal 2021;9:e144–60.*

Furthermore, the highest prevalence of blindness due to glaucoma is found in the Africa region.[5,28] Patients with glaucoma present with more advanced stages compared to other regions (Figure 3).[17]

***Figure 3: Severity of visual field loss at presentation in Tanzania and England***




*From Jones PR, Philippin H, Makupa WU, Burton MJ, Crabb DP. Severity of Visual Field Loss at First Presentation to Glaucoma Clinics in England and Tanzania. Ophthalmic Epidemiol. 2019 Sep 13:1-9*

The prevalence of exfoliation syndrome was reported in few population-based studies and some clinic-based studies.[29] A population-based study in South Africa found a prevalence of exfoliation syndrome (XFS) of 5.1% among Bantu subjects aged ≥ 30 years.[30,31] A population-based study of 1840 participants by Rotchford et al. in South Africa found a prevalence of XFS of 7.7% (95% CI 5.4-10.5%) in Hlabisa and 6.0% (95% CI 4.1-8.4%) in Temba.[14] The prevalence survey by Buhrmann et al. in Kongwa district, Tanzania, found no exfoliation syndrome in any of 3268 examined participants.[23]

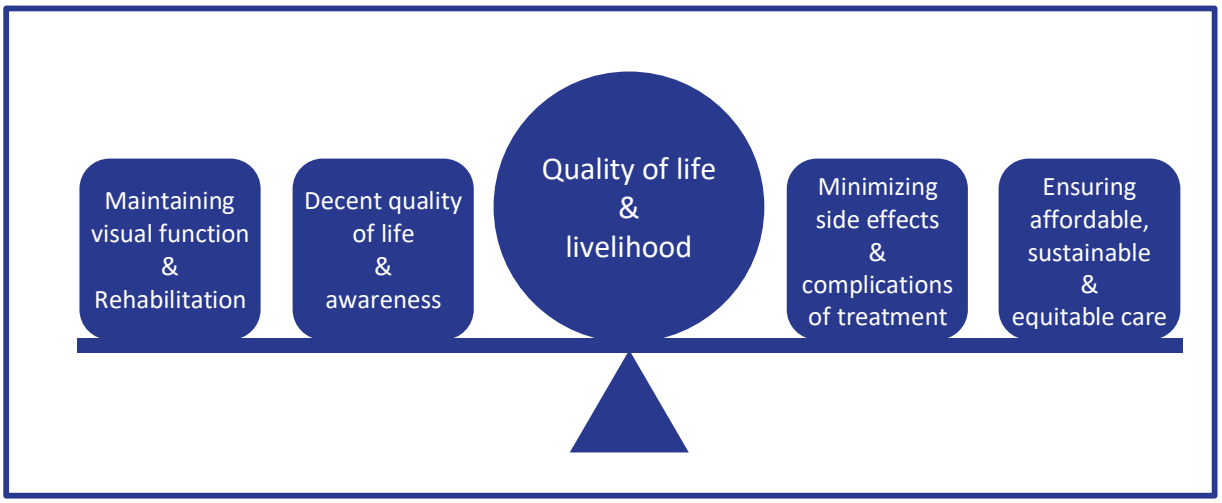
Concerning the relationship between XFS and glaucoma, Rotchford et al. found among black glaucoma patients a prevalence of XFS of 16% in patients aged ≥ 40 years.[24] Tenkir et al. reported from Jimma University Hospital in Ethiopia a proportion of 35.2% of XFG out of 335 consecutive new and follow-up patients with glaucoma.[32] A clinic-based study by Giorgis et al. of glaucoma patients presenting to Menelik II Hospital in Addis Ababa showed a prevalence of 26.6% of XFG among 602 patients with glaucoma.[33] 81% of the patients affected by XFG had advanced glaucoma. Overall, patients with advanced glaucoma were more than six times more likely to present with blindness (odds ratio 6.2 (95% CI 3.8 – 10.1) for right and 6.9 (95% CI 4.2 – 11.2) for left eyes).[33]

## 1.4 Management of glaucoma in Africa

### 1.4.1 Therapeutic goals for a person with glaucoma

The essential goal of glaucoma care for a person with glaucoma or at risk of glaucoma in an African country or elsewhere is to maintain and promote their quality of life and livelihood, while balancing side effects and other costs.[34] The main objective is to slow down progression (Figure 4), usually by lowering intraocular pressure (chapter 1.4.2).

***Figure 4: Balancing the costs and benefits of glaucoma care***




*Balancing the benefits and costs of glaucoma care are among the factors which determine the wellbeing or quality of life as well as the livelihood of a person with glaucoma. A decision to treat or not to treat is always a trade-off between benefit and harm for the person with glaucoma.*

### 1.4.2 Reducing intraocular pressure is the main lever to prevent progression

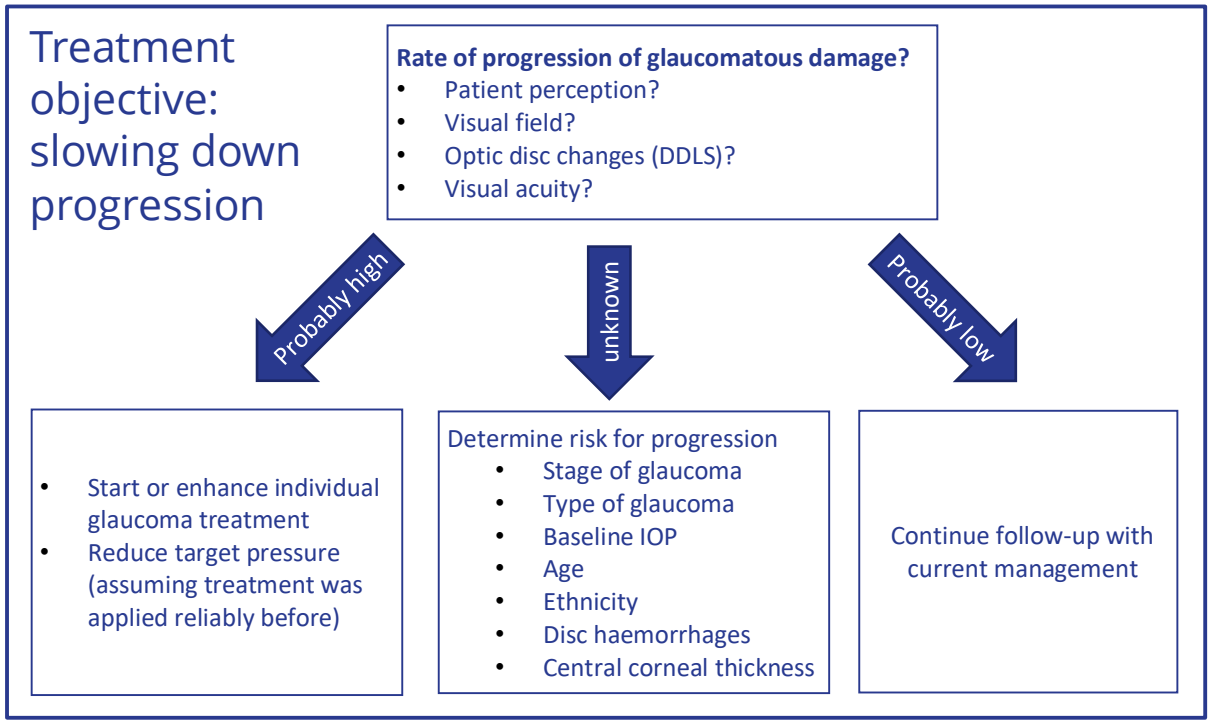
The glaucomas are a group of different diseases whose pathogeneses are only partly understood. However, reducing intraocular pressure is currently the most important lever in daily practice to slow down or stop progression of loss of vision.

Individuals show different susceptibility to optic nerve damage at given intraocular pressure (IOP) levels.[35,36] IOP is a complex result of aqueous humour flow, uveoscleral outflow, trabecular outflow and episcleral venous pressure (see chapter 1.2.2 on page 17).[37] IOP distribution in the general population resembles a Gaussian curve, with a skew toward the higher pressures. Leydhecker et al measured IOP in 10,000 individuals with no known eye disease ranging from 10 to 69 years of age. Mean IOP was 15.5±2.57, hence the authors interpreted the upper limit of normal as being two

standard deviations above mean IOP at around 21mmHg. This is misleading because IOP does not determine if a patient has glaucoma or not. It is now known that IOP is a causative risk factor for glaucoma but is not part of the definition.[38,39] A recent analysis of the Early Manifest Glaucoma Trial with a median follow-up of 8 years confirmed the results of earlier findings that elevated IOP is a strong factor for glaucoma progression, with a hazard ratio increasing by 11% for every 1mmHg of higher IOP.[40] In treated patients with advanced glaucoma, eyes with 100% of visits with IOP less than 18 mm Hg over 6 years had mean changes from baseline in visual field defect score of close to zero.[21]

The primary treatment objective is to halt or slow down progression and the decision to intervene is influenced by several factors indicting the risk and rate of progressive damage (Figure 5). Intraocular pressure can be lowered using eye drops or systemic medical treatment (see chapter 1.5, page 26), laser treatment (see chapter 1.6, page 30) or surgical interventions (see chapter 1.7, page 37).

***Figure 5: Reducing the rate of progression of glaucoma is the key objective of treatment.***

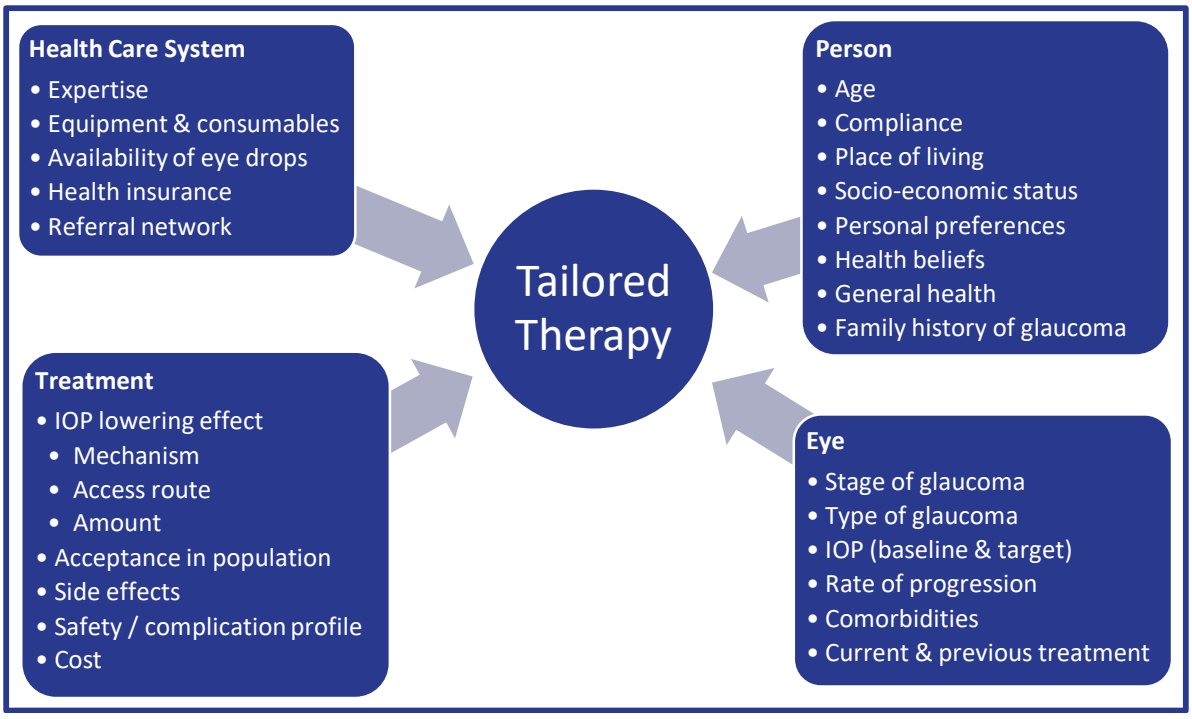



Ideally, the ***rate of progression*** is determined from several reliable visual field examinations, visual acuity or optic nerve head morphology measurements over a period of several months, as well as the patient's perception. However, in daily practice it can be difficult to determine the rate of progression as well as changes in the quality of life and livelihood which can be attributed to glaucomatous changes.

At initial clinical assessment visits often no follow-up data are available and at subsequent follow-up visits it can be challenging to differentiate the signals of actual deterioration from the background noise, common to most diagnostic methods. In many low-income regions, the determination of whether or not progression is occurring is even more difficult to make because the diagnostic modalities are frequently limited. Alternatively, the rate of progression can be estimated from risk factors for progression (also called prognostic factors). Older age, higher baseline or fluctuating IOP, low central corneal thickness, advanced glaucoma, exfoliation glaucoma, disc haemorrhages, and an African ethnicity may be associated with increased risk of progression.

Further important elements of glaucoma care which are often administered by different members of the glaucoma care team are rehabilitation, counselling, education and psychological support. Glaucoma treatment needs to be tailored to the patient and his or her eyes while considering treatment specific and health system related factors (Figure 6).[41]

***Figure 6: Factors to consider when tailoring an individual therapy for a person with glaucoma.***




*Adapted from Philippin H. Management of chronic open-angle glaucoma. Community Eye Health Journal, 2021;34:43–6.*

## 1.5 Medical treatment and timolol eye drops

### 1.5.1 Medical treatment of glaucoma – an overview

The medical treatment options of glaucoma can be divided into six drug classes (table 4). When combining different eye drops, it is recommended to use eye drops with different mechanisms of action for lowering intraocular pressure.

***Table 4: Six classes of medications to reduce intraocular pressure.***

| Main mode of IOP-lowering | Drug | Example | Efficacy | Side effects (selection) |
|---|---|---|---|---|
| Decreasing aqueous production | β-Blockers | Timolol | ++++ | Bronchospasm, bradycardia, depression |
| | Carbonic anhydrase inhibitors | Systemic: Acetazolamide | ++++++ | Metallic taste, electrolyte imbalance |
| | | Topical: Dorzolamide | ++ | Stinging, burning, headache |
| | α2-adrenergic agonists | Brimonidine | +++ | Toxic reaction of external eye, dry mouth |
| Enhanced aqueous outflow | Prostaglandin analogues | Latanoprost | +++++ | Eyelash growth, periorbital fat atrophy, increased iris pigmentation |
| | Rho-kinase inhibitors | Netarsudil | +++ | Conjunctival hyperaemia, headache |
| | Cholinergic agonists | Pilocarpine | ++ | Headache, dim vision |

*Osmotic agents are not mentioned as they are not suitable for long-term use. Adapted from Philippin H. Management of chronic open-angle glaucoma. Community Eye Heal J 2021;34:43–6.*

In 1978 the first topical β-blocker was introduced for treatment of glaucoma.[42] It was considered the gold standard first-line treatment until 1996 when the first prostaglandin analogue, latanoprost, was introduced.

### 1.5.2 Mechanism of action of β-blocker

Timolol is usually prescribed twice daily - although almost the same hypotensive effect can be achieved if used once a day.[43,44] The washout period after long-term application is around 2 weeks.[45]

After 4 weeks no hypotensive effect is remaining.[46] The mechanism of action is mainly through antagonizing β1 and β2 receptors in the ciliary body's non-pigmented epithelium, leading to a decreased aqueous humour secretion. One drop of timolol 0.5% has its peak effect 2 hours after instillation and can last for 24 hours. It might also have a neuroprotective effect on ganglion cells via its $Ca^{2+}$ channel blocking activity.[47]

### 1.5.3 The efficacy of timolol

A recent meta-analysis estimated the mean difference in IOP reduction between timolol and placebo at three months as 3·70mmHg (95% CI 3·16-4·24).[48] This reduction relative to a placebo compares favourably to other classes of anti-hypertensive eye drops (Table 5). Although prostaglandin analogues have a stronger anti-hypertensive effect than timolol, the overall difference is relatively modest.

***Table 5: Relative efficacy of topical glaucoma medication***

| | | | | |
|---|---|---|---|---|
| **Placebo** | | | | |
| 3.59 (2.89; 4.29) | **Brimonidine** | | | |
| 3.7 (3.16; 4.24) | 0.11 (-0.42; 0.64) | **Timolol** | | |
| 2.49 (1.85; 3.13) | -1.1 (-1.8; -0.4)* | -1.21 (-1.73; -0.69) | **Dorzolamide** | |
| 4.85 (4.24; 5.46)* | 1.25 (0.72; 1.8) | 1.15 (0.79; 1.5) | 2.36 (1.76; 2.95) | **Latanoprost** |

*Summary estimates for intraocular pressure at 3 months derived from a network analysis with posterior means (95% Bayesian credible intervals) are calculated by column – under the Lu and Ades homogeneous random effects model assuming consistency.*[49] *Mean difference <0 favours the drug in the column, and mean difference >0 the drug in the row. * no direct comparison published. Adapted from Li T, Lindsley K, Rouse B, et al. Comparative Effectiveness of First-Line Medications for Primary Open-Angle Glaucoma: A Systematic Review and Network Meta-analysis. Ophthalmology 2016; 123:129–40.*

The average reduction in IOP by timolol is around 27% after 3 months.[50] There is a slight loss of efficacy of timolol over time, probably due to adaption mechanisms.[51] In up to 20% of cases the initial IOP reduction can be lost within 2–3 weeks. This has been called "short-term escape" and probably is due to an up regulation in the number of ocular β-receptors after initial complete blockade.[52] Therefore, it is recommended to wait at least 4 weeks following initiation of therapy before assessing IOP effect. In some patients, there is a phenomenon called "long- term drift" in which IOP reduction may be lost after many years of therapy, or even within months.[52] Non-response (IOP reduction by timolol of less

than 6 mmHg) was reported as being around 20%.[53] Adherence to medical treatment is a general concern in this context.

### 1.5.4 Side-effects and complications of topical β-blocker

Local side effects of timolol are generally rare. They include allergic reactions and chronic inflammation. Inflammatory reactions during long-term application are mainly due to preservatives such as Benzalkonium-Chloride. An in vivo study has revealed no toxicity from topical timolol therapy to the human corneal endothelium.[54]

Systemic side effects comprise mainly cardiovascular, respiratory and central nervous system effects. Depression, fatigue, anxiety, confusion, sexual dysfunction, and impaired neuromuscular transmission have been reported with the use of topical β-blockers.[55] They can be reduced by nasolacrimal duct occlusion and/or eyelid closure for about 1 minute after instillation of the drops.[56] Still, it is prudent not to use timolol in patients who require respiratory drugs for conditions such as asthma, have bradycardia with a heart rate of less than 55 beats/minute or had heart failure in the past.

### 1.5.5 Significance of topical β-blocker in low-income settings

Although long-term medical treatment is relatively impractical and costly for the patient, it is often the only available treatment option in the African context[57] Non-adherence, cost, side effects, misunderstanding concerning lifelong treatment, physical inability to administer drops and health beliefs undermine the efficacy of conservative treatments such as timolol.

Timolol is probably the most commonly prescribed treatment for glaucoma in low-income settings due to high availability, low cost and long experience.[58–60] The patent for timolol has expired, so numerous generic products have entered the market. A bottle of timolol can be purchased for as little as £ 0.50 (IAPB Standard List Price). However, in low-income settings even generic β-blockers might cost more than daily necessities, hence many patients are not able to afford regular, long-term topical glaucoma treatment despite its availability.[61,62]

In 2017, a consensus meeting of 22 health care professionals from throughout Tanzania was held. The group reported giving medical treatment as first line therapy to 95% of patients.[59] For 12 of the attendees, medical treatment was the only available option.[59] Due to availability and affordability, timolol eye drops were the treatment of choice for a majority of participants.[59]

In contrast, the price of a bottle of latanaprost eye drops is substantially higher (table 6).[63] Latanaprost and other costlier topical glaucoma treatments are currently rarely used beyond the wealthier sectors of society, mostly in major urban centres in Africa.

Therefore, for the purpose of the work that follows, we have chosen on timolol eye drops as the most common standard treatment in our region as this is currently the most available and affordable intervention.

***Table 6: Proportion of Median Annual Household Income for timolol and latanoprost***

| | **Timolol** | **Latanoprost** |
|---|---|---|
| Egypt | NA | 8% |
| Ethiopia | 2.4% | 27.4% |
| Ghana | 5% | 16.3% |
| Nigeria | 2.1% | 24.4% |
| South Africa | 3.7% | 7.4% |

*NA=not available. Prices for timolol and latanoprost were divided by the median annual household income (MA-HHI) in each country and expressed as a percentage. Treatments costing less than 2.5% of the MA-HHI were considered affordable. Adapted from Zhao PY, Rahmathullah R, Stagg BC, Almobarak F, Edward DP, Robin AL, et al. A Worldwide Price Comparison of Glaucoma Medications, Laser Trabeculoplasty, and Trabeculectomy Surgery. JAMA Ophthalmol. 2018;136:1271.*

## 1.6 Laser treatment and selective laser trabeculoplasty

### 1.6.1 Laser treatment of glaucoma – an overview

Different laser types and treatment mechanisms are used to lower the intraocular pressure either by decreasing the aqueous production or enhancing aqueous outflow (table 7).

***Table 7: Overview of different types of laser treatment for glaucoma***

| Mode of IOP-lowering | Treatment mechanism | Laser | Comments |
|---|---|---|---|
| Decreasing aqueous production | Partial destruction of ciliary body epithelium which produces aqueous | Transscleral cyclo-photocoagulation (TSCPC) | Typically, diode laser (810nm) is used. Risk of irreversible hypotony. Therefore, fractional treatment is common. |
| | | Endoscopic cyclo-photocoagulation | Similar to TSCPC with a better complications profile but more invasive. |
| | | Micropulse transscleral cyclo-photocoagulation (MP-TSCPC) | Diode laser (810nm) with short bursts instead of continuous delivery of laser energy to reduce destruction of adjacent non-ciliary tissue. Might also enhance uveoscleral outflow. |
| Enhanced aqueous outflow | Increasing outflow through the trabecular meshwork | Argon laser trabeculoplasty (ALT) | Initial treatment with argon laser trabeculoplasty was at least as efficacious as initial treatment with topical medication (GLT). Risk of scarring of the trabecular meshwork and peripheral anterior synechiae formation. |
| | | Selective laser trabeculoplasty (SLT) | 532nm frequency doubled Q-switched Nd:YAG laser. Similar efficacy as ALT (LiGHT, KiGIP SLT trials) but less side effects and repeatable. |
| | | Micropulse laser trabeculoplasty (MLT) | Using 810nm, 532nm or 577nm lasers. Exact mechanism poorly understood. Possibly similar efficacy as SLT |
| | | Iridoplasty | Plateau iris, narrow angle glaucoma |
| | Improving aqueous flow from the posterior to the anterior chamber | Laser peripheral iridotomy (LPI) | Q-switched Nd:YAG laser (YAG laser 1064 nm), Argon laser. |

*Adapted from Philippin H. Management of chronic open-angle glaucoma. Community Eye Heal J 2021;34:43–6.*

### 1.6.2 Types of laser trabeculoplasty

In 1972, Krasnov first reported the use of a laser treatment applied to the trabecular meshwork.[64] Several different types of laser systems have been used for this purpose, e.g. argon laser trabeculoplasty (ALT), selective laser trabeculoplasty (SLT), and diode laser trabeculoplasty (DLT).[65] There have been two large formal trials examining the effectiveness of Argon laser trabeculoplasty compared to trabeculectomy.[66–69] In the Moorfields Primary Treatment Trial, trabeculectomy was found to be more effective in reducing IOP and preserving visual fields than ALT.[69] The advanced glaucoma intervention study (AGIS) also compared ALT to trabeculectomy. Interestingly, in the sub-analysis, African American participants had better visual function with ALT compared to trabeculectomy after 7 years.[67,70] The Glaucoma Laser Trial compared ALT with medical treatment (timolol) and found ALT to be superior to timolol.[71,72]

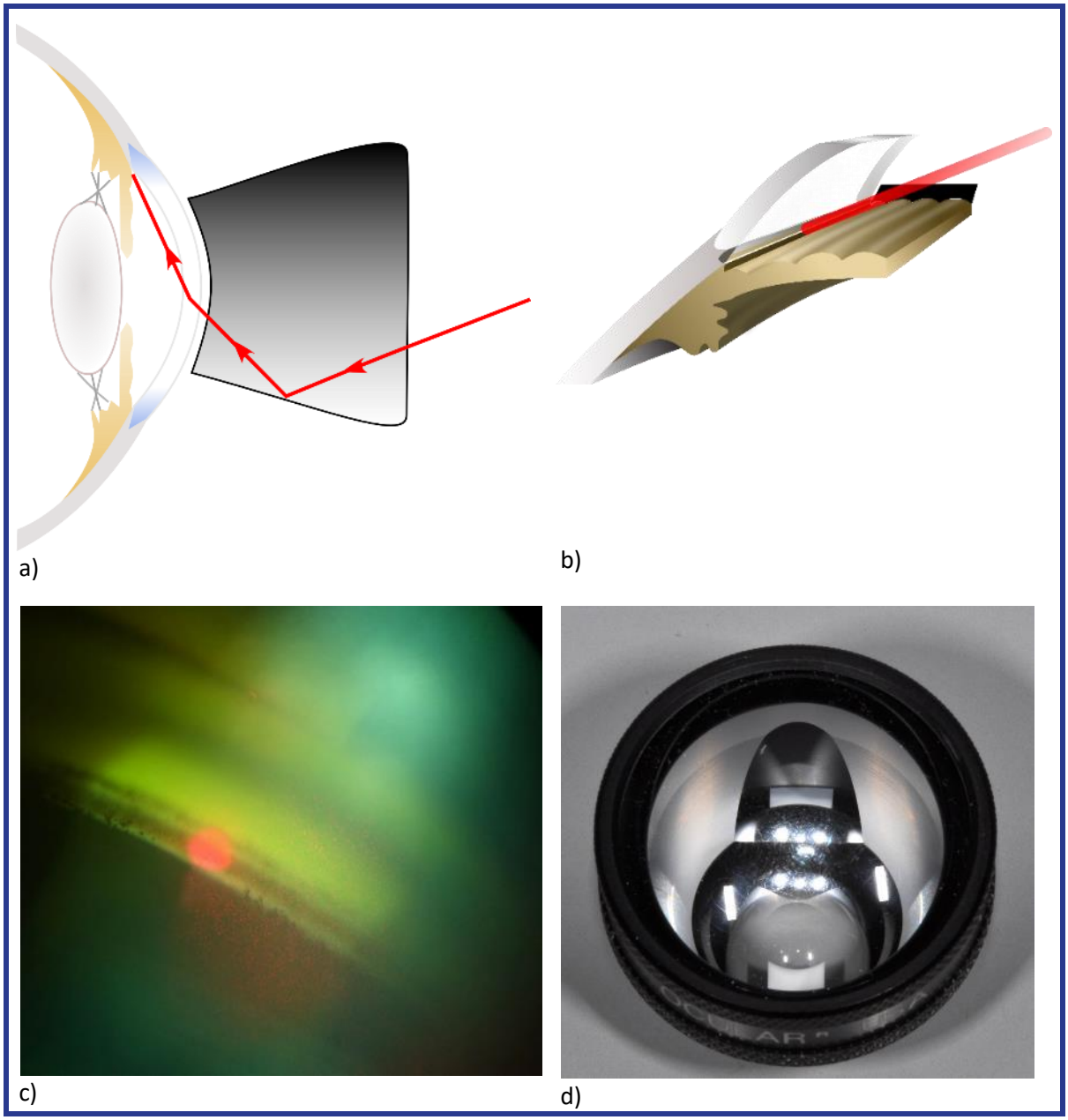
### 1.6.3 History of selective laser trabeculoplasty

In 1995, Latina and Park published their studies of the effect of a frequency-doubled Nd:YAG laser whose wavelength and pulse duration provided selective photothermolysis that targeted melanin and spared the surrounding non pigmented tissue *in vitro*.[73] They showed in an *in vitro* study of cultured bovine cells from the trabecular meshwork (TM) that pigmented TM cells could be killed using short bursts (1µs or less) but non pigmented TM cells would be spared. Their work led to the SLT which is in use today, a Q-switched frequency-doubled, 532nm ND:YAG laser which delivers a 400nm treatment spot for a duration of 3 ns. A study using scanning electron microscopy confirmed the relative lack of any thermal injury with the selective laser in contrast with the typical thermal burn observed when directing the argon laser at the trabecular meshwork of human cadaver eyes.[74]

### 1.6.4 Mechanism of action of selective laser trabeculoplasty

In terms of the concept of aqueous humour dynamics (see chapter 1.2.2, page 17), the main mechanism of action of selective laser trabeculoplasty is an increase in outflow facility which was shown using fluorophotometry and tonography.[75] SLT uses a micro-pulsed frequency doubled YAG laser to apply multiple treatment-spots to the trabecular meshwork after visualizing the chamber angle with a Latina SLT gonioscopy lens (Figure 7).

***Figure 7: Application of laser spots using selective laser trabeculoplasty***




*a) Cross section of an eye and a gonioscopy contact lens which enables visualisation of the chamber angle. b) Laser effects directed at the chamber angle. c) View of the aiming beam through the slit lamp located on the trabecular meshwork. d) Latina goniolens with single mirror and magnifying glass.*

At a cellular level, after application of SLT to human and monkey eyes the number of monocytes or macrophages in the trabecular meshwork increased substantially. Monocytes augmented both outflow facility and Schlemm's canal endothelium conductivity. Schlemm's canal drains aqueous from the chamber angle through the sponge-like trabecular meshwork into the venous system. These findings might indicate that monocytes play a role in aqueous outflow homeostasis through phagocytosing debris within the trabecular meshwork.[76] SLT has also been shown to cause changes in

gene expression, cytokine secretion, matrix metalloproteinase induction, and remodelling of the trabecular meshwork.[77]

### 1.6.5 Selective laser trabeculoplasty treatment parameters

In current practice, typical treatment parameters are 50-100 shots applied over 180°-360° of the trabecular meshwork, with energy levels between 0.4-1.4 mJ and an end point of small bubbles, also called "champagne bubbles".[78] Nagar et al conducted a prospective trial comparing SLT over 90°, 180°, and 360° degrees to latanoprost monotherapy. The IOP reduction in the SLT subgroups was greatest for the 180° and 360° treatments, which was comparable with latanoprost in efficacy.[79]

A retrospective study compared SLT treatment in phakic and pseudophakic eyes. It showed a delayed response in the group of 18 pseudophakic eyes versus the IOP-lowering effect in the group of 76 phakic eyes but the long term effectiveness was equal in both groups.[80]

### 1.6.6 Efficacy of selective laser trabeculoplasty

To date, eight randomised controlled trials have compared selective laser trabeculoplasty with eye drops which are summarized in table 8 (page 34).[81] The largest randomised controlled trial with a follow-up time of 36 months is the Laser in Glaucoma and ocular HyperTension (LiGHT) trial.[8] It compares SLT with any conservative treatment. Of the 536 eyes treated with SLT first, 419 (78%) required no additional medication to reach target IOP, and 321 (60%) required only a single SLT treatment (Table 10, page 36).[8] A retrospective study of real-world data (de-identified electronic medical records) of 831 SLT-treated eyes (first recorded SLT) confirmed a significant reductions in IOP (-4.2 (95% CI -4.7 to -3.7) at 12-18 months and -3.4 (95% CI -4.1 to -2.7) mmHg at 24 to 36 months, the majority of eyes failed within 1 year.[82]

At the time of developing the protocol for our trial, only four randomised controlled trials comparing SLT with medication had been published.[79,83–86] SLT showed an IOP lowering effect of around 30% in patients with glaucoma who were not previously treated.[79,87] In a study from St. Lucia, African-derived participants who were previously on medical treatment underwent a 4 weeks wash-out followed by SLT treatment. The 12-month Kaplan-Meier survival rate (≥10% IOP reduction from post washout baseline) was 77.7%, and 93% of successful subjects experienced IOP levels less than their previous with-medication values.[88] Furthermore, several case series studies on selective laser trabeculoplasty from African countries reported results in favour of SLT (Table 9, page 35).

***Table 8: RCTs comparing SLT with eye drops***

| Year, first author, region | Types of glaucoma included | Treatment before enrolment | Treatment (first line) of control group | SLT protocol of treatment group | Definition of success | Persons / eyes (n/n) | Age (mean years) | Gender (M/F) | Baseline IOP (mean) | Follow-up (months) | IOP reduction (mean (SD)) | | Success IOP control | Quality of life |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | SLT | Eye drops | | |
| 2004, Lai[85], Asia | POAG, OHT | Treatment naïve | No medication protocol | 360° | IOP < 21 mmHg | 29/58 | 51.9 | 13/16 | 26.5 | 60 | 8.6 (6.7) | 8.7 (6.6) | ~ | N/A |
| 2005, Nagar[79], Europe | OAG, OHT | Washout period of 5 weeks | Prostaglandin analogue | 90°, 180°, 360° | >20% or >30% IOP reduction | 167/167 | 63 | 77/90 | 29.3 | 12 | N/A* | N/A* | ~ | N/A |
| 2009, Nagar[86], Europe | OAG, OHT | Treatment naïve | Prostaglandin analogue | 360° | >20% IOP reduction | 40/40 | 66.4 | 21/19 | 16.6 | 6 | 6.2 (3.6) | 7.8 (3.6) | ~ | N/A |
| 2012, Katz[84], USA | OAG, OHT | Washout period 4 weeks | Prostaglandin analogue | 360° 1st step, 180° 2nd and 3rd step | >20% IOP reduction | 69/127 | N/A | 28/41 | 24.78 | 12 | 6.1 (3.6) | 7.5 (3.2) | ~ | N/A |
| 2014, Lee[89], Asia | POAG | Kept current eye drops | Kept current eye drops | 360° | NA | 41/82 | 66.04 | 22/19 | 24.45 | 6 | 2.4 (2.5) | 0.0 (2.35) | N/A | ~ (GQL-15) |
| 2017, Tufan[90], Europe | POAG | No washout period | Different fixed combinations with timolol | 2 groups: 180° and 360° | NA | 40/80 | 16.6 | 19/21 | 15.2 | 6 | 0.1 (2.71) | -0.2 (2.5) | N/A | N/A |
| 2017, De Keyser [91–93], Europe | POAG, OHT | Kept current eye drops | Kept current eye drops | 360° | >20% or >30% IOP reduction | 125/125 | 70.28 | 63/62 | 13.07 | 12 | 2.6 (3.14) | 1.6 (3.45) | N/A | + (TSS-IOP) |
| 2019, Gazzard, [8,94–99], Europe | POAG, OHT | Treatment naïve | Prostaglandin analogue | 360° | >20% or >30% IOP lowering | 718/1235 | 63.1 | 397/321 | 24.5 | 36 | 7.9 (4.5) | 8.1 (4.5) | ~ | ~ (EQ-5D 5L) |

*NA=not available. TSS-IOP=treatment satisfaction survey for intraocular pressure. GQL-15=Glaucoma Quality of Life-15. EQ-5D 5L=Euro Quality of Life 5 Dimensions 5 Levels. *IOP results were only shown in a graph. ~ SLT-related therapy was not significantly better than medication-only therapy. + SLT-related therapy was significantly better than medication-only therapy. Adapted from Chi SC, Kang YN, Hwang DK, Liu CJL. Selective laser trabeculoplasty versus medication for open-angle glaucoma: Systematic review and meta-analysis of randomised clinical trials. Br J Ophthalmol. 2020;104:1500–7*

***Table 9: Case series studies on selective laser trabeculoplasty from African countries***

| Year, first author, region | Study type | Types of glaucoma included | Treatment before study | Treatment protocol | Main outcome | Pts / eyes (n/n) | Age (mean years) | Baseline IOP (mmHg) | Follow-up (m) | Results |
|---|---|---|---|---|---|---|---|---|---|---|
| 2012, Abdelrahman, Cairo, Egypt[100] | Prosp non-randomised | POAG | Treatment naïve pts and pts on eye drops | 360° SLT | IOP drop, no of eye drops | 65/106 | 53.2 | 19.6 (SD 4.8) | 18 | Drop of IOP to 16 (SD 2.8 mHg) both groups, No of eye drops reduced in group 2 from 2.25 (SD 0.97) to 1.0 (SD 1.3). No serious complications. |
| 2015, Seck, Dakar, Sénégal[101] | Retrosp | POAG, OHT | Pts on glaucoma treatment | SLT of inferior 180°. Second session at 15 days or 1 month if IOP response after first SLT. | IOP < 21 mmHg after 1-month follow-up. No of eye drops | 40/69 | NA | 18.3 (SD 4.0) | 12 | At 2 weeks: 90% of pts responded, mean IOP decrease of 2.3 (SD 1.0) mmHg (13%). After 1 month and treatment of 360°: IOP reduced by 4.78 (SD 1.0) |
| 2016, Goosen, Durban, South Africa[102,103] | Retrosp | POAG | A) treatment-naïve pts. B) medical therapy and/or surgery | A) SLT first, medical treatment as needed. B) SLT as additional therapy to drops and/or surgery. | IOP drop ≥ 20% | 84/148 | 59.6 | A) 27.07, B) 18.97 | ≥ 12 | At 1 year: A) 13.33mmHg (mean IOP reduction -13.74mmHg); B) 12.90mmHg (mean IOP reduction -6.07mmHg). Higher IOP reduction in treatment naïve eyes, pts >70yrs, female pts, pts of African descent compared with Caucasians. |
| 2019, Ouattara, Abidjan, Côte d'Ivoire[104] | Retrosp | POAG | | 360° SLT in two sessions (each 180°) 15 days apart | IOP drop ≥ 3 mm Hg, no additional medications | 44/82 | 55.94 | 18.43 (SD 4.81) | 6 | At 15 days: mean IOP reduction 3.81 mmHg (20.67%), success rate 67.60%; at 6 months 4.95 mmHg (26.86%), success rate 80.43% |
| 2020, Soboka, Addis Ababa, Ethiopia[105] | Prosp non-randomised | POAG, XFG, OHT | Pts on medication and pts with primary SLT | 360° SLT | IOP drop > 20%, no repeat treatment. | 61/95 | | 24.3 (SD 2.5) | 12 | At 1 year: mean IOP reduction 6.7 (SD 4.2) mmHg (27.6%), success rate 60%, medication reduction 0.26 ± 1.34. Pts with primary SLT: mean IOP reduction 6.5 (SD 3.1) mmHg, pts on eye drops 6.8 (SD 2.8) mmHg. Post-SLT, pts reported transient ocular pain, headache, and/or blurring of vision in 31.6%, AC reaction in 36.8%, and IOP spike ≥ 6 mmHg in 11.6%. |
| 2021, Diallo, Bobo Dioulasso, Burkina Faso[106] | Prosp non-randomised | | | Inferior 180° SLT | IOP drop > 20% | 31/35 | 59.3 | 20.1 (SD 7.0) | 6 | At 30 days, 15.3 (SD 5.4) mmHg, 23.9% decrease. At 120 days, 43.3% of treated eyes had a decrease of at least 20% |

*Pts=participants. m=months. Prosp=prospective, retrosp=retrospective. AC=anterior chamber.*

*Table 10: Laser in Glaucoma and ocular HyperTension (LiGHT) trial*

| **LiGHT** | **Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (2019)** [8,94,95] |
|---|---|
| Research question | Is selective laser trabeculoplasty as a first-line treatment associated with better health-related quality of life, less need for topical medication, and lower cost? |
| Population | 718 newly diagnosed patients with OHT or POAG, no ocular comorbidities |
| Study design | • Multicentre, observer-masked, randomised controlled trial<br>• In both groups a treatment escalation was advised when there was any of the following:<br>○ IOP > target by 4mmHg or more at a single visit<br>○ Strong evidence of deterioration, irrespective of IOP (i.e. GPA: likely progression HRT rim area loss >1% per year, or (P<0.001)<br>○ IOP > target by ≥ 2 and < 4mmHg for 2 consecutive visits and less strong evidence for progression (.e. GPA possible progression or HRT rim area >1% per year (P<0.01) |
| Intervention | SLT laser as the first intervention (356 participants) |
| Comparator | Initial eye drops (362 participants) |
| Outcomes | • Primary outcome was health-related quality of life (EQ-5D) at 3 years<br>• Secondary outcomes were cost and cost-effectiveness, disease-specific HRQoL, clinical effectiveness, and safety |
| Analysis | • 652 participants (91%) analysed after 36 months |
| Results | • No difference of EQ-5D after 3 years<br>• 74% of the SLT arm achieved the target IOP without additional eye drops after three years and needed fewer trabeculectomies compared with the eye drop arm<br>• SLT laser was safe and cost-effective |
| Discussion | • Selective laser trabeculoplasty should be offered as a first-line treatment for open angle glaucoma and ocular hypertension, supporting a change in clinical practice |

### 1.6.7 Repeatability of selective laser trabeculoplasty

Due to the selective effect on melanin in trabecular meshwork cells, SLT causes only very limited collateral damage and is considered to be repeatable.[73] Several studies have explored the effects of repeat interventions.[94,107–111] For example, a study from 2009 showed a 15% reduction in IOP 5-8 months after repeat 360° SLT (100 spots/360°).[110] Another study found an IOP reduction similar to initial treatment (40-50 spots/360°).[108]

### 1.6.8 Risks and complications of selective laser trabeculoplasty

Although SLT has fewer side effects than ALT, there are still a few documented adverse reactions after SLT treatment. The low complication rates can be attributed to an energy delivery of 1% of that of ALT.[73] Side effects of SLT are mainly revolving around ocular discomfort, anterior chamber inflammation and IOP spikes. Complications are usually reported as mild and transient. Transient Ocular discomfort was described by several authors and affects between 10-40% of patients treated with SLT.[79,112,113] Ocular discomfort was significantly less comparing it with ALT.[113] Anterior chamber inflammation or transient uveitis is another adverse event which is described regularly ranging from 50-83% of patients.[112,113] In an early study in 1998 by Latina et al., 83% showed mild-to-moderate

inflammation within 1 hour after SLT which started decreasing after 24h and resolved within 5 days.[112] IOP spikes, usually defined as an IOP rise > 5mmHg after the procedure, is a transient side effect which manifests within 1-2 hours after treatment and usually resolves within 24 hours.[79,85,112,114] Usually an alpha agonist or other hypotensive topical agent is administered one hour before the intervention to reduce the risk of the transient post-laser IOP spike. Single case reports described transient corneal changes[115] or hyphema.[116]

## 1.7 Glaucoma surgery

### 1.7.1 Surgical treatment of glaucoma – an overview

There are different surgical approaches to lowering IOP, e.g. to enhance outflow into the sub-Tenon space with a trabeculectomy. These are summarised in table 11. The main surgical routes of access to the draining site are either through the anterior chamber (*ab interno*) or from the surface of the eye (*ab externo*) which have certain implications, e.g. procedures using a surgical access through the anterior chamber require a clear cornea and deep anterior chamber. On the other hand, the conjunctiva does not need to be incised which avoids scaring.

### 1.7.2 Glaucoma surgery in Africa

Verrey et al [18] reviewed the records of 397 patients with chronic glaucoma in rural Ghana and found that only 17% of patients receiving medical treatment had IOPs lower than 22mmHg. In contrast, 84% of patients treated surgically had IOPs lower than 22mmHg.So several commentators suggest that the primary treatment in Africa should be surgical treatment, especially trabeculectomy, which seems to be a feasible alternative.[18,117] Overall there is high-quality evidence that trabeculectomy can be beneficial in preventing progression in advanced glaucoma (e.g. TAGS Table 12 , or AGIS Table 17, page 52). A well trained surgeon supported by a strong team can achieve good results in any world region.[118–120] However, glaucoma surgery has a long learning curve and in the African context is only performed by few ophthalmologists in few eye units.[57] Its uptake by patients and surgeons is challenged by the fact that the visual function doesn't improve after surgery. Expectations are high since the most common surgical procedure is cataract surgery. A study from Nigeria reported that fewer than 5% of people offered surgery (trabeculectomy) returned for the procedure.[121] In a report of 22 eye health care professionals from Tanzania in 2017 many felt that offering surgery at an initial visit would discourage patients from returning to the centre and few eye health centres would therefore offer this option. In addition, a fear of surgery was felt to exist in both patient and surgeons.[59]

***Table 11: Overview of surgical interventions* for *glaucoma treatment***

| Main mode of IOP-lowering | Surgical route of access | Surgery | Comments |
|---|---|---|---|
| Enhanced aqueous outflow into the sub-Tenon space | Ab externo | Trabeculectomy | Gold standard, low-cost procedure to create a guarded fistula between the anterior chamber and sub-Tenon space, requires adherence to follow-up. Moorfields safer technique common variation (e.g. using releasable sutures), also suitable in low-resource settings |
| | | Glaucoma drainage devices | Aravind aurolab drainage implant, Ahmed valve, Baerveldt shunts (250/350), Paul Glaucoma Implant |
| | | PreserFlo microshunt | Microshunt between the anterior chamber and sub-tenon's space, drains more posteriorly. |
| | Ab interno | XEN gel stent | A 6mm porcine-derived gelatin with an inner lumen of 45 µm and outer diameter of 150 µm. |
| Enhanced aqueous outflow through the trabecular meshwork | ab externo | Canaloplasty | Dilation of Schlemm's canal using viscoelastics and a suture. |
| | | Trabeculotomy | Accessing Schlemm's canal via a partial scleral flap. A curved probe (trabeculotome) is rotated gently into the anterior chamber to incise through the trabecular meshwork. |
| | | Deep sclerectomy | Non-penetrating surgery otherwise similar to trabeculectomy. |
| | | Iridectomy | Improving aqueous flow from the posterior to the anterior chamber |
| | Through the anterior chamber (ab interno) | iStent | 360 µm stent with a central lumen of 80 µm implanted into the trabecular meshwork. |
| | | Hydrus | A permanent, 8mm long, slightly curved microstent to dilate Schlemm's canal |
| | | Goniotomy | Typically used for childhood glaucoma. The trabecular meshwork is incised under direct gonioscopic visualization using a goniotomy knife (e.g. 25-gauge needle on a syringe). |
| | | Gonioscopy-assisted transluminal Trabeculotomy (GATT) | Ab interno 360-degree trabeculotomy using a microcatheter or suture without removing trabecular meshwork.[122] |
| | | Kahook Dual Blade | Ab interno trabeculectomy device using a dual blade to create parallel incisions and removing a strip of trabecular meshwork. |
| | | Trabectome | Ab interno trabeculectomy device which ablates (electrocautery) the trabecular meshwork. |
| Enhanced aqueous outflow through the suprachoroidal space | Ab externo | Gold Micro-Shunt | Two fused leaflets with fluid channels and holes |
| | | STARflo | Plate with micropores shaped like an arrowhead. Evidence still growing. |
| | Ab interno | iStent supra | A 4-mm long curved stent with a lumen of 0.165 mm inserted into the suprachoroidal space. |

*Adapted from Philippin H. Management of chronic open-angle glaucoma. Community Eye Heal J 2021; 34:43–6.*

***Table 12: TAGS - the treatment of advanced glaucoma study***

| **TAGS** | **The Treatment of Advanced Glaucoma Study - TAGS (2021)** [120,123,124] |
|---|---|
| Research question | What is the clinical and cost-effectiveness of primary medical management compared with primary surgery for people presenting with advanced open-angle glaucoma? |
| Population | 453 patients recruited with newly diagnosed advanced glaucoma (mean MD -15.0 dB) |
| Study design | Pragmatic multicentre randomized controlled trial. Using target IOPs according to the recommendations of the Canadian Glaucoma Society Target IOP workshop algorithm.[125] However, this was not prescriptive, and, in keeping with the pragmatic nature of the trial, the patient's clinician determined the target intraocular pressure in each case.[120] |
| Intervention | Augmented trabeculectomy |
| Comparator | Medical treatment escalated as needed |
| Outcomes | • Primary outcome was vision-related quality of life (NEI-VFQ25) at 24 months<br>• Secondary outcomes included general health status (HUI-3, EQ-5D-5L, glaucoma related quality of life, clinical effectiveness (intraocular pressure, visual field, visual acuity), and safety, incremental cost per QALY gained |
| Results | • After 2 years, vision-related quality of life showed no difference,<br>• Mean intraocular pressure was 12.4 (SD 4.7) mmHg for trabeculectomy and 15.1 (SD 4.8) mmHg for medical management ($p<0.001$).<br>• Adverse events occurred in 88 (39%) patients in the trabeculectomy arm and 100 (44%) in the medical management arm (relative risk 0.88).<br>• Serious side effects were rare in both groups including wipe-out. |
| Discussion | • Trabeculectomy and medical treatment showed no difference in vision-related quality of life<br>• Trabeculectomy was safe and achieved a greater reduction of IOP |

## 1.8 Glaucoma treatment outcomes

The ultimate aim of glaucoma treatment is to preserve vision while minimizing a compromise of quality of life. There are different perspectives on how to describe the outcome of glaucoma treatment: patients, clinicians, and health care providers and societal. The outcomes for a study on glaucoma need to be carefully chosen, so that the results are able to answer the research question and have relevance to real-life conditions. The primary outcome determines the sample size of a study.

### 1.8.1 Patient's perspective

#### Definition of quality of life

Quality of life (QoL) can be defined as an individual's assessment of their own physical, psychological and social well-being. In other words, the level of an individual disability is primarily defined by the person affected.

The World Health Organization (WHO) describes in the International Classification of Functioning, Disability and Health (ICF) health and disability by considering two factors: *functioning and disability* as well as *contextual factors*. The first includes body structures and functions and also activities and participation. The latter consists of environmental and personal factors.[126] Contextual factors such as culture, climate or coping style need to be included in the concept of quality of live especially in relation to perceptions of being healthy and associated rehabilitation goals.

#### Quality of life and glaucoma

Glaucoma is a chronic disease currently without a cure. It entails life-long follow-up, often requiring treatment. QoL related to glaucoma depends on many components such as the amount of visual impairment, cost and side-effect of treatment and the psychological effect of suffering from a potentially blinding disease. In some societies connotations of being cursed or punished might play a role as well.

Considering QoL of glaucoma patients is an important concept in glaucoma management since the nature of a chronic condition requires a balance between long-term cost and benefit of treatment, viewed from the affected individual's perspective. Only a balance between cost and benefit in several aspects can lead to a successful long-term management of the disease.

Hence, an important question is the perception of the patient regarding the visual impairment, the disease of glaucoma itself and particularly when comparing different treatment modalities, such as laser and eye drops.

In the work that follows we use a number of tools, including semi-structured interviews on the history of glaucoma, monetary costs encountered by the patient and the glaucoma symptom scale,[127] a comprehensive and short patient outcome and experience measure (POEM),[128] the WHO visual functioning questionnaire,[129] and the glaucoma symptom scale (GSS).[127] Finally, focus group discussions elucidated particular differences between intervention groups. Here some additional background on these different tools.

## Tools to evaluate quality of life

### Introduction

Quality of life can be captured with patient-reported outcome measures (PROM's). There are numerous PROMs available to measure different aspects of QoL. Information can be gathered either through interview-administered or self-reported questionnaires. It can be measured in absolute terms or may be measured in change. Absolute terms, such as subjective vision, are sometimes easier to assess in comparison to change, for instance the extent to which a symptom has improved or worsened in a certain period of time.

Types of PROMs include 1) those assessing general health, 2) those which are system specific in their questioning, 3) and those which are disease specific. Each of these types has been used to assess QoL in patients with glaucoma.

A PROM consists of different components. PROMs are structured interviews with pre-coded responses and often the intention is to use a quantitative method of data analysis. Specific questions are known as items; interviewees choose answers from two or more options. Related items form a domain or subscale. Following the WHO International Classification of Functioning, Disability and Health (WHO ICF) [126] , domains reflect disease impact on

(1) bodily symptoms or functions,
(2) activities or
(3) social participation.

Other types of interviews include semi-structured and unstructured or in-depth interviews. They can be important to get insights from a different angle and provide additional information, for example about the impact of contextual factors on perceptions of health. Semi-structured interviews follow topics or questions which are planned in advance but instead of closed questions like in structured interviews, semi-structured interviews are based on open-ended questions. In a semi-structured interview, the interviewer can probe the interviewee to elaborate on the previously given response. Unstructured or in-depth interviews are discussions of a limited number of topics and successive questions evolve from the interviewee's previous response.

### Assessing general health related quality of life

Tools assessing general health related quality of life measure the overall impact of sickness or surgery. They allow comparisons between different diseases. The **SF-36** (The Medical Outcomes Study Short Form-36) is a medical health survey containing 36 questions.[130] It takes around 10 minutes to administer and is easy to use. But there is a weak correlation between the 36 domains and visual field impairment [131] and other visual functions.[132]

The **SIP** (Sickness Impact Profile) was developed to measure perceived health status and to be robust enough to detect changes in health status over time or between groups.[133] With 136 categories and 12 domains, it takes more than 30 minutes to perform and is difficult to use. It was used for the Collaborative Initial Glaucoma Treatment Study (CIGTS) to collect longitudinal data on QoL in newly diagnosed glaucoma patients. However, it showed no correlation between reduced health status and newly diagnosed glaucoma.[134] Due to weak correlations, general health questionnaires are rarely used in isolation for the assessment of the QoL impact of glaucoma.

### Assessing vision related quality of life

Several vision specific instruments exist which are used to quantify the subjective status of glaucoma patients. The **NEI-VFQ** (National Eye Institute Visual Function Questionnaire) [135,136] is a 51 item, 12-domain tool that takes 15 minutes to use. The 25-item National Eye Institute Visual Function Questionnaire (**NEI-VFQ-25**) [137] is a 25-item shortened version taking around 5 minutes and is easy to use. It has been translated into many languages. However, it does not consider visual field changes.

These questionnaires are commonly used in research. But only few questionnaires are applicable in low-income settings (high rate of illiteracy, few driving patients, predominantly subsistence farming etc.). A globally widely accepted questionnaire for all regions is the WHO / Prevention of Blindness and Deafness 20-item Visual Functioning Questionnaire (**WHO/PBD VF20**, chapter 10.7, page 168).[129] This tool was adapted from the Indian VF33 and proposed by the WHO as a tool for assessing vision related QoL (**VRQoL**) in low-income settings.[138] The questionnaire includes 20 items in three subscales including visual symptoms (3 items), general visual functioning (12 items) and psychosocial well-being (4 items) plus one overall eyesight rating item.[138,139] Each item allowed 5 responses with a score of one for the most positive and five for the most negative response.[139] For cross-sectional studies, the VRQoL sub-scale scores were summed to create a total sub-scale score. The three total sub-scale scores of each patient were converted into a per cent score with the formula ([individual score – lowest possible score] / [highest possible score – lowest possible score]) x 100. [140]

It was translated into Kiswahili and validated by field testing by Polack et al. They described the relationship between cataract visual impairment and vision- and health-related quality of life, in people >50 years of age in Nakuru district, Kenya.[141] The WHO/PBD VF20 has been used to evaluate the impact of microbial keratitis in Uganda.[142] It was also used in a longitudinal study to describe the impact of trichiasis surgery in Ethiopia on vision-related quality of life.[140]

### Glaucoma Symptom Scale

The **GSS** (Glaucoma Symptom Scale) [127] is a 10 item, 2-domain questionnaire. It covers non-visual symptoms and functional impairment as well as vision related symptoms (*Table 13*). It is a modified version of the OHTS symptom checklist. The checklist was designed to assess the side effects of a topical ocular hypotensive agent in a clinical trial. The items include 10 ocular complaints that are often associated with treatments for glaucoma in two domains. The first domain with 6 items consists of non-visual symptoms. The second domain with 4 items covers visual ocular complaints. Each eye is queried separately.

The questionnaire can be self-administered or filled with help from clinic staff or accompanying relatives. The patient has to decide first if he experiences a symptom or not. If yes, he grades the symptom. This results in a 5-level scale. For the analysis, for each eye, a 5-level score is generated and then transformed to a 0 to 100 scale, with 100 representing absence of a problem and 0 representing presence of a very bothersome problem.

GSS is a quality of life assessments for patients with glaucoma.[143] Like most questionnaires in ophthalmology, the GSS was also developed using traditional psychometric methods, the classical test theory (CTT).[144] Gothwal et.al. did not recommend the use of GSS to assess patients with glaucoma having moderate to severe field loss but with relatively good central vision).[144]

**Table 13: Glaucoma symptom scale (GSS):**

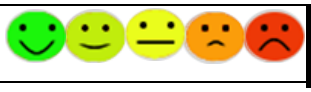
| **"Have you experienced any of the following problems in the last 4 weeks?".**Answer for right and left eyes separately. If the answer is yes, please ask **"how <u>bothersome</u> has it been? / *Je, unasumbuka na hali hiyo?*"** and choose one of the following levels: **1** Not at all / *Hakuna kabisa* **2** A little / *kidogo* **3** Somewhat / *Mara chache* **4** Very / *Sana* | Right Eye / *Jicho la kulia* | | Left Eye / *jicho la kushoto* | |
|---|---|---|---|---|
| | Yes / No | If yes, indicate level 1-4 | Yes / No | If yes, indicate level 1-4 |
| Burning, Stinging / *Mwako, uchungu (kama sabuni ikiingia machoni)* | | | | |
| Tearing / *Machozi* | | | | |
| Dryness / *Ukavu* | | | | |
| Itching / *Mwasho* | | | | |
| Soreness, Tiredness / *Uvimbe, uchovu* | | | | |
| Blurry/Dim Vision / *Uoni hafifu, maruerue* | | | | |
| Feeling of something in your eye / *Unahisi kitu kwenye macho yako* | | | | |
| Hard to see in daylight / *Ugumu kuona wakati wa mchana* | | | | |
| Hard to see in dark places / *Ugumu kuona kwenye giza* | | | | |
| Halos around lights / *Mzunguko wa kivuli cha mwanga wa taa* | | | | |

***Lee BL, Gutierrez P, Gordon M, et al. The Glaucoma Symptom Scale. A brief index of glaucoma-specific symptoms. Arch Ophthalmol 1998;116:861-6.***

### The Glaucoma Patient Outcome and Experience Measure

Administering questionnaires is time consuming for the interviewee and interviewer so it is usually not feasible to capture all aspects of QoL with different questionnaires. A brief comprehensive questionnaire which is designed to be quickly administered and used in clinical routine is the glaucoma **POEM** (patient-reported outcome and experience measure).[128] It consists of eight questions and incorporates the results of focus group discussions with glaucoma patients (Table 14).

**Table 14: Glaucoma patient outcome and experience measure (POEM)**

| **How much do you agree with the following statements? Enter the number accordingly**<br>***Ni kwa kiasi gani una kubaliana na taarifa zifatazo?*** | | | | | | |
|---|---|---|---|---|---|---|
| | **(1)**<br>Strongly disagree<br>Sikubaliani kabisa | **(2)**<br>Disagree<br>Sikubaliani | **(3)**<br>Neither agree nor disagree<br>*Kwa wastani* | **(4)**<br>Agree<br>*Nakubaliana* | **(5)**<br>Strongly agree<br>*Nakubaliana sana* | **(6)**<br>Unable to rate<br>*Siju i* |
| **1** | I know the name of my eye problem.<br>*Ninafahamu jina la ugonjwa wangu.*<br>Comments: | | | |  | |
| **2** | I understand how my eye problem is managed.<br>Ninaelewa jinsi shida ya macho yangu inavyotibika.<br>Comments: | | | |  | |
| **3** | My glaucoma treatment (& any side-effects) are acceptable to me.<br>*Matibabu ya ugonjwa wangu wa pressure ya macho na adha zake (kama zipo) zinavumilika.*<br>Comments: | | | |  | |
| **4** | My glaucoma interferes with my daily life.<br>*Ugonjwa wangu wa pressure ya macho unaathiri shughuli zangu za kila siku.*<br>Comments: | | | |  | |
| **5** | I think my glaucoma is getting worse.<br>*Ninafikiri ugonjwa wangu wa pressure ya macho unaendelea vibaya.*<br>Comments: | | | |  | |
| **6** | I'm worried about losing vision from glaucoma.<br>*Ninaogopa kupata upofu kwa ugonjwa wa pressure ya macho.*<br>Comments: | | | |  | |
| **7** | I feel safe under the care of my glaucoma team at KCMC<br>*Ninaridhishwa na wataalamu wanaonipa huduma hapa KCMC*<br>Comments: | | | |  | |
| **8** | My glaucoma care is well organised<br>*Huduma za ugonjwa wangu zimepangiliwa*<br>Comments: | | | |  | |

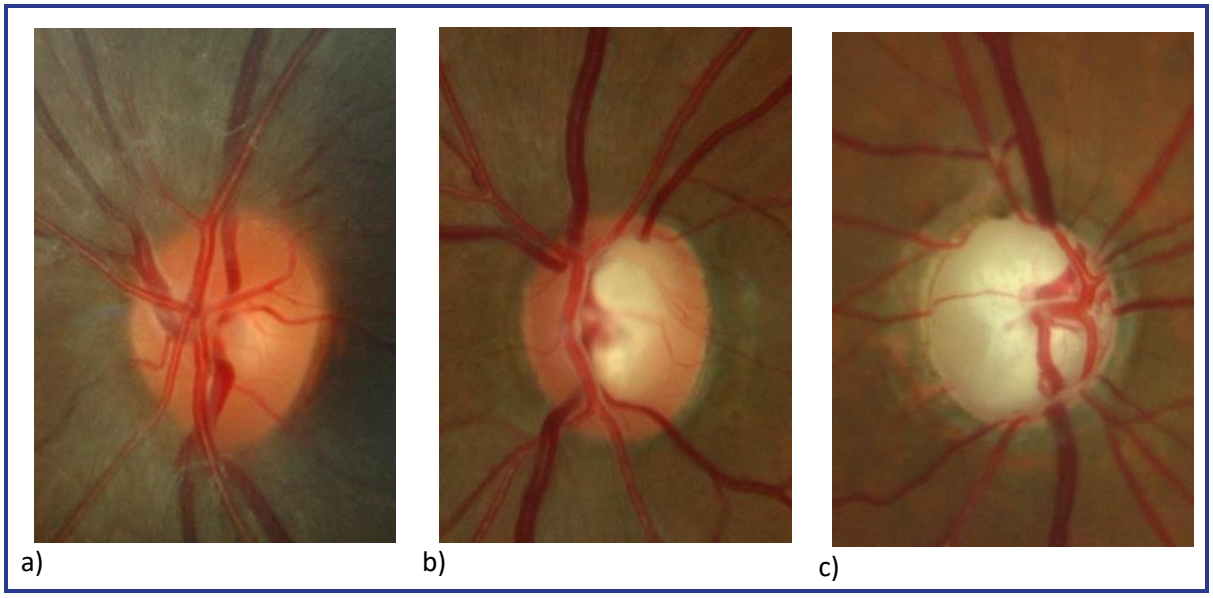
### 1.8.2 Clinical perspective

Most clinical outcomes belong to three main areas of glaucoma related changes: structure, function and intraocular pressure.

#### Structural changes

Glaucoma can be defined as an optic neuropathy - hence the evaluation of the optic nerve is essential in diagnosing, staging and management of glaucoma (Figure 8). The optic nerve can be directly visualized at the slit lamp. Its size can be measured with a device integrated into the slit lamp and using a conversion factor depending on the indirect lens which is used for fundoscopy.[145,146] Drawing a sketch of the optic nerve head can help describe and determine glaucomatous features.

***Figure 8: Optic nerve appearance in different stages of glaucoma.***



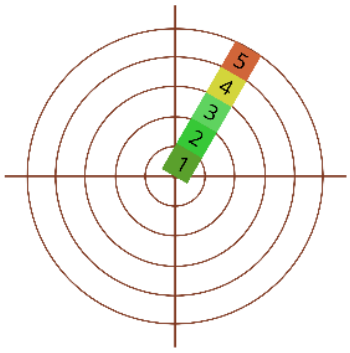
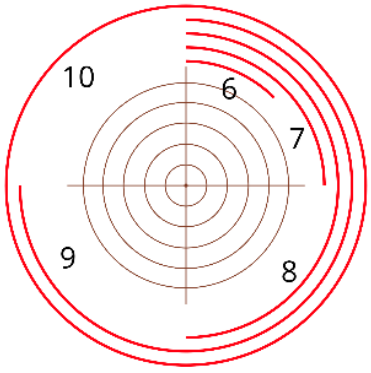

*(a) Normal optic disc: vertical CD-ratio (vCDr) 0.2, DDLS 2, orange-pink appearance. (b) Moderate glaucoma: vCDr 0.7, DDLS 5, notch at 1 o' clock. "Bajonetting" of the vein at 5 o' clock. Wedge of nerve fibre layer from 12 to 2 o' clock. (c) Advanced glaucoma: vCDr 1.0, DDLS 10, pale disc.*

A commonly used system to quantify the features of the disc is to determine the ratio of cup and disc size. The cup/disc ratio system was introduced by Armaly in 1969 and since then gained widespread popularity (Figure 8).[147] It can be applied easily to summarize the state of a glaucomatous damage for the purpose of communication and follow-up. However, the cup/disc ratio has two critical short comings.[15] First, it assumes that the cup is located centrally and enlarges concentrically. Second, its correlation with glaucomatous damage depends on the size of the disc which is not included in the system.[148] Another disadvantage is its limited capability to differentiate reliably different advanced

stages beyond a CD-ratio of 0.9 which is relevant especially in areas with a high prevalence of advanced glaucoma.

An alternative system was developed by Spaeth et al., the Disc Damage Likelihood Scale (DDLS), *Table 15* and Figure 8. It is probably the second most commonly used method, is user-friendly, has a high reliability[149] and is able to detect long-term progression of glaucoma.[150] It uses 10 stages to describe the width of the narrowest rim area or circumferential extent of rim absence in advanced disease. It considers the size of the optic nerve head and has three stages where the CD-ratio would be described as 1.0. Overall, these two methods to describe and measure structural changes of the optic disc are fast and cost-effective.

**Table 15: Disc Damage Likelihood Scale (DDLS)**

<table>
<tr><th>Glaucoma grade</th><th>DDLS Stage</th><th>Definition</th><th>Anatomical descriptor</th></tr>
<tr><td rowspan="5">At risk</td><td>1</td><td>0.4 ≤ RDr</td><td rowspan="6">Narrowest rim width [Rim/Disc ratio (RDr)]<br>  </td></tr>
<tr><td>2</td><td>0.3 ≤ RDr < 0.4</td></tr>
<tr><td>3</td><td>0.2 ≤ RDr < 0.3</td></tr>
<tr><td>4</td><td>0.1 ≤ RDr < 0.2</td></tr>
<tr><td rowspan="2">Glaucoma damage</td><td>5</td><td>RDr < 0.1</td></tr>
<tr><td>6</td><td>1° ≤ extension < 45°)</td><td rowspan="5">Rim absence [extension (°)]<br>  </td></tr>
<tr><td>7</td><td>45° ≤ extension < 90°</td></tr>
<tr><td rowspan="3">Glaucoma disability</td><td>8</td><td>90° ≤ extension < 180°</td></tr>
<tr><td>9</td><td>180° ≤ extension < 270°</td></tr>
<tr><td>10</td><td>270° ≤ extension</td></tr>
</table>

*DDLS is based on the radial width of the neuroretinal rim measured at its thinnest point. Because rim width is a function of disk size, disk size must be evaluated prior to attributing a DDLS stage. For small disks (< 1.50mm) the DDLS should be increased by 1, for large disks (> 2.00mm) the DDLS stage should be decreased by 1.*[15] *Corrective factors for Volk 90D X 1.33.*[146]

Structural changes of the optic nerve can also be described through different imaging techniques. They include confocal scanning laser tomography, optical coherence tomography and scanning laser polarimetry.

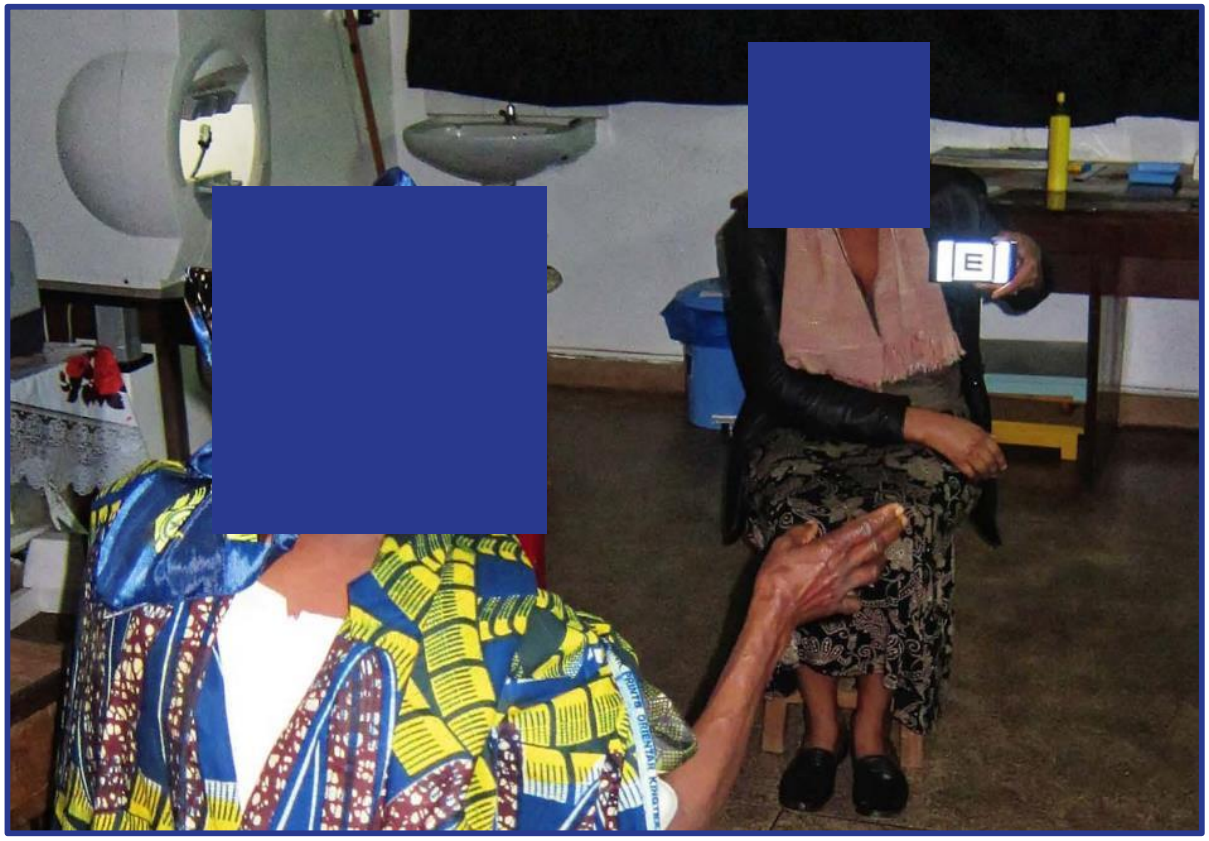
Confocal scanning laser tomography (e.g. Heidelberg Retina Tomograph, HRT) uses a 670nm diode laser to scan the retina in several focal planes. For glaucoma-related diagnostics the scan is centred on the optic disc and the shape of the optic nerve including the cup are measured and described by different parameters. Optical coherence tomography (e.g. Zeiss Cirrhus OCT) is based on low-coherence interferometry of the retina with an 810nm light source. It is analogous to the A-mode ultrasound only using light instead of sound. Scanning laser polarimetry (e.g. GDx VCC) uses birefringence of the retinal nerve fibre layer (RNFL) to measure its thickness around the optic nerve but it is less commonly used to date. However, these evaluation techniques are time consuming and in many eye care facilities around the world these devices are not available due to very high costs of purchasing and maintenance.

Disc stereophotography analysed by an expert panel are still considered as the gold standard by some authors when comparing the different techniques in their ability to discriminate between normal and glaucomatous optic nerve heads.[151]

### Functional changes

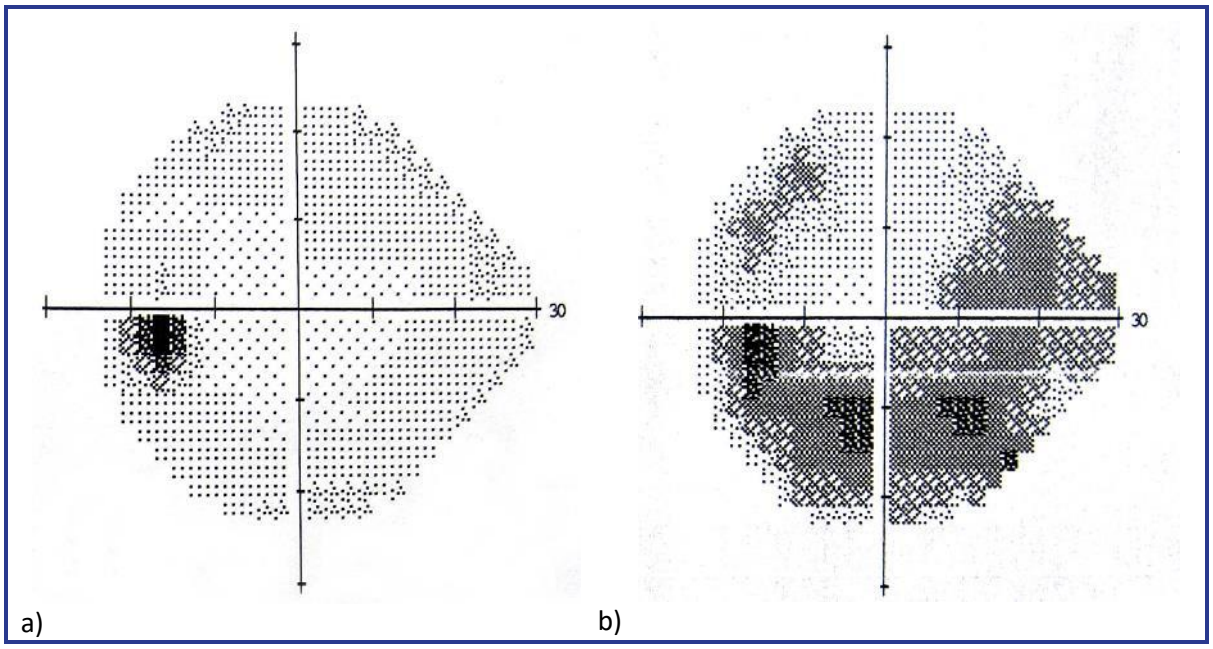
Glaucoma has an impact on different visual functions. Reduced visual acuity (Figure 9, page 49), contrast sensitivity[152], decreased light sensitivity when dark adapted[153,154] or reduced sensitivity to colours[155] were described in patients with glaucoma or ocular hypertension. Most commonly, an assessment of the visual field is used to detect functional loss due to glaucoma (Figure 10, page 49). Several glaucoma studies have used visual field examinations to detect progression of glaucoma (e.g. CIGTS - Table 16 [156], AGIS - Table 17 [68,157]). Visual field analyses can detect functional damage before the patient is aware of a loss of visual function. But it is a subjective test, susceptible to short- and long-term fluctuations and artefacts. For example, 86% of an individual's initial visual field defects in OHTS were not reproducible.[158] When a defect was found in two VF tests, the third was normal in 66% whereas if three VF were abnormal, the fourth was normal in 12%.[159] Another aspect is the high cost of equipment, which limits the availability in low-income settings.

***Figure 9: Measuring visual acuity with Peek Acuity***



*The study protocol included visual acuity and contrast sensitivity measurements using a smartphone. Visual field analyser in the top left corner.*

**Figure 10: Static visual fields**




*a) Normal visual field. b) Advanced glaucomatous visual field defect with typical glaucomatous features: arc shaped visual field depression in the lower field (Bjerrum scotoma) which joins with the upper defect at the nasal horizontal axis (raphé) forming a nasal step (Rønne nasal step).*

**Table 16: CIGTS - Collaborative Initial Glaucoma Treatment Study**

| **CIGTS** | **Collaborative Initial Glaucoma Treatment Study (2001)** [134,156,160] |
|---|---|
| Research question | Is initial trabeculectomy or are eye drops superior as initial treatment for newly-diagnosed persons with open-angle glaucoma. |
| Population | 607 patients with newly diagnosed open-angle glaucoma. Baseline IOP 27mmHg |
| Study design | Randomized controlled trial. Formula for individual target IOP (=1-[baseline IOP + VF score]/100) x baseline IOP |
| Intervention | Eye drops |
| Comparator | Trabeculectomy (with or without 5-fluorouracil) |
| Outcomes | • Primary outcomes: visual field progression and quality of life.<br>• Secondary outcomes: visual acuity, IOP, and cataract |
| Results | • During the first five years, mean visual field progression was small and similar in both groups. After 8 years 21% of surgical patients and 25% of medical patients had progressed (worsening of MD by 3 dBs).<br>• Quality of life (QoL) was initially higher in the eye drops group but there was no difference in QoL at the last follow-up. Worry about becoming blind was reported by 50% of CIGTS participants at baseline, but decreased in both treatment groups to 25% and remained constant thereafter.<br>• The surgical group did have more ocular surface-related irritation (but no difference in quality of life).<br>• IOP was lower after trabeculectomy (48%; mean IOP 14-15 mmHg) compared to pressure reduction in the eye drops group (35%; mean IOP 17-18 mmHg).<br>• Larger IOP variations were associated with significantly worse mean defects after 3 to 9 years in the medication arm but not in the trabeculectomy group (after adjusting for baseline risk factors).<br>• In the trabeculectomy group, 1.1% had developed an endophthalmitis after 5 years and underwent cataract surgery more than twice as often as patients in the medical treatment group.<br>• Reversal of optic disc cupping was seen in 13% in the surgical group, but was not associated with improved visual function.<br>• Risk factors for progression included<br>o Higher baseline IOP,<br>o Worse baseline VF status (had less risk of progression when they received initial surgery versus medication, but VF progression among participants with diabetes who received surgery was greater than those receiving medication. Greater VF progression was observed among medication arm participants who reported poorer adherence to medications.)<br>o Lower level of education.<br>• A subgroup analysis of the CIGTS demonstrated that patients who presented with advanced disease, defined as a mean deviation < -10 dB, had slower VF progression than medically treated patients who had a higher mean IOP after treatment. |
| Limitations | • Inclusion criteria might have allowed OHT with low risk of progression |
| Discussion | • Among the first large glaucoma RCTs which considered quality of life as a primary outcome |

### Target intraocular pressure

Large randomised controlled clinical trials show that glaucomatous damage is related to IOP at almost all levels of pressure. Lowering IOP prevents or delays the onset or progression of glaucoma.[22,161] However, there is no specific IOP threshold which applies to all patients but it is recommended to set and subsequently adapt an individual target intraocular pressure (IOP).[125,162] It can be defined as the intraocular pressure that slows down the rate of progression of the glaucomatous damage enough to maintain the patient's quality of life and livelihood during their lifetime.[34]

Intraocular pressure needs to be evaluated carefully at each follow-up visit. Different types of tonometer may result in different measurements, and eye related factors (e.g. astigmatism) need to be considered. The examiner should follow a standardized protocol. Repeating IOP can provide a more robust result. Low adherence or persistence of the use of eye drops or a fading effect of a laser treatment might lead to a difference between the IOP measured on the day of the follow-up visit and the level of IOPs since the last follow-up visit.

The ***target intraocular pressure*** may be defined as a fixed upper threshold IOP, a calculated threshold IOP using several attributes of a patient, or a percentage reduction.[163] There is only weak evidence on how to determine a specific threshold or percentage for the individual patient with glaucoma. Several concepts are based on the recommendations of the Canadian Glaucoma Society which are mainly based on the results of two post hoc analyses of the advanced glaucoma intervention study (AGIS), Table 17.[21,125]

In the associative post hoc analysis of AGIS, eyes with IOP <18 mmHg at 100% of 6-monthly visits showed no visual field progression.[21] In contrast, those who did have IOP > 18mm Hg at some follow-up visits on average did progress but rates of field progression differed little between those with IOP less than 18mmHg at 75-100% of visits (mean IOP 14.7 mm Hg), 50-75% of visits (mean IOP 16.9 mm Hg) or more than 50% visits (mean IOP 20.2 mm Hg).[21,163] Sometimes, an upper IOP threshold of 12mmHg is recommended for patients with very advanced glaucoma. This is also mainly based on the results from the post hoc analysis of the AGIS (the predictive analysis) which showed patients with no progression had a mean IOP of 12.3 mmHg. However, not all non-progressing patients had an IOP of 12.3mmHg. This average value of 12.3 mmHg includes patients with both lower and higher IOP that overlaps to some extent with the group with mean IOP of 14.7 mmHg.[163] In addition, participants in AGIS were randomized to specific treatment protocols, not target IOPs.

***Table 17: AGIS - Advanced Glaucoma Intervention Study***

| **AGIS** | **Advanced Glaucoma Intervention Study (1998)** |
|---|---|
| Research question | Are eyes with open-angle glaucoma and insufficient IOP lowering despite maximally tolerated eye drops better treated with initial Argon Laser Trabeculoplasty or initial trabeculectomy? |
| Population | US American patients with moderate to advanced open-angle glaucoma who could not be controlled by maximally-tolerated eye drops alone (IOP ≥ 18mmHg, MD > -16dB).[164] 591 patients (789 eyes) were enrolled between 1988 and 1992 and randomly assigned to two treatment protocols (ATT or TAT). |
| Study design | Multicentre, prospective, randomised study |
| Intervention | ALT, followed by trabeculectomy, followed by a second trabeculectomy (ATT) supplemented with medical therapy to achieve a target IOP < 18mmHg. |
| Comparator | Trabeculectomy, followed by ALT, followed by a second trabeculectomy (TAT) |
| Outcomes | Primary outcome: visual function (visual field (Humphrey 24-2) and visual acuity (ETDRS)). Secondary outcomes: IOP, complications |
| Results | • In African American patients, less eyes showed a decreased visual acuity or VF progression in the ATT group compared to the TAT arm<br>• In Europeans, initial trabeculectomy slowed the progression of glaucoma more effectively<br>• Risk factors associated with progression were older age, longer follow-up, increasing number of glaucoma interventions<br>• Mean IOP reduction was greater for eyes assigned to the TAT regime, and the cumulative probability of failure of the first intervention was greater for eyes assigned to the ATT protocol after 7 years.<br>• The percentage of eyes with reduced visual acuity or visual field progression was lower for ATT than for TAT in African American patients.<br>• Initial trabeculectomy slowed the progression of glaucoma more effectively in patients with white European ancestry.<br>• The probability of cataract formation after 5 years was 78% after trabeculectomy,<br>• IOP fluctuations were a risk factor for VF progression only in patients with low mean IOP.<br>• Both ALT and trabeculectomy failed more often in younger patients and in eyes with higher pre-treatment IOP.<br>• The surgical methods for performing trabeculectomy changed during the study period. Before 1990, no antimetabolites were used during surgery whereas after 1990, 5-fluorouracil was used postoperatively. After 1991, mitomycin-C was used intraoperatively.<br>• **Two post-hoc analyses**, which were not specified at the time of planning the trial, evaluated different IOP levels in relation to visual field loss after 7 years. These analyses provide a rough guidance for setting an initial target IOP in advanced glaucoma. Eyes with at least 6 years of follow-up were included.<br>**a) Predictive analysis of 738 eyes:** if the average IOP was greater than 17.5mmHg over the first 1.5 years of follow-up (three visits 6 months apart from each other), the eyes showed more commonly visual field loss compared to eyes with an average IOP below 14mmHg.<br>**b) Associative analysis:** If eyes had an IOP below 18mmHg during all follow-up visits, there was almost no *average* progression of the visual field.[21]<br>• Examples of different reports: AGIS 4 (ethnicity and treatment) [67], AGIS 6 (improvement of visual field and visual acuity after cataract surgery) [165], AGIS 8 (risk of cataract after trabeculectomy) [166], AGIS 9 (outcomes in patients of different ethnicities within treatment groups) [68], AGIS 12 (risk factors for visual field and visual acuity loss) [167] |
| Discussion | • Today, more eye drops are available, e.g. prostaglandins, and laser trabeculoplasty as well as surgical methods have evolved. |

In a post hoc analysis the benefit of randomisation is reduced such that equivalence between groups is not guaranteed. The difference between eyes who show progression and no progression may not be caused by the target IOP alone.[163] So 18 mmHg may be a good starting point for an upper threshold but some patients might need a lower IOP to prevent progression. If there is evidence of progression despite achieving an IOP below the initial target IOP, it needs to be lowered. On the other hand, if achieving the target IOP causes unacceptable side effects or a negative impact on the patient's quality of life, the target pressure might need to be raised.

A percentage reduction instead of a specific level is calculated in relation to the baseline IOP at which damage probably occurred, typically using percentages from 20% to 40%. The concept is based on several trials which used a percentage reduction to calculate target IOP, e.g. OHTS (Table 18) followed a minimum 20% reduction [161], EMGT (Table 19) a 25% reduction [40] and CNTGS (Table 20) a 30% reduction.[168]

**Table 18: OHTS - Ocular Hypertension Treatment Study**

| **OHTS** | **Ocular Hypertension Treatment Study (2002)** |
|---|---|
| Research question | Does treatment of ocular hypertension prevent POAG? |
| Population | • Enrolled 1,636 patients with elevated IOP but no evidence of glaucomatous disc or field damage , 40-80 years, 56% female, 70% Caucasian, 25% African-American, 35% with family history of glaucoma, CDr 0.4, CCT 570µm |
| Study design | • Randomized controlled trial |
| Intervention | • Treatment to achieve ≥ 20% IOP reduction or IOP < 24mmHg (whichever is lower) |
| Comparator | • Observation only |
| Outcomes | • Developing glaucomatous damage |
| Results | • The treated group of patients showed an IOP reduction of 22.5% versus 4% in the control group<br>• At 60 months, patients in the observation group had a greater cumulative probability of manifesting primary open-angle glaucoma than treated patients: 9% in the control group and 4.4% of treated eyes developed POAG.<br>• Rate of progression from OHT to glaucoma at 5 years was reduced in the treatment group compared with the observation group<br>• Thus 90% of untreated patients did not convert to POAG<br>• Baseline factors that predicted the onset of POAG: older age, larger vertical and horizontal cup/disc ratio, higher IOP, thin cornea, optic disc haemorrhage |
| Discussion | • Treatment of eyes with ocular hypertension reduces the risk of a conversion to primary open-angle glaucoma<br>• However, the overall risk of developing POAG is low for eyes with ocular hypertension |

**Table 19: EMGT - Early Manifest Glaucoma Trial**

| **EMGT** | **Early Manifest Glaucoma Trial (2002)** [22] |
|---|---|
| Research question | Is it better to start IOP-lowering treatment immediately or to start with observing of patients with newly diagnosed open-angle glaucoma? |
| Population | • Enrolled 255 newly diagnosed (early) glaucoma patients from a population based survey between October 1992 and April 1997<br>• Exclusion criteria: Advanced visual field loss (MD ≤ 16dB or threat to fixation), mean IOP > 30mmHg (or any IOP > 35mmHg in at least one eye), visual acuity < 0.5 in either eye, |
| Study design | • Randomised controlled trial |
| Intervention | • Standard protocol of argon laser trabeculoplasty and betaxolol (current practice at that time in Sweden) for 129 patients |
| Comparator | • Observation only of 126 patients |
| Outcomes | • EMGT Progression<br>  ○ Increase of visual field loss in three consecutive C30-2 Humphrey tests (vfs performed every 3 months)<br>  ○ Optic disc changes (flicker chronoscopy and side-by-side comparison of fundus photographs done by masked, independent evaluators) |
| Results | • The standardised treatment achieved a mean IOP reduction of 25%, which was associated with a 45% rate of progression over 5 years as compared with a 62% rate of progression in patients who were observed only<br>• Each 1 mm Hg increase in posttreatment IOP conferred a 12% to 13% increase in the risk of progression (HR, 1.12–1.13 per mm Hg higher).<br>• Ocular hypertensive patients (IOP 24–31 mm Hg) with pseudoexfoliation were more likely than age-, sex-, and IOP-matched patients without pseudoexfoliation to develop glaucoma (55% vs 28% at a mean of 8.7 years).<br>• Risk factors for progression were higher IOP, exfoliative syndrome, more baseline damage, higher age, disc haemorrhages, thinner CCT in high tension glaucoma, and low blood pressure in normal tension glaucoma |
| Limitations | • Not double-masked, not placebo controlled<br>• Quality of life measure was not part of the initial protocol |
| Discussion | • First RCT to compare treatment vs no treatment of early glaucoma |

**Table 20: CNTGS - Collaborative Normal Tension Glaucoma Study**

| CNTGS | Collaborative Normal-Tension Glaucoma Study (1998) |
|---|---|
| Research question | Is a reduction of IOP relevant for normal-tension glaucoma? |
| Population | • Enrolled 230 patients with normal-tension glaucoma randomized to receive no therapy or IOP lowering by 30%<br>• To be eligible for randomization, the normal-tension glaucoma eyes had to show documented progression of field defects or a new disk haemorrhage or had to have field defects that threatened fixation when first presented for the study. [169] |
| Study design | • Randomized controlled trial |
| Intervention | • Target IOP lowering of 30% for 140 randomly assigned to restricted medical (61 eyes) or surgical (79 eyes) treatment |
| Comparator | • No treatment |
| Analysis | • Survival analysis compared time to progression of all randomly assigned patients during the course of follow-up from the initial baseline at randomization. In a separate analysis, data of patients developing cataracts were censored at the time that cataract produced 2 lines of Snellen visual acuity loss. |
| Outcomes | • Primary outcome: change from a three-field field baseline in five of six follow-up visual fields |
| Results | • 12% of eyes progressed in the treatment group, compared with 35% of the control group<br>• Time to progression was significantly longer in the treatment group<br>• Despite 30% IOP lowering, some treated eyes showed progression and not all untreated eyes progressed (65% of untreated eyes showed no further progression at five years) |
| Discussion | • The CNTGS found that IOP plays a significant role in the pathogenesis of normal-tension glaucoma and supports the aggressive lowering of IOP in patients at risk for progression.<br>• However, 65% of untreated eyes showed no further progression at five years which suggests that treatment should have minimal side effects, so it does not cause harm or reduce quality of life |

The concept of establishing a target pressure helps summarize the complexities of glaucoma care in a single numerical value which can be explained easily to the patient and helps the clinician to manage glaucoma. But it is a dynamic target, not a rigid number and it must be continuously adapted to the rate of progression, quality of life and livelihood of the patient with glaucoma.

### 1.8.3 Health economics perspective

The cost of glaucoma to the health care provider and to society depends on the treatment cost and the consequences of the disease, e.g. visual impairment or blindness. Blindness and low vision from glaucoma reduces the ability of an affected individual to work and contribute to society. The social and economic burden of glaucoma might have a different magnitude in high-income societies compared to low-income settings due to a higher life expectancy, higher production and human resources costs and a higher per capita gross domestic product. At the same time lower mortality rates and higher per capita gross domestic product might increase the relative cost-effectiveness of treatment interventions.[170]

Health economic evaluation can be defined as a comparison between alternative options in terms of costs and consequences and can be broadly divided into four categories.[171] By alternative options we mean the range of interventions or programmes in which health care ressources can be applied to increase population health or wellbeing. Costs refer to the value of resources used to produce a good service. Costs may be incurred by many entities including governments, healthcare providers or patients. Consequences refers to all the effects (positive or negative) interventions or programmes other than those on resource, including individuals' health.

1. **Cost analyses** assess the costs of the intervention in monetary terms, either to describe the cost of a program (cost-consequences) or to compare the cost of programs that achieve the same effectiveness (cost-minimization). The type of intervention that can be evaluated with this method is rather limited and might only be justifiable in situations where two treatments are based on near-identical technology. The effectiveness of the intervention is not considered in this. Therefore, they are considered partial economic evaluation studies.

The following three types of health economic evaluations also take into account the consequences or outcomes of the intervention. The analyses consider the relative consequences of the alternatives and compare them with relative cost.

2. If the effectiveness is measured in natural units such as life-years gained, disability days, or adverse events or cases of infection avoided, then such studies are described as a **cost-effectiveness analysis**. So outcomes are one-dimensional measures common to both alternatives that may differ in different magnitudes. Cost effectiveness analysis has been applied to many different types of health interventions. They are useful in comparing options within a certain disease area since it uses disease specific measures.

3. Studies that look at benefit as measured by the number of life-years saved adjusted to account for the loss of quality from morbidity or side effects from the intervention are **cost-utility analysis**. So here outcomes are multi-dimensional measures (e.g. QALYs, DALYs). Multi-dimensional measures combine measures of both quantity and quality of life. The most common measures in cost-utility analysis are the quality-adjusted life-years (QALYs) and the disability adjusted life years (DALYs). A cost-utility analysis can be used to compare interventions across different diseases including diseases that may have very different profiles in terms of morbidity and mortality, e.g. to compare acute versus chronic illnesses.

4. Finally, if the effectiveness of the intervention is measured in terms of the monetary costs saved or added, then the study is labelled a **cost-benefit analysis**. This measures both the cost and outcomes in monetary terms. This means that options can be both compared within the health sector and across other sectors. The outcome is not a health specific measure. However, it is often difficult to value health in monetary terms so the analysis can be challenging.

# 2 Rationale and objectives

*The research team explained the details and rationale of the trial before enrolment and during the course of the study.*

## 2.1 Problem statement

Resource constraints frequently mean that regular adherence to glaucoma eye drops can be erratic or unaffordable. Sometimes patients assume a single course of treatment is sufficient. Many eye units only have limited treatment options and untreated glaucoma invariably progresses in the long-term, leading to the suggestion that primary treatment for glaucoma should be a surgical intervention in Africa.[117]

However, patients are often reluctant to accept glaucoma surgery because they are asymptomatic and it does not have the prospect of improving sight. They may also have met people who have had an unsatisfactory visual outcome.

Many people known to have glaucoma in SSA probably go inadequately treated for much of the time.[20] In the Kilimanjaro Region most glaucoma patients made numerous visits to eye care facilities before they went blind from glaucoma.[172] Therefore, in view of these particular challenges in SSA, alternative treatment approaches are needed that provide an effective once-off intervention, which is affordable and sustainable. One such possibility may be SLT-laser treatment.

## 2.2 Rationale

There is a reasonable body of evidence indicating that a single outpatient treatment with SLT to reduce intraocular pressure (IOP) could provide long-term control, replacing eye drops without surgical risks. Several trials in Europe and the USA have compared laser trabeculoplasty to topical treatment[8,71,79,84] These have shown comparable or even slightly better results in the groups treated with laser. In a non-randomised study in an Afro-Caribbean population, SLT gave comparable results to topical treatment.[88] A one-off laser treatment with several years of effectiveness is also less dependent on adherence when compared with daily topical treatment. However, prior to our trial there was no evidence available from a randomised controlled trial comparing standard treatment with SLT in Africa (Table 9, page 35).

## 2.3 Hypotheses

The trial tested the hypotheses that (1) SLT is superior to timolol for reducing IOP of patients with glaucoma, and (2) that the SLT treatment is comparable with respect to the safety profile, acceptance among patients, preservation of visual acuity, change in vision-related quality of life, and cost after one year.

## 2.4 Research objectives

### 2.4.1 Primary objective

To evaluate, in a randomized controlled trial, whether SLT is superior to topical timolol for the treatment of glaucoma in a Tanzanian population.

### 2.4.2 Secondary objectives

1. To describe baseline characteristics of Tanzanian patients presenting with glaucoma and ocular hypertension including parameters such as IOP, visual acuity, visual field, corneal thickness and quality of life among others.

2. To compare the success rate, acceptance, vision related quality of life, preservation of central visual acuity, number of complications and cost of the two intervention arms after one year.

3. To investigate the reliability of clinical structural assessment of the optic disc in differentiating the stages of functional vision loss

4. To investigate the size and determinants of the intraocular pressure responses following primary and repeat SLT treatment.

# 3 Research setting and study overview

*Many trial participants lived on the slopes of Kibo (left) and Mawenzi (right), the two main peaks of Kilimanjaro. KCMC Eye Department in the foreground.*

## 3.1 Overview

The study enrolled participants mainly from Kilimanjaro Region and Arusha Region, although we also included people from other parts of Tanzania. The study was conducted at the Eye Department of Kilimanjaro Christian Medical Centre (KCMC) (chapter 3.2). Consecutive glaucoma patients self-referred or being referred to KCMC Eye Department were screened for eligibility following the inclusion and exclusion criteria (see chapter 5, page 87) and informed about the study in English or Swahili (appendix, chapter 10.14, page 178 and chapter 10.15, page 185). If the patients were interested to participate, they were invited for a baseline examination on a separate day, any questions related to the study were discussed and participants asked for informed consent. Randomisation and allocated treatment were done or started on the same day. Participants were invited for regular scheduled follow-up visits during the year following enrolment. Examination visits were organised using flow charts which also documented the treatment decisions to ensure a systematic implementation of the study protocol (see chapter 10.9, page 171).

The patient steering group included three members of the community in Kilimanjaro Region in Tanzania including glaucoma patients and was involved in the planning phase of the trial. The group reviewed the questionnaires during the piloting of the research tools and provided feedback to the overall design of the study from a patient and lay perspective.[173,174] Afterwards the group followed the conduct of the trial and provided further feedback.

A trial steering committee provided overall supervision and expert advice in trial related questions before and during the study. An independent Data Safety and Monitoring Board (DSMB) assessed the safety and efficacy of the selective laser trabeculoplasty as well as timolol treatment and monitored the overall conduct of the trial. They also reviewed the analysis plan.[175]

Ethical clearance of the randomised controlled trial was granted by the research ethics review committees of the National Institute for Medical Research (NIMR) in Dar es Salaam, Tanzania (NIMR/HQ/R.8a/Vol.IX/1929), the Kilimanjaro Christian Medical University College in Moshi, Tanzania (No. 800) and the London School of Hygiene & Tropical Medicine, UK (LSHTM Ethics Ref 7166). A patient steering committee.

See also chapter 5, page 87 for more details on the trial methods.

## 3.2 Eye Department at Kilimanjaro Christian Medical Centre

### 3.2.1 Clinical services

Kilimanjaro Christian Medical Centre is a comprehensive teaching hospital in Moshi in Northern Tanzania which was established in 1972. The eye department cares for patients from Northern Tanzania with a total catchment area of around 8 Million people. The department premises host a diagnostic centre including visual field testing machine, fundus photography including fluorescein angiography, optical coherence tomography, biometry and corneal topography. Services also include subspecialties in medical and surgical retina, paediatric ophthalmology, cornea, oculoplastics and glaucoma. Optical services with provision of spectacles are available on site.

The services also include two types of outreach activities in remote areas: day screening outreaches and weeklong surgical outreaches. About 30,000 patients are examined per year (Figure 11) and around 3000 patients receive surgery annually (Figure 12).

***Figure 11: Outpatient department of KCMC Eye Department***

*Waiting area for patients in the outpatient department of the KCMC Eye Department.*

### 3.2.2 Training

KCMC Eye Department offers training for several cadres of eye care personnel also in collaboration with Kilimanjaro Christian Medical University College. Undergraduate teaching for medical students includes rotations through clinic, ward and theatre as well as lectures on key aspects of ophthalmology. Postgraduate training in ophthalmology is a 4-year residency programme including training in phacoemulsification and glaucoma surgery. The 4-year programme includes the development of a research proposal, conducting the study, analysing results and writing of a dissertation. Residents are trained from many countries across Africa to work as Ophthalmologists in the future. The department further offers subspecialty training in paediatric ophthalmology and retina surgery and hosts students from the schools of optometry and ophthalmic nursing for their clinical rotations.

***Figure 12: Operating theatre of KCMC Eye Department***

*One of the operating theatres of KCMC Eye Department with several tables which is mainly used for cataract surgeries on adult patients. The setup also allows supervision and training of MMed residents.*

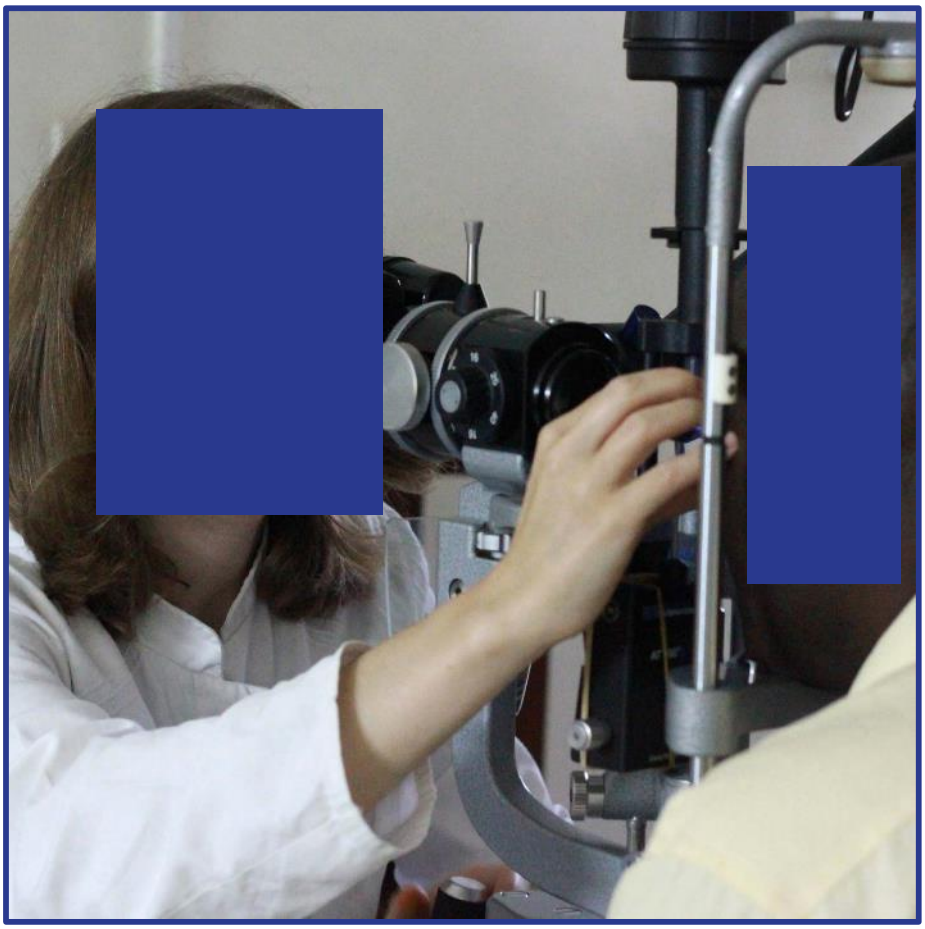
### 3.2.3 Research

The KCMC Eye Department hosts several research programmes, also to provide a framework for residents in the ophthalmology training programme and their research project in year three of the 4-year residency programme. Examples are the Kilimanjaro Diabetic Programme (KDP) which offers screening services to patients but also scientifically evaluates and improves screening methods to reduce blindness from diabetic retinopathy.[176–180] The Childhood Blindness prevention programme is covering different aspects of paediatric cataract services and their scientific evaluation.[181–183] The programme to prevent blindness from corneal diseases and trachoma does also extensive field work in addition to clinical studies.[184–186] The randomised controlled trial which is the core of this PhD thesis is part of the Kilimanjaro Glaucoma Intervention Programme (KiGIP). It was set up to harmonize and coordinate several research projects in line with a more comprehensive strategy to reduce blindness and vision impairment from glaucoma (Figure 14, page 143).[17,183,187,188] Many projects embedded in these research programmes and the related research capacity strengthening work are run through a close and longstanding collaboration with the International Centre for Eye Health (ICEH) at the London School of Hygiene & Tropical Medicine (Figure 13).

***Figure 13: KiGIP SLT trial team meeting at KCMC Eye Department***

*Some of members of the KiGIP SLT trial steering committee discussing ideas and experiences.*

# 4 Differentiating stages of functional vision loss from glaucoma using the Disc Damage Likelihood Scale and cup/disc ratio



*Examining the optic nerve head with indirect fundoscopy*

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| | |
|---|---|
| **Student** | Heiko Philippin |
| **Principal Supervisor** | Matthew Burton |
| **Thesis Title** | Selective laser trabeculoplasty versus 0.5% timolol eye drops for the treatment of glaucoma in Tanzania: a randomised controlled trial |

***If the Research Paper has previously been published please complete Section B, if not please move to Section C***

## SECTION B – Paper already published

Where was the work published?

When was the work published?

If the work was published prior to registration for your research degree, give a brief rationale for its inclusion

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## SECTION C – Prepared for publication, but not yet published

| | |
|---|---|
| Where is the work intended to be published? | British Journal of Ophthalmology |
| Please list the paper's authors in the intended authorship order: | H Philippin, E Matayan, KM Knoll, E Macha, S Mbishi, A Makupa, C Matsinhe, V Gama, M Monjane, AJ Ncheda, FA Mulobuana, E Muna, NF Guylene, G Gazzard, AP Marques, P Shah, D Macleod, WU Makupa, MJ Burton |
| Stage of publication | Submitted |

## SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

Literature research, trial design, data collection, data verification, statistical analysis, interpretation of results, writing first draft and review of manuscript.

**Student Signature:** [redacted] **Date:** April 15, 2022

**Supervisor Signature:** [redacted] **Date:** 23/04/2022

# Differentiating stages of functional vision loss from glaucoma using the Disc Damage Likelihood Scale and cup/disc ratio

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# Abstract

**Background**

Glaucoma staging is critical for treatment planning but has rarely been tested in severe/end-stage disease. We compared the performance of the Disc Damage Likelihood Scale (DDLS) and cup/disc ratio (CDR) using a functional glaucoma staging system (GSS) as the reference standard.

**Methods**

Post-hoc analysis of a randomised controlled trial at the Eye Department of Kilimanjaro Christian Medical Centre, Tanzania. Eligible participants (aged ≥18 years) with open-angle glaucoma, intraocular pressure (IOP) >21mmHg, were randomised to timolol 0.5% eye drops or selective laser trabeculoplasty. Fundoscopy established vertical and horizontal CDRs and DDLS. Visual acuity and static visual fields were graded (GSS). The study used area under the receiver-operating characteristics curves (AROCs) and Spearman's rank correlation coefficients to compare staging systems. Logistic regression with generalised estimating equations determined risk factors of functional severe/end-stage glaucoma.

**Results**

382 eyes (201 participants) were evaluated; 195 (51%) had severe or end-stage glaucoma; mean IOP was 26.7 (SD 6.9) mmHg. DDLS yielded an AROC of 0.90 (95% CI 0.87-0.93), vertical CDR 0.88 (95% CI 0.85-0.91), p=0.048, for identifying severe/end-stage disease. Correlation coefficients comparing GSS to DDLS and vertical CDRs were 0.73 and 0.71, respectively. Advanced structural stages, vision impairment, higher IOP, and less financial resources were risk factors of functional severe/end-stage glaucoma.

**Conclusion**

This study indicates that both structural staging systems can differentiate severe/end-stage glaucoma from less severe disease, with a moderate advantage of DDLS over CDR. Clinical examination of the optic disc plays an important role in addition to functional assessment when managing severe/end-stage glaucoma.

## Key Messages

**What is already known on this topic**

- Functional and structural descriptors of the optic nerve head damage can be used to distinguish between different stages of glaucoma, with most diagnostic studies focusing on earlier stages.
- We assessed eyes with predominantly later stages of glaucoma

**What this study adds**

- Disc Damage Likelihood Scale (DDLS) and cup/disc ratio are robust methods to discriminate late functional stages of glaucoma.

**How this study might affect research, practice or policy**

- These low-cost structural grading systems can support treatment planning for late stage glaucoma, which has a particularly negative impact on visual function and quality of life.

## Precis

Disc Damage Likelihood Scale (DDLS) and cup/disc ratio distinguished early/moderate/advanced from severe/end-stage glaucoma with DDLS achieving a significant larger area under the receiver-operating curve. Both techniques are important for planning the management of late-stage glaucoma.

## Keywords

advanced glaucoma; staging of glaucoma; Africa, cup/disc ratio, Disc Damage Likelihood Scale, DDLS, glaucoma, diagnostic test accuracy study, sensitivity, specificity, area under the ROC curve, AROC, AUC, structure-function-relationship

# Introduction

Glaucoma is the most common cause of irreversible blindness worldwide, leading to reduced quality of life and livelihood.[1] Sight loss from glaucoma is a result of damage to ocular nerve fibre tissue, mainly caused by increased intraocular pressure. Staging the damage is important for monitoring the progression of the disease and planning management accordingly. This typically includes appropriate reduction of intraocular pressure, along with other components of glaucoma care. Progression of this glaucomatous nerve fibre damage can be monitored with both functional and anatomical descriptors.

Functional glaucomatous damage is usually measured by static visual field examination (perimetry), with disease staging based on the extent and severity of field loss.[2] However, severe and end-stage glaucoma commonly affect the central visual acuity, so that static visual field testing cannot be reliably performed due to the eye's inability to fixate. Under these conditions, visual acuity can be used as an alternative means to describe advanced functional damage. Mills et al. proposed a glaucoma staging system (GSS) based on static visual field examinations, and added categories for severe and end-stage glaucoma, the latter applies if a static visual field test cannot be performed due to a central scotoma or the eye has a visual acuity ≤ 20/200.[3] This provides for categorisation of glaucomatous functional damage ranging from pre-diagnosis to end-stage disease.

Assessment of anatomical or structural damage due to glaucoma focuses mainly on the optic nerve head rim and cup, formed by optic nerve fibres.[4] The most commonly used grading system measures the cup/disc ratio (CDR), usually by slit-lamp indirect ophthalmoscopy. Armaly et al. described it in 1967 as the ratio of the vertical and horizontal diameters of the optic disc cup to the overall diameters of the disc.[5] Spaeth et al. later developed the Disc Damage Likelihood Scale (DDLS), which identifies the narrowest rim width in relation to the disc diameter (rim/disc ratio). If no rim is present anymore in a particular sector of the disc, the scale quantifies the circumferential extent of the rim loss.[6] This allows a structural grading ranging from a normal optic nerve head to a complete loss of the neuroretinal rim in the final stage of the disease.

Many glaucoma diagnostic studies have focused on distinguishing between normal eyes and early or moderate glaucoma typically with preserved central visual acuity, using perimetry as the main method for disease staging. More advanced glaucoma is often associated with a reduced visual acuity which has additional negative effects on mental health status, morbidity, mortality, and the cost of glaucoma management.[7] Each further stage of glaucoma can lead to relevant changes in quality of life.[8,9] Worldwide, advanced glaucoma is more prevalent in low-resource settings where expensive

equipment might be less available.[10–12] Our aim was to evaluate the low-cost structural DDLS and CDR grading systems for their ability to discriminate different functional stages of glaucoma in a study population with predominantly advanced disease.

# Methods

## Study design

This study was based on a post-hoc analysis of the Kilimanjaro Glaucoma Intervention Programme (KiGIP) SLT trial. This was a randomised, controlled, parallel group, single masked clinical trial which tested the hypothesis that selective laser trabeculoplasty (SLT) is superior to timolol eye drops for the treatment of open-angle glaucoma, the design and main results have been previously reported.[13]

The KiGIP SLT trial was approved by the research ethics review committees of the National Institute for Medical Research (NIMR/HQ/R.8a/Vol.IX/1929) in Dar es Salaam, Tanzania, the Kilimanjaro Christian Medical University College (No. 800) in Moshi, Tanzania and the London School of Hygiene & Tropical Medicine (LSHTM Ethics Ref 7166) in London, UK. It was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation–Good Clinical Practice. At the time of the baseline assessment written informed consent was obtained in Swahili before participants were enrolled. A patient reference group provided input on different aspects of the study design and conduct. The KiGIP SLT trial was registered with the Pan African Clinical Trials Registry (PACTR201508001235339).

## Participants

Participants who attended the eye clinic at Kilimanjaro Christian Medical Centre (KCMC), Moshi, Tanzania, were screened consecutively for eligibility between August 31, 2015, and May 12, 2017. Inclusion criteria for the trial were an intraocular pressure (IOP) > 21mmHg, structural changes of the optic nerve head (Disc Damage Likelihood Scale ≥ 5 or a vertical cup/disc ratio (vCDR) ≥ 0.7, or a vCDR asymmetry between two eyes ≥ 0.2), and functional changes (glaucomatous visual field defect, Mills glaucoma staging system ≥ 1).[3] Categories of high-risk glaucoma suspect (IOP > 25mmHg, structural changes as above, no visual field defect) or high-risk ocular hypertension (IOP > 32mmHg, no structural or functional defect) were also permitted. Exclusion criteria included participants being aged < 18 years or eyes with no perception of light. More details are described elsewhere.[13]

## Diagnostic methods

The visual function was assessed using the logarithm of the minimum angle of resolution (logMAR) visual acuity measured at 2m with the Peek Acuity Smartphone app (version 3.5.0, Peek Vision, London, UK) in a dimmed room.[14] Static visual field perimetry was performed using the Swedish interactive threshold algorithm standard 24-2 or 10-2 programmes (II-I series system software version 4.2, Humphrey HFA II 740i Visual Field Analyzer, Carl Zeiss Meditec AG, Jena, Germany).

Glaucoma-related structural features were assessed by slit-lamp examination of the anterior segment, pachymetry (central corneal thickness (CCT)), gonioscopy, fundus imaging and indirect fundoscopy (using a Digital 1.0X Volk slit lamp lens) of the optic nerve head, macula and peripheral retina. The lens and the slit-lamp calliper were used to measure the optic nerve head diameter. The investigator was masked to the visual field examination, which was performed by a different examiner. All examinations were done prior to randomisation and treatment allocation.

The structural glaucomatous damage of the optic nerve head was classified using the Disc Damage Likelihood Scale (DDLS), the vertical, and the horizontal CDR.[5,6] DDLS was determined by locating the thinnest neuroretinal rim and, if still present, calculating the rim/disc ratio or, if absent, estimating the circumferential extension of the absence of neuroretinal rim tissue in degrees. After measuring the disc diameter, the DDLS was established accordingly (see table 3). To determine the cup/disc ratios, the vertical and horizontal cup diameters were related to the respective disc diameters.

## Analysis

For the purpose of this post hoc analysis, all eyes enrolled in the trial were staged according to the mean deviation categories of Mills Glaucoma Staging System (GSS) including stage 5 (end-stage disease) if an eye was unable to perform a visual field examination attributable to central scotoma.[3] The functional GSS stages were used as the reference standard to compare with structural changes in advanced glaucoma.

The median GSS was used to subdivide eyes into two groups of glaucoma severity: (a) GSS 1-3 (early, moderate, and advanced glaucoma) and (b) GSS 4-5 (severe and end-stage glaucoma). The performance of CDRs and DDLS for discriminating between these two groups of functional damage were evaluated with receiver-operating characteristic (ROC) curves adjusted for inter-eye correlation. Curves were compared using the area under the ROC curve (AROC). ROC curve analyses were also used to identify the best threshold to achieve the highest combination of specificity and sensitivity.

The correlation between the GSS, DDLS, and the CDRs was assessed using Spearman's rank correlation coefficient. The arithmetic mean CDR was calculated from the vertical and horizontal cup/disc ratio measurements.

Logistic regression models were constructed to determine potential risk factors of severe/end-stage glaucoma with generalised estimating equations adjusting for the correlation between eyes.[15] The association between each potential risk factor and severe/end stage glaucoma was first estimated in a univariable (unadjusted) model before adjusting for confounding variables. Potential confounders were assessed through a change-in-estimate (CIE) approach[16] by adding covariates to the unadjusted model and retaining them if the odds ratio of the covariate of interest changed by around 10% or more. Multicollinearity was checked for by evaluating change of standard errors of the coefficient estimates.

## Results

201 participants (382 eyes) were enrolled into this study. Their mean age was 66.3 (SD 11.6) years and 83/201 (41%) were female (table 1). The visual field assessments of participants' eyes showed an average mean deviation (MD) of -17.2 (SD 11.1) dB for 347 eyes using the 24-2 Humphrey visual field test, and an average MD of -32.3 (SD 3.4) dB in 8 eyes using the 10-2 test. A visual field test was not possible for 27 eyes due to a low visual acuity (table 1).

Sub-dividing the GSS into two groups resulted in 187 eyes (49.0%) with early/moderate/advanced glaucoma and 195 eyes (51.0%) with severe/end-stage glaucoma. Predicting this dichotomous variable using DDLS yielded an area under the receiver-operating characteristic (ROC) curve of 0.90 (95% CI 0.87-0.93), Figure 1. Using a cut-off point of DDLS 8 and above, 83.5% of eyes were correctly classified resulting in a sensitivity of 90.3% and specificity of 76.5%. For the vertical CDR, the area under the ROC curve was 0.88 (95% CI 0.85-0.91). Using a cut-off point of 0.9 and above, 83.0% of eyes were correctly classified with a sensitivity of 88.7% and a specificity of 77.0%. The difference in the two areas under the curve of DDLS and vertical CDR was statistically significant (p=0.048), Figure 1. When combining the vertical and horizontal CDR by calculating the mean CDR, the area under the ROC curve was 0.89 (95% CI 0.86-0.93), sensitivity and specificity were 85.5% and 80.8% respectively. Spearman's rank correlation values comparing GSS with DDLS was 0.73 and with vertical CDR 0.71.

Risk factors associated with severe/end-stage glaucoma with $p<0.05$ in univariable analyses were a lower level of education, less financial resources, presence of exfoliation glaucoma, lower central

corneal thickness, higher intraocular pressure at baseline, presence of vision impairment and advanced structural stage of glaucoma (DDLS and vCDR). The adjusted analyses showed an association ($p<0.05$) between severe/end-stage glaucoma and financial resources ≤2US$/day, intraocular pressure ≥25mmHg, the presence of vision impairment (VA <6/12), and advanced structural stage of glaucoma (DDLS ≥ 8, vCDR ≥ 0.9), see also table 2 and table 3.

Two functional descriptors of glaucomatous damage, static visual field examination (continuous mean deviation) and visual acuity (logMAR) compared to two structural descriptors DDLS and vertical cup/disc ratio are shown in Figure 2. The mean deviation drops rapidly starting from DDLS 8 and vertical CDR 0.9 (vCDR). Visual acuity initially increases slowly but shows a steep increase towards DDLS 10 and vCDR 1.

**Table 1: Patient and ocular characteristics.**

| **Patient characteristics (number of patients)** | | **Total N=201** | |
|---|---|---|---|
| Sex | Female | 83 | (41.3%) |
| | Male | 118 | (58.7%) |
| Age, years (mean, SD) | | 66.3 | (11.6) |
| Education | < Secondary level | 133 | (66.2%) |
| | ≥ Secondary level | 68 | (33.8%) |
| Ethnic group | Chagga | 111 | (55.2%) |
| | Pare | 41 | (20.4%) |
| | Meru | 8 | (4.0%) |
| | Maasai | 5 | (2.5%) |
| | Sambaa | 5 | (2.5%) |
| | Other | 31 | (15.4%) |
| Financial resources | ≤ 2 US$/day | 76 | (38.2%) |
| | > 2 US$/day | 123 | (61.8%) |
| Travel distance | < 50 km | 105 | (52.2%) |
| | ≥ 50 km | 96 | (47.8%) |
| Family history of glaucoma* | No | 153 | (76.1%) |
| | Yes | 48 | (23.9%) |
| **Ocular characteristics (number of eyes)** | | **Total N=382** | |
| Prior topical glaucoma treatment | No | 157 | (41.1%) |
| | Yes | 225 | (58.9%) |
| Prior timolol treatment | No | 174 | (45.5%) |
| | Yes | 208 | (54.5%) |
| Pseudophakia | No | 362 | (94.8%) |
| | Yes | 20 | (5.2%) |
| Exfoliation glaucoma | No | 333 | (87.2%) |
| | Yes | 49 | (12.8%) |
| Central corneal thickness, µm (mean, SD)** | | 521.0 | (34.7) |
| Angle pigmentation, Spaeth | light pigmentation (0-2) | 320 | (83.8%) |
| | strong pigmentation (3-4) | 62 | (16.2%) |
| Intraocular pressure, mmHg (mean, SD) | | 26.7 | (6.9) |
| Visual acuity, | No vision impairment (VA ≥ 6/12) | 244 | (63.9%) |
| Snellen, WHO categories, ICD-11 | Mild vision impairment (6/18 ≤ VA < 6/12) | 48 | (12.6%) |
| | Moderate vision impairment (6/60 ≤ VA < 6/18) | 40 | (10.5%) |
| | Severe vision impairment (3/60 ≤ VA < 6/60) | 3 | (0.8%) |
| | Blindness (1/60 ≤ VA < 3/60) | 2 | (0.5%) |
| | Blindness (PL ≤ VA < 1/60) | 44 | (11.5%) |
| | Blindness (NPL) | 1 | (0.3%) |
| Functional stage of glaucoma (GSS) | Early | 88 | (23.0%) |
| | Moderate | 55 | (14.4%) |
| | Advanced | 44 | (11.5%) |
| | Severe | 168 | (44.0%) |
| | End-stage | 27 | (7.1%) |
| Disc Damage Likelihood Scale | 5 | 76 | (19.9%) |
| | 6 | 42 | (11.0%) |
| | 7 | 44 | (11.5%) |
| | 8 | 87 | (22.8%) |
| | 9 | 66 | (17.3%) |
| | 10 | 67 | (17.5%) |
| Disc Damage Likelihood Scale (mean, SD) | | 8.0 | (1.8) |
| Visual field, 24-2, mean deviation, dB *** | | -17.2 | (11.1) |
| Visual field, 10-2, mean deviation, dB **** | | -32.3 | (3.4) |

Data of 382 eyes at entry into the KiGIP SLT trial are mean (SD) or n (%). *In a first-degree relative. **Central corneal thickness measurements missing in 13 eyes due to temporary failure of the pachymeter. ***24-2 visual field results of 347 eyes.

****10-2 visual field results of 8 eyes. No visual field possible in 27 eyes due to reduced central vision. SD=standard deviation GSS=glaucoma staging system

**Table 2: Predicted odds ratios for functional severe/end-stage glaucoma at entry into the KiGIP SLT trial.**

| Variable | severe and end-stage glaucoma | unadjusted analyses | | adjusted analyses | |
|---|---|---|---|---|---|
| | n/N (%) | OR (95% CI) | p value | OR (95% CI) | p value |
| **Sex** | | | | | |
| Female | 77/159 (48%) | 1 (ref) | | 1 (ref) | |
| Male | 118/223 (53%) | 1.18 (0.74-1.88) | 0.49 | 0.96 (0.54-1.72) | 0.90 |
| **Age groups, years** | | | | | |
| < 70 | 118/233 (51%) | 1 (ref) | | 1 (ref) | |
| ≥ 70 | 77/149 (52%) | 1.04 (0.65-1.67) | 0.87 | 1.04 (0.65-1.67) | 0.87 |
| **Education** | | | | | |
| < Secondary level | 139/251 (55%) | 1 (ref) | | 1 (ref) | |
| ≥ Secondary level | 56/131 (43%) | 0.60 (0.37-0.98) | 0.043 | 0.85 (0.43-1.67) | 0.64 |
| **Ethnic group** | | | | | |
| Chagga | 99/209 (47%) | 1 (ref) | | 1 (ref) | |
| Pare | 39/81 (48%) | 1.03 (0.57-1.85) | | 0.73 (0.34-1.59) | |
| Meru | 12/15 (80%) | 4.59 (1.05-20.19) | | 2.63 (0.43-16.26) | |
| Maasai | 5/9 (56%) | 1.49 (0.33-6.80) | | 1.09 (0.09-13.62) | |
| Sambaa | 6/10 (60%) | 1.68 (0.38-7.40) | | 2.50 (0.34-18.44) | |
| Other | 34/58 (59%) | 1.57 (0.81-3.07) | 0.31* | 1.18 (0.47-2.96) | 0.70* |
| **Financial resources, US$/day** | | | | | |
| ≤ 2 | 91/143 (64%) | 1 (ref) | | 1 (ref) | |
| > 2 | 104/239 (44%) | 0.44 (0.27-0.72) | 0.00085 | 0.47 (0.24-0.95) | 0.036 |
| **Travel distance, km** | | | | | |
| < 50 | 100/201 (50%) | 1 (ref) | | 1 (ref) | |
| ≥ 50 | 95/181 (52%) | 1.13 (0.71-1.79) | 0.61 | 0.68 (0.35-1.33) | 0.26 |
| **Family history of glaucoma**** | | | | | |
| No | 148/290 (51%) | 1 (ref) | | 1 (ref) | |
| Yes | 47/92 (51%) | 1.01 (0.59-1.72) | 0.98 | 1.55 (0.77-3.12) | 0.22 |
| **Prior timolol treatment** | | | | | |
| No | 90/174 (52%) | 1 (ref) | | 1 (ref) | |
| Yes | 105/208 (50%) | 0.95 (0.60-1.51) | 0.84 | 1.15 (0.62-2.16) | 0.66 |
| **Pseudophakia** | | | | | |
| No | 187/362 (52%) | 1 (ref) | | 1 (ref) | |
| Yes | 8/20 (40%) | 0.79 (0.30-2.04) | 0.62 | 0.39 (0.10-1.55) | 0.18 |
| **Exfoliation glaucoma (XFG)** | | | | | |
| No | 165/333 (50%) | 1 (ref) | | 1 (ref) | |
| Yes | 30/49 (61%) | 2.05 (1.03-4.09) | 0.041 | 1.28 (0.47-3.45) | 0.63 |
| **Central corneal thickness, µm** | | | | | |
| < 520 | 106/181 (59%) | 1 (ref) | | 1 (ref) | |
| ≥ 520 | 80/188 (43%) | 0.53 (0.34-0.84) | 0.0064 | 0.70 (0.39-1.24) | 0.22 |
| **Angle pigmentation** | | | | | |
| Light pigmentation | 164/320 (51%) | 1 (ref) | | 1 (ref) | |
| Strong pigmentation | 31/62 (50%) | 0.90 (0.49-1.66) | 0.74 | 1.61 (0.67-3.89) | 0.29 |
| **Intraocular pressure, mmHg** | | | | | |
| < 25 | 57/175 (33%) | 1 (ref) | | 1 (ref) | |
| ≥ 25 | 138/207 (67%) | 4.07 (2.59-6.41) | < 0.0001 | 2.77 (1.54-4.97) | 0.001 |
| **Vision impairment, VA<6/12** | | | | | |
| No | 88/244 (36%) | 1 (ref) | | 1 (ref) | |
| Yes | 107/138 (78%) | 5.82 (3.68-9.22) | < 0.0001 | 3.54 (1.89-6.64) | < 0.001 |
| **Stage of glaucoma, DDLS** | | | | | |
| Moderate (stage 5-7) | 19/162 (12%) | 1 (ref) | | 1 (ref) | |
| Advanced (stage 8-10) | 176/220 (80%) | 29.20 (16.19-52.64) | < 0.0001 | 18.11 (9.59-34.20) | < 0.001 |
| **Stage of glaucoma, vertical CDR** | | | | | |
| Moderate (< 0.9) | 22/166 (13%) | 1 (ref) | | 1 (ref) | |
| Advanced (≥ 0.9) | 173/216 (80%) | 26.06 (14.67-46.30) | < 0.0001 | 17.70 (9.40-33.34) | < 0.001 |

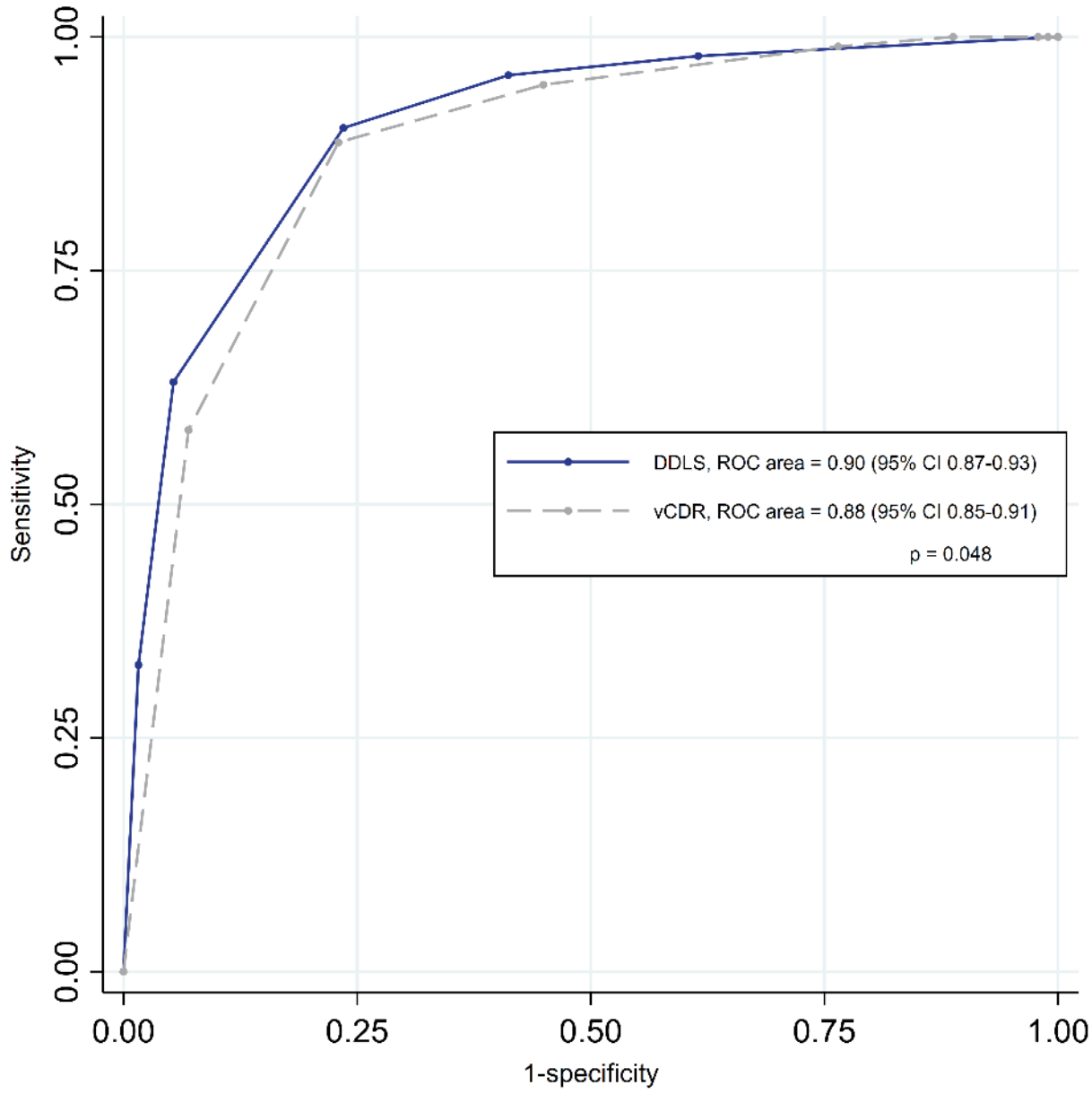
Results of 382 eyes analysed at entry into the KiGIP SLT trial using unadjusted and adjusted logistic regression models with general estimating equations of potential factors associated with functional severity of glaucoma. OR=odds ratio. DDLS=Disc Damage Likelihood Scale. * Wald test for trend. **In a first-degree relative.

**Table 3: Disc Damage Likelihood Scale (DDLS)**

| Glaucoma grade | DDLS Stage | Definition | Anatomical descriptor |
|---|---|---|---|
| At risk | 1 | 0.4 ≤ RDr | Narrowest rim width [rim/disc ratio (RDr)] |
| | 2 | 0.3 ≤ RDr < 0.4 | |
| | 3 | 0.2 ≤ RDr < 0.3 | |
| | 4 | 0.1 ≤ RDr < 0.2 | |
| Glaucoma damage | 5 | RDr < 0.1 | |
| | 6 | 1° ≤ extension < 45°) | Extent of rim absence [extension (°)] |
| | 7 | 45° ≤ extension < 90° | |
| Glaucoma disability | 8 | 90° ≤ extension < 180° | |
| | 9 | 180° ≤ extension < 270° | |
| | 10 | 270° ≤ extension | |

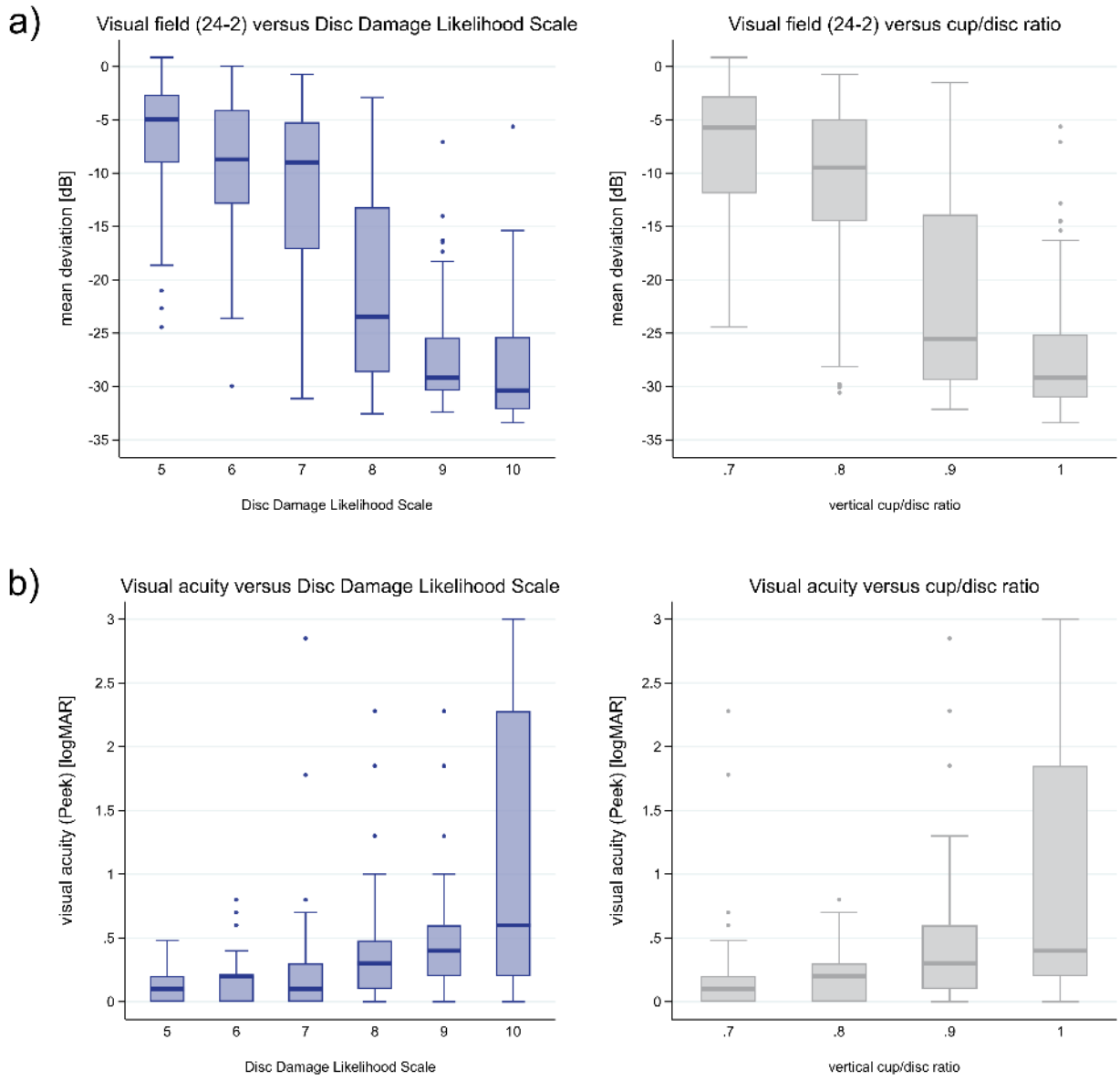
The Disk Damage Likelihood Scale (DDLS) is based on the narrowest radial neuroretinal rim width. As the rim width also depends on the disc size, the DDLS should be increased by one for small discs (< 1.50mm) and decreased by one for large discs (> 2.00mm). Adapted from Spaeth GL et al.[6]

**Figure 1: Receiver operating characteristic (ROC) curves**




Receiver operating characteristic (ROC) curves of Disc Damage Likelihood Scale (DDLS, solid line) and vertical cup/disc ratio (vCDR, dashed line) and the binary classifier of functional glaucoma stages: early/moderate/advanced versus severe/end-stage. CI = confidence interval.

***Figure 2: Boxplots***




Comparison of the Disc Damage Likelihood Scale and vertical cup/disc ratio with (a) visual field mean deviation, (b) visual acuity (logMAR). Boxes show median, upper, and lower quartiles. Whiskers represent scores outside the middle 50%. Outliers are presented as individual dots.

## Discussion

This study found that the two structural optic disc staging systems, Armaly's CDR[5] and Spaeth's DDLS[6], were both able to discriminate between functionally mild/moderate/advanced glaucoma and severe/end-stage glaucoma. There was some evidence (p=0.048) of a larger area under the ROC curve for DDLS compared to the vCDR.

Prior studies of DDLS have reported mainly AROCs for the discrimination between normal and glaucomatous eyes for the purpose of glaucoma detection. Danesh-Meyer et al. compared people without glaucoma and patients with glaucoma, defined by a combination of glaucomatous optic disc and visual field changes and IOP. Clinical examination using DDLS had the highest area under the ROC curve for identifying glaucoma from suspect or normal (AROC=0.91) followed by cup/disc ratio (AROC=0.81), MD of visual field (VF) examination (AROC=0.78), Hodapp-Parrish-Anderson VF score (AROC=0.75), and HRT-II rim area (AROC=0.62).[17] Kara-José et al. reported similar findings but with no significant differences between DDLS and CDR.[18] Our results showed comparable AROCs which is noteworthy because optic disc changes are more pronounced in early glaucoma than in severe or end-stage disease compared to functional tests.[7,19] The ocular hypertension treatment study showed that the earliest signs of progression from ocular hypertension to glaucoma are more likely detected by structural changes of the optic disc than by functional visual field changes.[20] The results from this study suggest that DDLS and, to a lesser extent, vertical CDR can provide a staging of the glaucomatous optic disc damage up to end-stage glaucoma, including stages where automated perimetry is no longer possible. Then the optic disc grading may be supplemented by visual acuity measurements. The visual acuity categories "hand movement" and "counting fingers" are separated by three 0.1 logMAR units or "lines" at 30 cm confirming the clinical impression that the difference is relevant for a person with severe or end-stage glaucoma even beyond the possibility of using a static visual field device.[9]

AROCs of cup/disc ratios increased slightly in our study when using the mean of vertical and horizontal CDRs. A possible explanation for this might be that early glaucomatous changes of the neuroretinal rim thickness start in the infero- and supero-temporal parts of the cup[21], predominantly captured by the vertical CDR. Temporal and lastly nasal neuroretinal rim areas are affected as the glaucomatous damage progresses to more advanced stages, increasingly captured by the horizontal CDR as well.[22] This typical course of thinning of the different sectors of the optic disc rim is also reflected in the two anatomical descriptors of the DDLS (narrowest rim thickness (DDLS 1-5) and extension of rim absence

(DDLS 6-10), table 3). DDLS therefore also allows finer grading of advanced glaucoma stages compared to CDR (Figure 2) which is only based on changes of the cup diameter.

Rim/disc ratio also performed better than cup/disc ratio in fully automated fundus image processing to categorize optic discs when comparing them to expert clinician annotations.[23] DDLS has been shown to be more accurate and repeatable than the CDR[24,25] and is also used in community screening and shared glaucoma care models.[26,27]

Apart from the anatomical descriptors DDLS and CDR, the current study found a higher IOP was a risk factor for severe and end-stage glaucoma, which has previously been reported by several other studies including from Africa.[28,29] Financial resources ≤ 2 US$/day of a patient were another risk factor for severe and end-stage glaucoma. Several studies report associations between advanced glaucoma and a low socioeconomic status.[30,31] This is also in line with a general link between poverty and an increased risk of vision impairment.[1,30,31]

Our study has several limitations. The data were acquired during a clinical trial by examiners who followed standard operating procedures but the data were not externally validated with image analysis. We were also not able to capture consistent optical coherence tomography (OCT) images: after a failure of the initially used time-domain OCT device, it had to be replaced by a spectral-domain OCT device, whose measurements were not interchangeable.[32] While OCT can be useful in assessing advanced glaucoma,[33] described limitations included artefacts, segmentation errors, and the OCT reference database may not be relevant for the particular patient.[34] A further limitation of the current study is that trial participants were randomised to treatments rather than glaucoma severity, which could bias the results of the post-hoc analysis. Furthermore, two exposures of interest and the outcome were involved in the inclusion criteria for the trial (cut-offs of DDLS ≥ 5 or CDR ≥ 0.8; GSS > 0). This could mean that the estimates of the strength and size of the association between each of these and the outcome could be different in a more general population which also includes all glaucoma patients.

In conclusion, DDLS and CDR are low-cost and feasible methods for describing and discriminating structural stages related to functionally mild/moderate/advanced glaucoma versus severe/end-stage glaucoma. The DDLS may be advantageous over the CDR due to the larger AROC, more categories to differentiate advanced glaucoma and a better fitting description of the course of glaucomatous optic disc damage. This study supports use of these grading systems also in advanced glaucoma. They can be implemented with affordable equipment without a need for complex technology. Both can play an important role in the assessment of advanced glaucoma damage and progression and help clinicians with treatment decisions to prevent further visual disability.

# Statements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## Competing interests

GG reports personal fees from Alcon, Allergan, Belkin, Equinox, Genentech–Roche, Glaukos, Ivantis, Reichert, Sight Sciences, and from Thea; grants from Belkin, Santen, and from Thea; and non-financial involvement with the patient advocacy group GlaucomaUK, outside the submitted work; he is also a co-investigator on three other major SLT trials (LIGHT, COAST, and Belkin laser). All other authors declare no competing interests.


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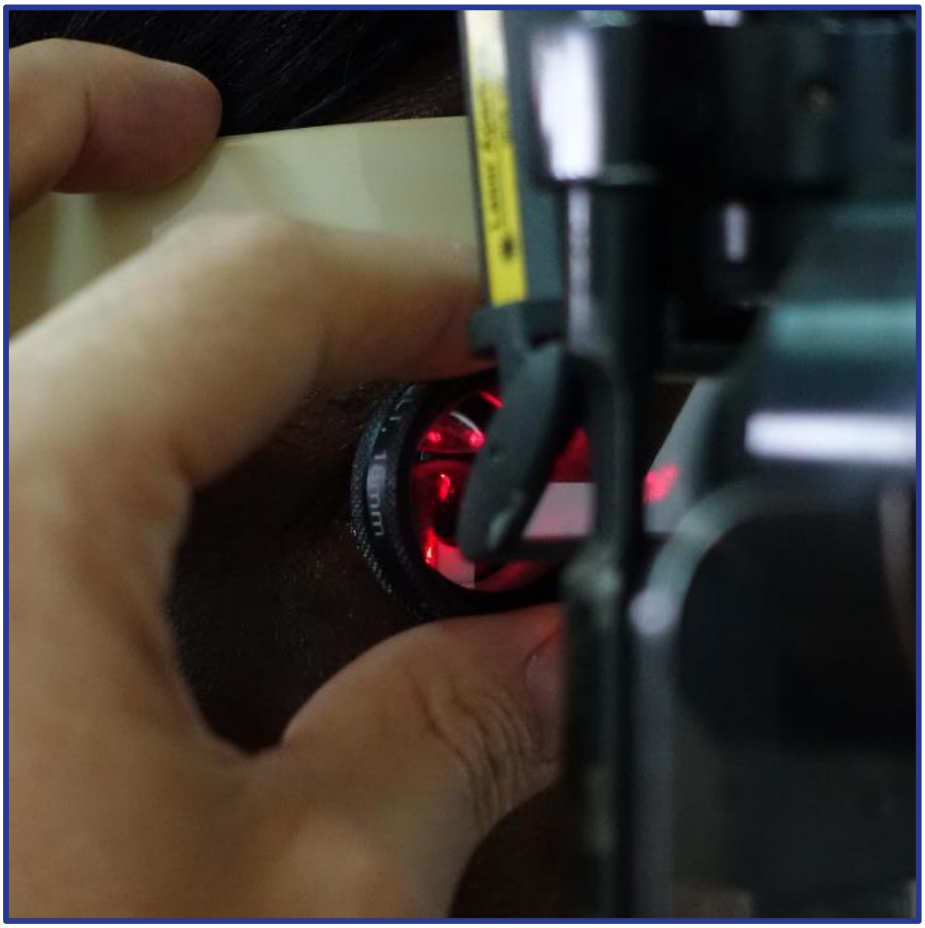
# 5 Selective laser trabeculoplasty versus 0.5% timolol eye drops for the treatment of glaucoma in Tanzania: a randomised controlled trial



*Goniolens with red aiming beam before starting the selective laser trabeculoplasty*

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| **Student** | Heiko Philippin |
| **Principal Supervisor** | Matthew Burton |
| **Thesis Title** | Selective laser trabeculoplasty versus 0.5% timolol eye drops for the treatment of glaucoma in Tanzania: a randomised controlled trial |

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# Selective laser trabeculoplasty versus 0·5% timolol eye drops for the treatment of glaucoma in Tanzania: a randomised controlled trial

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## Summary

**Background** Glaucoma is a major cause of sight loss worldwide, with the highest regional prevalence and incidence reported in Africa. The most common low-cost treatment used to control glaucoma is long-term timolol eye drops. However, low adherence is a major challenge. We aimed to investigate whether selective laser trabeculoplasty (SLT) was superior to timolol eye drops for controlling intraocular pressure (IOP) in patients with open-angle glaucoma.

**Methods** We did a two-arm, parallel-group, single-masked randomised controlled trial at the Eye Department of Kilimanjaro Christian Medical Centre, Moshi, Tanzania. Eligible participants (aged ≥18 years) had open-angle glaucoma and an IOP above 21 mm Hg, and did not have asthma or a history of glaucoma surgery or laser. Participants were randomly assigned (1:1) to receive 0·5% timolol eye drops to administer twice daily or to receive SLT. The primary outcome was the proportion of eyes from both groups with treatment success, defined as an IOP below or equal to target pressure according to glaucoma severity, at 12 months following randomisation. Re-explanation of eye drop application or a repeat SLT was permitted once. The primary analysis was by modified intention-to-treat, excluding participants lost to follow-up, using logistic regression; generalised estimating equations were used to adjust for the correlation between eyes. This trial was registered with the Pan African Clinical Trials Registry, number PACTR201508001235339.

**Findings** 840 patients were screened for eligibility, of whom 201 (24%) participants (382 eligible eyes) were enrolled between Aug 31, 2015, and May 12, 2017. 100 (50%) participants (191 eyes) were randomly assigned to the timolol group and 101 (50%; 191 eyes) to the SLT group. After 1 year, 339 (89%) of 382 eyes were analysed. Treatment was successful in 55 (31%) of 176 eyes in the timolol group (16 [29%] of 55 eyes required repeat administration counselling) and in 99 (61%) of 163 eyes in the SLT group (33 [33%] of 99 eyes required repeat SLT; odds ratio 3·37 [95% CI 1·96–5·80]; p<0·0001). Adverse events (mostly unrelated to ocular events) occurred in ten (10%) participants in the timolol group and in eight (8%) participants in the SLT group (p=0·61).

**Interpretation** SLT was superior to timolol eye drops for managing patients with open-angle high-pressure glaucoma for 1 year in Tanzania. SLT has the potential to transform the management of glaucoma in sub-Saharan Africa, even where the prevalence of advanced glaucoma is high.

**Funding** Christian Blind Mission, Seeing is Believing Innovation Fund, and the Wellcome Trust.



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For the Kiswahili translation of the abstract see Online for appendix 1

For the French translation of the abstract see Online for appendix 2

For the Portuguese translation of the abstract see Online for appendix 3

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## Introduction

Glaucoma is a group of diseases that affect the optic nerve and lead to a progressive and irreversible loss of vision. Early stages of glaucoma can be asymptomatic, or individuals might notice missing or blurred areas in their field of vision.[1] Late stages of the condition can lead to irreversible absolute blindness, particularly if left untreated. The main modifiable risk factor is elevated intraocular pressure (IOP); lifelong IOP control can halt disease progression.[2,3]

Globally, glaucomas are the most frequent cause of irreversible blindness.[4] Africa has the highest prevalence of glaucoma of all world regions, which is estimated to be 4·8%, as well as the highest incidence, with an expected increase from 10·31 million new cases in 2020 to 19·14 million in 2040 due to increasing life expectancy and population growth.[5] The prevalence of blindness due to glaucoma is higher in sub-Saharan Africa than in any other world region.[4] This situation is met by limited resources in many regions of sub-Saharan Africa; the mean number of ophthalmologists is 3·7 per million people in low-income countries versus 76·2 per million people in high-income countries.[6]

Reducing IOP by medical therapy with eye drops, surgery, or laser treatment is currently the only available treatment approach for delaying glaucoma progression. In sub-Saharan Africa, most people are either treated with the low-cost eye drops, timolol, or with surgery.[7,8] However, regular application of drops is often hampered by non-adherence, scarce availability, long-term costs,

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## Research in context

### Evidence before this study

Preventing irreversible blindness from glaucoma can be achieved by reducing intraocular pressure (IOP) with daily eye drops, eye surgery, and laser treatment. African populations have the highest prevalence and incidence of open-angle glaucoma and the highest prevalence of blindness due to glaucoma worldwide. The *Lancet Global Health* Commission on global eye health called for research into cost-effective glaucoma interventions, especially those that are applicable in low-income and middle-income countries. Timolol eye drops are the most affordable and most commonly available treatment among drugs to reduce IOP. However, erratic application, systemic and local side-effects, and high long-term costs led to a search for alternatives methods to reduce IOP, such as selective laser trabeculoplasty (SLT). We did several literature searches using MEDLINE (via PubMed), ISRCTN, and PACTR trial registries, without any language or date restrictions, between Oct 3, 2012, and March 16, 2015, for published or ongoing trials of SLT as an alternative to timolol. Applying the terms "selective laser trabeculoplasty" (or "SLT") and "timolol" showed no results. A wider search using "selective laser trabeculoplasty" (or "SLT") without "timolol" found five randomised controlled trials that compared SLT with more expensive eye drops in different settings and reported SLT to be a feasible and safe alternative to medical ocular treatment.

### Added value of this study

This trial was done in Tanzania and enrolled 201 patients with predominantly advanced glaucoma, reflecting the typical spectrum and associated challenges of glaucoma care in this region. By contrast, most patients in the previous trials involving SLT and more expensive eye drops had early or moderate glaucoma. Both eyes were enrolled if eligible and analysed using statistical methods that considered the correlation between the two eyes of a participant. This methodology efficiently used all available data, saving time and resources, and making optimal use of participants' engagement. 12 months after randomisation, the estimated odds for success using SLT were 3·37 times higher than those for success using 0·5% timolol eye drops. The odds ratio was not modified by other factors. Mean IOP reduction was 1·5 mm Hg (SD 7·5) in the timolol group and 6·3 mm Hg (6·4) in the SLT group between the baseline visit and visits at failure, success at 1 year, or before loss to follow-up. Safety, acceptance, vision-related quality of life, and preservation of visual acuity were similar in both groups after 1 year. Eye care units in the region would need to treat around 500 eyes per year with SLT to cover the cost of the procedure, which would cost an amount similar to a 1-year supply of timolol eye drops.

### Implications of all the available evidence

This trial adds to the existing evidence that SLT is an important addition to the treatment options for glaucoma, and extends this evidence to regions where advanced glaucoma is more common and treatment resources and options are limited. The prevalence of glaucoma is expected to increase in the coming decades due to increasing life expectancy and population growth, especially in low-income and middle-income regions. Therefore, SLT could help to prevent vision loss and blindness from glaucoma in regions where its prevalence is highest.

and side-effects. Trabeculectomy, the main surgical procedure for treating glaucoma, can effectively reduce IOP; however, the operation has a long learning curve, is offered in relatively few eye units across sub-Saharan Africa, can have clinically significant complications, and has a low uptake in some populations.[8–12] Selective laser trabeculoplasty (SLT) is a rapid outpatient procedure used to reduce IOP. SLT increases aqueous fluid outflow from the eye, which drains through the trabecular meshwork. There is increasing evidence supporting its use as a primary intervention.[13,14] Lasers, especially SLT, could be part of future treatment for glaucoma in sub-Saharan Africa.[15] However, to date, there have been no published trials of SLT in sub-Saharan Africa, and no trials worldwide have compared SLT with timolol as the standard treatment option.

We aimed to investigate whether SLT was superior to timolol eye drops for controlling IOP in patients with open-angle glaucoma in a Tanzanian setting.

## Methods

### Study design

We did a two-arm, parallel-group, single-masked randomised controlled trial at the Eye Department of Kilimanjaro Christian Medical Centre (KCMC), Moshi, northern Tanzania.

The trial was approved by the research ethics review committees of the National Institute for Medical Research in Dar es Salaam, Tanzania (NIMR/HQ/R.8a/Vol IX/1929), the Kilimanjaro Christian Medical University College in Moshi, Tanzania (number 800), and the London School of Hygiene & Tropical Medicine in London, UK (LSHTM Ethics Ref 7166). The trial was done in compliance with the Declaration of Helsinki and the International Conference on Harmonisation–Good Clinical Practice. An independent data and safety monitoring board was appointed by the trial steering committee. A patient steering group provided input on different aspects of the trial such as study design and questionnaires.

### Participants

Patients who attended the ophthalmology clinic at KCMC were screened for eligibility. The main inclusion criterion was diagnosis of chronic high-pressure open-angle glaucoma, defined as an IOP of more than 21 mm Hg and a combination of structural and functional changes (category 1 of the International Society of Geographic and

Epidemiologic Ophthalmology).[16] Structural changes were specified as thinning of the optic nerve head rim (stage 5 or above on the Disc Damage Likelihood Scale, a cup-to-disc ratio of ≥0·7, or a cup-to-disc ratio asymmetry between two eyes of ≥0·2).[17] Functional changes included a glaucomatous visual field defect or relative afferent pupil defect. Inclusion criteria also permitted high-risk glaucoma suspect (IOP >25 mm Hg, structural changes as above, no visual field defect) or high-risk ocular hypertension (IOP >32 mm Hg, no structural or functional defect), and International Society of Geographic and Epidemiologic Ophthalmology category 2 (cup-to-disc ratio of ≥0·8 or cup-to-disc ratio asymmetry of ≥0·3 if a visual field could not be satisfactorily completed).[16] Exclusion criteria included being aged younger than 18 years or having an opaque cornea, narrow angle (<2 on the Shaffer scale in two quadrants), absolute blindness (no perception of light), history of previous uveitis, any previous glaucoma surgery or laser treatment, neovascular or traumatic glaucoma, and history of asthma or bradycardia, which can be exacerbated by timolol eye drops. The full exclusion criteria are listed in appendix 4 (p 2). Patients who reported using eye drops before the trial had a 4-week washout period. Eligible patients were informed about the study in detail in Kiswahili and, if interested, invited to return on a different day for the baseline examination. During this assessment, written informed consent was obtained in Kiswahili before participants were enrolled.

### Randomisation and masking

The randomisation sequence was generated by an independent statistician with a variable block size between 4 and 8. Sequentially numbered and sealed opaque envelopes contained the allocation of participants to either the SLT or the timolol group (1:1). One or both eyes were enrolled, depending on eligibility, and were treated identically. Participants were enrolled and assigned to an intervention arm together by at least two of the following individuals: HP, EdM, SM, KMK, and EiM. Due to the nature of the interventions, participants, principal investigators, and health-care staff administering treatments could not be masked to treatment allocation; however, the clinicians who examined IOP were masked to the trial arm, the individual IOP threshold, and previous IOP measurements of the participant, and were not involved in any other aspect of the trial.

### Procedures

During the baseline assessment, a detailed clinical history was taken. We assessed vision-related quality of life using the 20-item cross-cultural WHO visual functioning questionnaire (WHO/PBD-VF20).[18] Additional questionnaires included the Patient Outcome and Experience Measure and the Glaucoma Symptom Scale.[19,20]

Visual acuity was measured at 2 m in a dimmed room (Peek Acuity app [version 3.5.0]). Static visual field perimetry was done with the Swedish interactive threshold algorithm standard 24-2 or 10-2 programme (II-i series system software version 4.2) of the Humphrey HFA II 740i Visual Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany).[21] The Disc Damage Likelihood Scale was used to stratify glaucoma severity into moderate (stage 5–7) and advanced (stage 8–10). Glaucoma-related structural features were assessed by slit-lamp examination of the anterior eye segment, pachymetry (central corneal thickness), gonioscopy, fundus imaging, and indirect fundoscopy of the optic nerve head.

Standardised examiners measured baseline IOP before treatment allocation, following a standard operating procedure. This procedure included measuring IOP with a calibrated Goldmann Applanation Tonometer (Haag Streit, Koeniz, Switzerland) twice within 5 mins. If the difference between the first two measurements was up to 2 mm Hg, the mean IOP was noted. Otherwise, a third measurement was obtained and the median was recorded.[22] The repeatability coefficient of Goldmann tonometry is around 2·5 mm Hg.[23]

Several focus group discussions involving patients, relatives, and eye care specialists were held on the two treatment options and other contextual factors for glaucoma during the trial. The results from the questionnaires, focus group discussions, and other glaucoma-related functional or structural changes will be reported elsewhere.

Following the baseline assessment and enrolment, patients randomly assigned to the SLT laser intervention (SLT group) received amethocaine (topical anaesthesia), 0·2% topical brimonidine (IOP spike prevention), and 1·0% topical prednisolone (inflammatory response control) 15 mins before the procedure. The chamber angle was then visualised with the Latina goniolens supplied with the SLT laser (Lumenis Selecta II Lumenis, Yokneam, Israel). Approximately 100 laser spots were applied to cover 360° of the trabecular meshwork. Starting energy level was 0·6 mJ, which was continuously titrated in steps of 0·1 mJ until cavitation bubbles appeared in around a third of laser spot applications. The eye, including IOP, was examined about 1 h after SLT. All SLT procedures were done on the day of treatment allocation by one ophthalmologist (HP), who was trained in the procedure at University Hospitals Birmingham (Birmingham, UK) by PS and had completed around 100 SLT procedures before the trial.

Participants randomly assigned to the standard treatment arm (timolol group) received 0·5% timolol eye drops to administer twice daily. The importance, side-effects, and application of eye drops were explained by a study assistant to participants and accompanying helpers in Kiswahili using a standard protocol (appendix 4 pp 12–13). Adherence was estimated by asking participants at each follow-up visit how frequently they had missed their eye drops. Both treatment options were

See Online for appendix 4

provided free of charge to the patient, and transport cost was subsidised to further increase adherence.[8,24]

Follow-up assessments were scheduled at 2, 6, 9, and 12 months. Masked examiners measured IOP on each follow-up visit following the same procedure as was used during baseline assessment. Additional safety visits were arranged if the supervising clinician considered this to be necessary. One IOP measurement of up to 2 mm Hg above target IOP was allowed on one of the follow-up visits without triggering a repeat intervention or being considered a treatment failure. If the IOP was more than 2 mm Hg above target or up to 2 mm Hg above target for the second time, repeat SLT or counselling was provided. If the IOP exceeded the target on any subsequent occasion again, the eye was considered to have a treatment failure and exited from the trial, and the patient received additional treatment (including the intervention from the other intervention arm, additional eye drops, or trabeculectomy; appendix 4 p 4). Furthermore, if the IOP was more than 40 mm Hg at any visit, the eye was considered to have a treatment failure and was exited from the trial immediately; additional treatment was provided to the participant's eye.

To estimate the cost of an SLT laser procedure, we followed a bottom-up micro-costing approach assuming that the equipment had a lifetime of 10 years and that the SLT treatment was done on demand during a glaucoma clinic by an ophthalmologist earning a standard salary.[13,25] Variable and fixed costs were calculated and a threshold analysis was done estimating total costs for eight production scenarios, depending on the annual number of treatments (appendix 4 pp 10–12). The annual cost of timolol eye drops was identified using the median of three prices at pharmacies across Tanzania and was used as a reference to determine the number of SLT procedures that would result in comparable cost. Both annual treatment costs were then compared with an affordability threshold of 2·5% of Tanzania's gross domestic product per capita, as a proxy of income.[26]

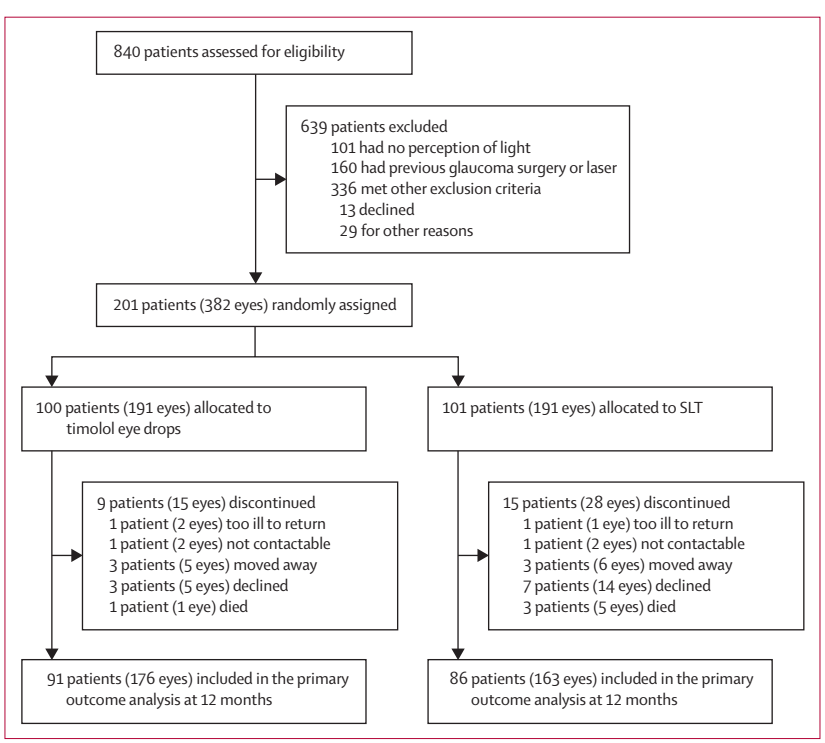


***Figure 1:*** **Trial profile**
SLT=selective laser trabeculoplasty. The full list of reasons for exclusion are provided in appendix 4 (p 3).

## Outcomes

The primary outcome was the proportion of eyes from both intervention groups with treatment success at 12 months following randomisation. For patients with advanced glaucoma (stage 8–10 according to the Disc Damage Likelihood Scale), this target IOP was 18 mm Hg or below and for those with moderate glaucoma (stage 5–7), this target was 21 mm Hg or below. Secondary outcomes were safety, acceptance, vision-related quality of life, adherence, preservation of visual acuity and visual fields, other glaucoma-related functional or structural changes, other IOP-related outcomes, analyses of focus group discussions, cost, and treatment affordability.

## Statistical analysis

The trial was powered to test the hypothesis that SLT is superior to timolol eye drops. From the literature and retrospective data from the Eye Department at KCMC, we anticipated that the proportions of success after 12 months would be 60% for timolol and 75% for SLT.[27] Allowing for a loss to follow-up of 20%, a sample size of 360 eyes was estimated to provide 80% power with 95% confidence to detect such a difference.

The primary outcome was a binary variable defined as treatment success at 12 months, compared between the two treatment arms. Analysis of the primary outcome was by modified intention-to-treat using a logistic regression model, in which participants lost to follow-up were excluded, with generalised estimating equations (GEE) to account for the absence of independence between eyes, if both eyes were included. The primary analysis was unadjusted, although baseline characteristics were examined for balance between arms.

Secondary outcomes were described and compared between the two treatment arms. A change in visual acuity of two or more lines on the logarithm of the minimum angle of resolution (logMAR) chart (equals ≥0·2 logMAR between baseline and the last visit, either in the event of a failure, before loss to follow-up, or success at 12 months) was defined as a loss of central vision and compared using logistic regression with GEE by arm.[28] Acceptance was described as the number of times a participant refused an intervention at any of the follow-up visits after being randomly assigned. WHO/PBD-VF20 items were

| | Timolol group | SLT group |
|---|---|---|
| **Participant characteristics** | | |
| Number of participants | 100 | 101 |
| Age, years | 65·09 (10·79) | 67·40 (12·33) |
| Sex | | |
| Female | 46 (46%) | 37 (37%) |
| Male | 54 (54%) | 64 (63%) |
| Ethnic group | | |
| Chagga | 54 (54%) | 57 (56%) |
| Pare | 18 (18%) | 23 (23%) |
| Meru | 4 (4%) | 4 (4%) |
| Maasai | 4 (4%) | 1 (1%) |
| Sambaa | 3 (3%) | 2 (2%) |
| Other | 17 (17%) | 14 (14%) |
| Education | | |
| Less than secondary level | 70 (70%) | 63 (62%) |
| Secondary level or higher | 30 (30%) | 38 (38%) |
| Family history of glaucoma* | | |
| No | 76 (76%) | 77 (76%) |
| Yes | 24 (24%) | 24 (24%) |
| Travel distance, km | | |
| <50 | 51 (51%) | 54 (53%) |
| ≥50 | 49 (49%) | 47 (47%) |
| **Ocular characteristics** | | |
| Number of eyes | 191 | 191 |
| Visual acuity (logMAR) | 0·48 (0·69) | 0·49 (0·66) |
| Visual acuity (WHO categories) | | |
| Normal vision | 147 (77%) | 145 (76%) |
| Low vision | 20 (10%) | 23 (12%) |
| Blind | 24 (13%) | 23 (12%) |
| Exfoliation glaucoma | | |
| No | 167 (87%) | 166 (87%) |
| Yes | 24 (13%) | 25 (13%) |
| Pseudophakia | | |
| No | 185 (97%) | 177 (93%) |
| Yes | 6 (3%) | 14 (7%) |
| Vertical cup-to-disc-ratio | 0·85 (0·15) | 0·84 (0·16) |
| Intraocular pressure, mm Hg | 26·96 (7·52) | 26·38 (6·28) |
| Optic nerve head damage (DDLS) | | |
| 5 | 34 (18%) | 42 (22%) |
| 6 | 20 (10%) | 22 (12%) |
| 7 | 25 (13%) | 19 (10%) |
| 8 | 47 (25%) | 40 (21%) |
| 9 | 33 (17%) | 33 (17%) |
| 10 | 32 (17%) | 35 (18%) |
| Stage of glaucoma (DDLS) | | |
| Moderate (stage 5–7) | 79 (41%) | 83 (43%) |
| Advanced (stage 8–10) | 112 (59%) | 108 (57%) |
| Visual field (24-2), mean defect, dB† | −18·29 (11·09) | −16·02 (10·94) |
| Visual field (10-2), mean defect, dB† | −33·92 (0·58) | −30·71 (4·40) |
| Central corneal thickness, µm‡ | 522·89 (34·79) | 519·16 (34·51) |
| Previous timolol eye drops§ | | |
| No | 83 (43%) | 93 (49%) |
| Yes | 108 (57%) | 98 (51%) |

(Table 1 continues in next column)

(Continued from previous column)

Data are mean (SD) or n (%), unless otherwise indicated. SLT=selective laser trabeculoplasty. logMAR=logarithm of the minimum angle of resolution. DDLS=Disc Damage Likelihood Scale. *In a first-degree relative. †Visual field examinations: 347 eyes completed 24-2 (175 in timolol group *vs* 172 in SLT group); eight eyes completed 10-2 only (four in timolol group *vs* four in SLT group); no visual field possible in 27 eyes (12 in timolol group *vs* 15 in SLT group) due to reduced central vision. ‡Central corneal thickness measurements missing in 13 eyes (five in timolol group *vs* eight in SLT group) due to temporary failure of the pachymeter. §Based on patient history.

***Table 1:*** **Baseline participant and ocular characteristics**

divided into the general functioning, visual symptoms, and psychosocial subscales, and summary scores were transformed to a scale (0–100), with 100 as the highest possible vision-related quality of life score.[18] Affordability was described as whether a person had sufficient income to pay for health-care services, treatment, or costs (appendix 4 p 12).[29]

We tested for evidence of effect modification by the stage of glaucoma and baseline IOP. A sensitivity analysis was done to provide the most conservative estimate, considering all participants lost to follow-up as failure in the more successful arm and as success in the less successful arm. Patients lost to follow-up were compared with those who completed the trial with respect to age, sex, stage of glaucoma, intervention, visual field defect, visual acuity, and travel details using logistic regression with GEE. Differences between arms in time to an event were assessed by plotting survival curves and a Cox regression analysis, by use of a shared frailty model to account for dependency between the two eyes. Other potential determinants of success were investigated using logistic regression with GEE. To prevent multicollinearity in a fully adjusted model, all potential determinants were first screened for inclusion using a univariable model and GEE. Any factor in which $p<0·2$ was included in the fully adjusted model. Backward stepwise selection was then employed to find the most parsimonious logistic regression model, with $p<0·05$ for all predictors.

Data were managed in a custom built database in Microsoft Access 2016. Stata (version 16.1) was used to compute the statistical analysis. A data safety monitoring board oversaw the study. This trial was registered with the Pan African Clinical Trials Registry, number PACTR201508001235339.

### Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

840 patients with glaucoma who attended the Eye Department at KCMC were screened for eligibility (figure 1; appendix 4 p 3). Of those screened, 201 (24%) eligible participants (382 eyes) were enrolled between Aug 31, 2015, and May 12, 2017, of whom 100 (50%) of participants (191 eyes) were randomly assigned to the timolol group and 101 (50%; 191 eyes) to the SLT group. All participants were members of one of the ethnic groups living in Tanzania (table 1). At 12 months, 177 (88%) patients (339 eyes) were included in the analysis; 24 (12%) patients (43 eyes) had been lost to follow-up. The mean age of 201 people enrolled in the trial was 66·3 years (SD 11·6) and 83 participants were female. The mean age of 639 patients not enrolled was 65·0 years (15·5) and 268 participants were female.

| | Success | Univariable OR (95% CI) | p value | Multivariable OR (95% CI) | p value |
|---|---|---|---|---|---|
| **Intervention** | | | | | |
| Timolol | 55/176 (31%) | 1 (ref) | .. | .. | .. |
| SLT | 99/163 (61%) | 3·37 (1·96–5·80) | <0·0001 | 5·35 (2·77–10·31) | <0·0001 |
| **Sex** | | | | | |
| Female | 66/142 (46%) | 1 (ref) | .. | .. | .. |
| Male | 88/197 (45%) | 0·92 (0·54–1·57) | 0·77 | .. | .. |
| **Age groups, years** | | | | | |
| <70 | 101/211 (48%) | 1 (ref) | .. | .. | .. |
| ≥70 | 53/128 (41%) | 0·74 (0·43–1·28) | 0·28 | .. | .. |
| **Education** | | | | | |
| Less than secondary level | 92/225 (41%) | 1 (ref) | .. | .. | .. |
| Secondary level or above | 62/114 (54%) | 1·68 (0·97–2·93) | 0·066 | .. | .. |
| **Travel distance to KCMC, km** | | | | | |
| <50 | 87/185 (47%) | 1 (ref) | .. | .. | .. |
| ≥50 | 67/154 (44%) | 0·86 (0·51–1·46) | 0·58 | .. | .. |
| **History of timolol eye drops** | | | | | |
| No | 75/151 (50%) | 1 (ref) | .. | .. | .. |
| Yes | 79/188 (42%) | 0·73 (0·44–1·22) | 0·24 | .. | .. |
| **Pseudophakia** | | | | | |
| Phakic | 145/324 (45%) | 1 (ref) | .. | .. | .. |
| Pseudophakic | 9/15 (60%) | 1·16 (0·41–3·29) | 0·78 | .. | .. |
| **Exfoliation glaucoma** | | | | | |
| No | 147/297 (49%) | 1 (ref) | .. | .. | .. |
| Yes | 7/42 (17%) | 0·16 (0·06–0·44) | 0·0004 | 0·16 (0·05–0·46) | 0·0009 |
| **Central corneal thickness, µm*** | | | | | |
| <520 | 67/164 (41%) | 1 (ref) | .. | .. | .. |
| ≥520 | 85/172 (49%) | 1·43 (0·88–2·33) | 0·15 | .. | .. |
| **Angle pigmentation** | | | | | |
| Light pigmentation | 132/289 (46%) | 1 (ref) | .. | .. | .. |
| Strong pigmentation | 22/50 (44%) | 1·06 (0·53–2·14) | 0·87 | .. | .. |
| **Stage of glaucoma (DDLS)** | | | | | |
| Moderate (stage 5–7) | 108/145 (74%) | 1 (ref) | .. | .. | |
| Advanced (stage 8–10) | 46/194 (24%) | 0·14 (0·09–0·23) | <0·0001 | 0·11 (0·06–0·20) | <0·0001 |
| **Intraocular pressure, mm Hg** | | | | | |
| <25 | 100/153 (65%) | 1 (ref) | .. | .. | |
| ≥25 | 54/186 (29%) | 0·27 (0·17–0·44) | <0·0001 | 0·33 (0·19–0·60) | 0·0003 |
| **Visual acuity (WHO categories)** | | | | | |
| Normal vision | 135/263 (51%) | 1 (ref) | .. | .. | .. |
| Low vision | 12/33 (36%) | 0·64 (0·33–1·25) | .. | .. | .. |
| Blind | 7/43 (16%) | 0·38 (0·21–0·71) | 0·0060† | .. | .. |

(Table 2 continues on next page)

Loss to follow-up was not associated with age, sex, stage of glaucoma, intervention arm, or level of visual acuity. There was evidence that patients with advanced visual field defects were less likely (p=0·0018) and patients who needed a guide for their journey to the eye hospital were more likely (p=0·016) to be lost to follow-up. However, these inferences are based on few patients who were lost to follow-up (24 patients [12%]; figure 1).

A successful IOP reduction 1 year after the start of treatment was reported in 55 (31%) of 176 eyes in the timolol group (16 [29%] of 55 eyes required repeat counselling) and in 99 (61%) of 163 eyes in the SLT group (33 [33%] of 99 eyes required a repeat SLT). The unadjusted logistic regression model (ie, GEE) for the relationship between intervention and success estimated an odds ratio (OR) of SLT over timolol eye drops of 3·37 (95% CI 1·96–5·80; p<0·0001; table 2). Cox regression analysis showed a hazard ratio of 0·16 (0·09–0·30; p<0·0001; figure 2). Detailed IOP results can be found in the appendix 4 (pp 5–6).

A reduction of central vision occurred in 36 (19%) of 187 eyes in the timolol group and in 40 (21%) of 188 in the SLT group. There was no evidence of a difference between interventions (OR 1·16 [95% CI 0·66–2·06]; p=0·60). Vision-related quality of life measured with the WHO/PBD-VF20 showed no differences between the two groups (table 3).

Self-reported adherence to eye drop use in the timolol group was high (table 4). 56–75% of patients reported daily application of eye drops during the 2 weeks before the follow-up visit, 15–24% of patients reported missing eye drops for 1–2 days, and only 4–20% of patients reported missing eye drops for more than 2 days. No participant refused either timolol eye drops or SLT within the first year, including repeat interventions.

From an eye care provider's perspective, the variable cost per SLT treatment was estimated to be US$2·57. Annual fixed costs were $4960, including the depreciation of the initial purchase over the 10 years, the annual inspection, and an assumption of two repairs.[13] Travel expenses of technicians were added, which might be substantial where services are not available in a country (appendix 4 pp 10–12). The SLT laser has been in operation at KCMC since 2015 without needing repair. With a scenario of 500 eyes treated per year, the total

costs for one procedure are approximately $12·49. Since both eyes are often treated, this figure corresponds to 250–400 patients treated per year to cover the costs and offer the laser treatment at a price of $12·49 per treatment using a not-for-profit eye care service model (appendix 4 p 11). To achieve successful treatment with SLT in this study, 33 eyes required two procedures and 66 eyes were treated after one treatment. Thus, from the patient's perspective, an average of 1·33 treatments would be required, increasing the average cost to approximately $16·61 per eye for a successful outcome, excluding travelling expenses. Annual therapy with timolol eye drops cost around $16·32 per eye in Tanzania. Therefore, with around 500 treatments per year, the SLT treatment can be offered, covering costs, at a similar price as timolol eye drops. The annual GDP per capita in Tanzania in 2019 was reported to be $1122·12, so any annual treatment cost below $28·05 can be considered affordable. Thus, the annual treatment cost of timolol and SLT for one eye are below this threshold (assuming 500 procedures per year in an eye health unit). For SLT, the treatment costs for two eyes can also be considered affordable for most patients as 66 (67%) of 99 eyes only required one treatment for a successful outcome (annual treatment cost for two eyes of $24·98).

We used a sensitivity analysis to assess whether the primary outcome results were possibly influenced by loss to follow-up. The hypothetical scenario considered all patients who were lost to follow-up in the SLT group to be failures and those in the timolol group to be successes, assuming the worst possible scenario for the SLT group. The OR of success of SLT was 1·88 (95% CI 1·13–3·11; p=0·015).

There was no evidence of an effect modification in the OR of SLT over timolol by the stage of glaucoma (p=0·55) or by the baseline IOP (p=0·14; appendix 4 p 8).

Other potential determinants for success were evaluated (table 2). The most parsimonious multivariable model showed an association between success and SLT (*vs* timolol) as the randomisation arm (OR 5·35 [95% CI 2·77–10·31]; p<0·0001), high (*vs* low) IOP at baseline (0·33 [0·19–0·60]; p=0·0003), advanced (*vs* moderate) stage of glaucoma (0·11 [0·06–0·20]; p<0·0001), and the presence (*vs* absence) of exfoliation material (0·16 [0·05–0·46]; p=0·0009).

In total, there were ten (10%) ocular and systemic adverse events in the timolol group and eight (8%) in the SLT group (OR 0·77 [95% CI 0·29–2·05]; p=0·61; table 5). Four patients died during the 1-year follow-up period (one in the timolol group *vs* three in the SLT group) from known pre-existing general medical conditions. SLT was associated with several transient (<1 h) side-effects (appendix 4 p 9). The baseline SLT procedure caused no pain during 69 (36%) of 191 baseline laser procedures, mild pain during 103 (54%), moderate pain during 15 (8%), and severe pain during one (<1%). No baseline SLT procedure triggered an IOP

| | Success | Univariable OR (95% CI) | p value | Multivariable OR (95% CI) | p value |
|---|---|---|---|---|---|
| (Continued from previous page) | | | | | |
| **Glaucoma categories** | | | | | |
| Early | 63/81 (78%) | 1 (ref) | .. | .. | .. |
| Moderate | 31/46 (67%) | 0·46 (0·23–0·94) | .. | .. | .. |
| Advanced | 15/35 (43%) | 0·33 (0·15–0·73) | .. | .. | .. |
| Severe | 40/150 (27%) | 0·13 (0·07–0·23) | .. | .. | .. |
| End stage | 5/27 (19%) | 0·10 (0·04–0·27) | <0·0001† | .. | .. |

Data are n/N (%). Results of 339 eyes analysed at 12 months using univariable and multivariable analyses of potential factors associated with success using logistic regression with general estimating equations. Parameters with p<0·2 in the log likelihood ratio test were included in the initial multivariable model. Backward stepwise selection was then employed to find the most parsimonious logistic regression model, in which all predictors had p<0·05. This final model included intervention, intraocular pressure at baseline, stage of glaucoma, and exfoliation glaucoma. OR=odds ratio. SLT=selective laser trabeculoplasty. KCMC=Kilimanjaro Christian Medical Centre. DDLS=Disc Damage Likelihood Scale. *Central corneal thickness missing for three eyes. †Wald test for trend.

***Table 2:*** **Predicted ORs for success**

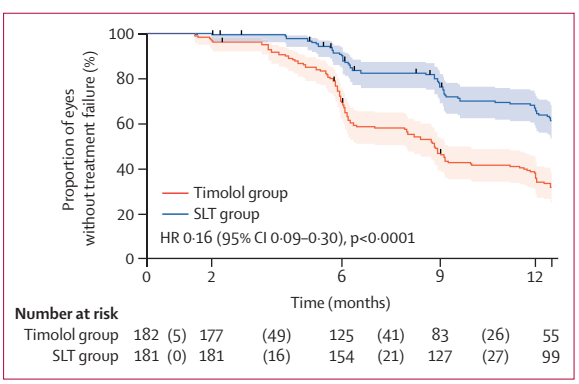


***Figure 2:*** **Kaplan-Meier curve of time to treatment failure**
Differences between the two intervention groups in time to an event was assessed with a Cox regression analysis using a shared frailty model to account for dependency between the two eyes. HR=hazard ratio. SLT=selective laser trabeculoplasty.

| | Timolol group (n=28) | SLT group (n=50) | Estimated group Δ (95% CI) | p value |
|---|---|---|---|---|
| **General functioning** | | | | |
| Baseline visit | 79·5 (17·7) | 72·5 (21·2) | 1·91 (–6·17 to 10·00) | .. |
| 12-month visit/Δ (SD) | 88·2 (15·6)/8·6 (19·7) | 83·1 (15·8)/10·5 (15·6) | .. | 0·64 |
| **Visual symptoms** | | | | |
| Baseline visit | 66·4 (17·3) | 68·3 (21·9) | –2·67 (–11·89 to 6·55) | .. |
| 12-month visit/Δ (SD) | 74·7 (16·9)/8·3 (23·8) | 74·0 (16·9)/5·7 (16·9) | .. | 0·57 |
| **Psychosocial** | | | | |
| Baseline visit* | 77·2 (17·3) | 74·4 (21·1) | –5·29 (–15·02 to 4·44) | .. |
| 12-month visit/Δ (SD) | 87·5 (17·3)/10·3 (15·2) | 79·3 (24·2)/5·0 (23·1) | .. | 0·28 |

Data are mean (SD), unless otherwise indicated. Mean (SD) of total scores (0–100) of three subscales of WHO/PBD-VF20 questionnaires for patients with success at 12 months (if both eyes were enrolled, the status of the right eye was considered), so 28 patients in the timolol group and 50 patients in the SLT group. Higher scores represent a better vision-related quality of life. Estimated group difference (Δ), 95% CI, and p values from linear regression of differences between interventions. SLT=selective laser trabeculoplasty. Δ=delta or difference. *Data of one patient missing in the SLT group.

***Table 3:*** **Vision-related quality of life**

| | 2-month visit (n=95) | 6-month visit (n=90)* | 9-month visit (n=51)† | 12-month visit (n=36) |
|---|---|---|---|---|
| Adherence every day | 53 (56%) | 62 (69%) | 35 (69%) | 27 (75%) |
| Non-adherence for 1–2 days | 23 (24%) | 13 (14%) | 10 (20%) | 7 (19%) |
| Non-adherence for >2 days | 19 (20%) | 14 (16%) | 2 (4%) | 2 (6%) |

Adherence to treatment was assessed at each follow-up by asking participants how frequently they took their eye drops during the previous 2 weeks. Assessment continued for participants until the respective study exit (eg, failure, loss to follow-up, or success at 12 months). *One reply missing. †Three replies missing.

*Table 4:* **Self-reported adherence to eye drops for participants in the timolol group**

| | Timolol group (n=100) | SLT group (n=101) | All (n=201) |
|---|---|---|---|
| Total | 10 (10%) | 8 (8%) | 18 (9%) |
| Ocular | | | |
| Conjunctiva injected | 2 (2%) | 1 (1%) | 3 (1%) |
| Persistent cells in anterior chamber, hyphaemia | 0 | 0 | 0 |
| Systemic* | | | |
| Cardiovascular event | 1 (1%) | 1 (1%) | 2 (1%) |
| Diabetes | 3 (3%) | 1 (1%) | 4 (2%) |
| Orthopaedic condition | 2 (2%) | 2 (2%) | 4 (2%) |
| Prostate surgery | 1 (1%) | 0 | 1 (<1%) |
| Death | 1 (1%) | 3 (3%) | 4 (2%) |

Data are n (%). *Requiring hospital admission.

*Table 5:* **Adverse events**

spike of more than 5 mm Hg within the first hour, and two (2%) of 104 repeat SLT procedures were followed by reversible IOP spikes.

## Discussion

This randomised controlled trial compared timolol eye drops with SLT in patients with glaucoma in Tanzania. SLT was superior to timolol in controlling IOP, with an OR of 3·37 in favour of SLT (95% CI 1·96–5·80; p<0·0001). This difference between the two interventions was not significantly modified by the stage of glaucoma or baseline IOP.

A previous meta-analysis estimated the mean difference in IOP reduction between timolol and placebo at 3 months as 3·70 mm Hg (95% CI 3·16–4·24).[30] We observed a comparable IOP reduction in the timolol group of 3·22 mm Hg (SD 7·51) at the 2-month visit. IOP lowering in the SLT group at the 2-month visit was 6·28 mm Hg (SD 6·13). To our knowledge, no previous direct comparison has been made between SLT and timolol eye drops, the most affordable and commonly available IOP lowering drug.[26,30]

Gazzard and colleagues[13] compared SLT with any conservative treatment to reduce IOP in a predominantly White study population in the UK. The authors followed an algorithm to define individual target IOPs and progression rules. Of the 536 eyes treated with SLT first, 419 (78%) required no additional medication to reach target IOP, and 321 (60%) required only a single SLT treatment.[13] Realini and colleagues[31] reported a study of 72 participants from an African Caribbean population with a 12-month success rate of 78%, using a 20% reduction from baseline IOP as success criterion.

Our adjusted multivariable model showed that a more advanced stage of glaucoma, higher baseline IOP, and the presence of exfoliation glaucoma were all associated with a decreased probability of success. In our study protocol, the stage of glaucoma determined the target IOP, which needs to be lower in advanced glaucoma.[2] A greater reduction in IOP is more difficult to achieve in general; therefore, the probability of success is likely to be lower in eyes with advanced glaucoma and a higher baseline IOP (appendix 4 p 7) than in those with moderate glaucoma and a lower baseline IOP. Exfoliation glaucoma reduced the probability of success in both intervention groups. To date, few clinical trials with small sample sizes have shown inconclusive results concerning the role of exfoliation glaucoma.[32] Our results suggest that, although the subtype of exfoliation glaucoma is challenging to treat overall, SLT might still be a better option than timolol (appendix 4 p 7). Some regions in sub-Saharan Africa are affected by a particularly high prevalence of exfoliation glaucoma.[33]

Only mild adverse effects and no serious treatment-related adverse events were reported in either group, similarly to other studies.[13] SLT caused reversible changes in the anterior chamber and corneal endothelium, as well as no or mild pain in most patients.[34] After excluding patients with asthma and bradycardia, timolol eye drops caused no clinically significant complaints. The extensive counselling by two Tanzanian research assistants probably played an important role in the high acceptance of both treatment methods, which could have possibly been lower otherwise. This trusting relationship and the provision of treatment at no cost probably contributed to the higher adherence to timolol eye drops in this trial compared with that observed in other studies.[22,35]

There was no significant difference in preserving visual function or vision-related quality of life between the two groups. Gazzard and colleagues[13] compared conservative treatment with SLT for patients with newly diagnosed glaucoma, in which general quality of life was the primary outcome. The trial did not find a difference in quality of life between the two intervention groups.

Besides the superior efficacy, comparable safety, and acceptance of SLT, cost is also an important factor. Out-of-pocket payment is still common in many countries and, even if national health insurance options are available, uptake might still be low.[15] If an eye care unit uses SLT to treat at least 500 eyes with glaucoma per year, SLT laser therapy can be offered for around US$12·50, including estimates for salaries, cost of repair, and maintenance. The cost of repairing imported equipment

can be high in regions where specialised service personnel sometimes need to be flown in or the equipment needs to be shipped abroad for maintenance or repair.[36] The salaries of ophthalmologists and other eye care professionals are a crucial component. Both treatments can be offered as an affordable intervention for glaucoma using the annual gross domestic product per capita as a surrogate for income and an affordability threshold of 2·5%.[26]

Our trial has several limitations. To establish the IOP-lowering effect or the efficacy as accurately as possible, adherence to regular follow-up visits and eye drops was promoted through intensive counselling, phone call reminders, and subsidies for travel and treatment expenses. Although these efforts resulted in high follow-up rates, they are also a limitation of the study given that the results probably underestimate the difference between laser and eye drops, favouring timolol through the provision of free treatment, more intensive counselling, and transport support. Eye drops need to be applied daily and new bottles need to be purchased every few weeks for consistent IOP control. By contrast, SLT treatment requires only occasional IOP measurements and retreatments, if the IOP increases. SLT was consistently performed by one experienced eye surgeon, which assisted in determining the best possible efficacy of the procedure; however, such efficacy might not always be achieved, especially while eye care professionals are in their learning curve. A further limitation is the follow-up of 1 year. Although 1 year is a sufficient period to estimate the IOP-lowering potential of the interventions in our cohort, changes in visual outcomes, vision-related quality of life, long-term effects on IOP lowering, and the progression of glaucoma might only become apparent over a longer period of time. Longer follow-up would also allow target IOPs to be evaluated on and adjusted for particular eyes if necessary. Treatment affordability and cost were used to compare the two treatment alternatives, which is of particular relevance in regions with a high proportion of out-of-pocket payments. However, more comprehensive economic evaluations, such as an extended cost-effectiveness analysis that adds non-health benefits, including the financial risk protection and distributional consequences (eg, equity), are also particularly relevant in these regions and should be considered in future studies. Furthermore, it could be argued that alternative topical treatments, such as prostaglandin analogues, might have been more effective than timolol. However, our choice was deliberate because timolol is the current standard of care in the region, and such alternatives are either unavailable or prohibitively expensive.[8]

The target threshold of 18 mm Hg for advanced glaucoma was informed by the associative analysis of the AGIS trial, which found this threshold to be protective against further progression during a follow-up period of 6 years. It is noteworthy that AGIS also included patients with low baseline IOP, whereas our study enrolled patients with high-pressure glaucoma only (IOP >21 mm Hg).

The results from this trial suggest that SLT can be used instead of timolol eye drops, the current first-line treatment in sub-Saharan Africa. If glaucoma progresses further, SLT can be repeated or combined with eye drops before resorting to trabeculectomy, which remains an important treatment option for patients with glaucoma. Additionally, if surgeons are not confident in performing trabeculectomy (eg, in patients with end-stage glaucoma or when patients refuse surgery), SLT could have an important role. The initial investment cost can be offset, in this context, by completing around 500 procedures per year over 10 years. The laser treatment option could be embedded in a comprehensive glaucoma management network strategy based around large eye units equipped with an SLT laser. This strategy would need to be closely associated with improving community awareness, enabling early detection of glaucoma in primary care settings, and strengthening the referral pathways to these large eye units. Such an approach could increase the demand for affordable and convenient glaucoma treatment options, such as SLT.[15]

In summary, the prevalence of glaucoma is set to increase due to ageing and population growth, mainly in resource-limited settings.[5,37,38] The *Lancet Global Health* Commission on global eye health suggested that research action is urgently needed to develop contextually relevant management strategies for glaucoma.[38] The findings from this trial clearly indicate that SLT is superior to timolol eye drops in controlling IOP in patients with open-angle glaucoma in Tanzania. Both interventions showed similar safety profiles, acceptance by patients, vision-related quality of life, and preservation of visual acuity. Depending on the number of procedures and the funding model, SLT treatment can be offered at a similar cost to a 1-year supply of timolol eye drops. Ultimately, this trial, completed in Africa, provides strong evidence that SLT can contribute to an affordable management strategy for preventing blindness from glaucoma.

**Contributors**

HP, PS, and MJB did the literature search. HP, PS, GG, WUM, and MJB designed the trial. HP, EiM, KMK, EdM, SM, APM, CM, MM, AJN, FAM, VdG, ElM, and NF collected the data. HP, KMK, MJB, and DM verified the data. HP, DM, AM, and MJB did the statistical analysis. HP, DM, PS, AM, and MJB interpreted data. HP and MJB wrote the first draft of the research report. All authors critically revised the manuscript. HP and MJB obtained funding. MJB and WUM were the study supervisors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Declaration of interests**

GG reports personal fees from Alcon, Allergan, Belkin, Equinox, Genentech–Roche, Glaukos, Ivantis, Reichert, Sight Sciences, and from Thea; grants from Belkin, Santen, and from Thea; and non-financial involvement with the patient advocacy group GlaucomaUK, outside the submitted work; he is also a co-investigator on three other major SLT trials (LIGHT, COAST, and Belkin laser). All other authors declare no competing interests.

### Data sharing

The National Institute for Medical Research in Tanzania requires that all data sharing requests are reviewed and approved by them before data can be shared. Deidentified participant data is available to any researcher under reasonable request. To facilitate the data access process, please contact ethics@lshtm.ac.uk. The study protocol and statistical analysis plan are available from the corresponding author under reasonable request.

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# Selective Laser Trabeculoplasty na timolol 0·5% kwa ajili ya matibabu ya shinikizo la maji ya jicho nchini Tanzania: jaribio ya kulinganisha

## *Muhtasari*


**Usuli**

Shinikizo la maji ya macho ni sababu kuu ya upotevu wa uoni duniani kote, hali inatokea zaidi barani Afrika. Tiba ya kawaida na rahisi inayotumika kudhibiti ugonjea huu ni dawa ya matone aina ya timolol ambayo hutumika kwa muda mrefu. Hata hivto uzingatiaji wa matibabu ni changamoto kubwa.

Utafiti ulikuwa na lengo la kuchunguza kama matibabu ya mionzi ya laser kudhibiti shinikizo la maji ya macho, ijulikanayo kiingereza kama Selective Laser Trabeculoplasty (SLT), ni bora zaidi kuliko dawa ya matone aina ya timolol.

**Njia iliyotumika.**

Jaribio hili la kitafiti lililofanyiaka Idara ya Macho katika Hospitali ya rufaa ya Kilimanjaro Christian Medical Centre, Moshi, Tanzania, liliweka makundi mawili sambamba bila ya washiriki kuchagua aina ya matibabu na pasipo daktari kujua matibabu yatakayotolewa. Washiriki walikuwa wana umri wa miaka ≥18, walikuwa na shinikizo la maji ya macho (Primary Open Angle Glaucoma), walikuwa na shinikizo la zaidi ya 21mmHg, hawajawahi kufanyiwa upasuaji wa jicho ili kushusa shinikizo, hawajawahi kupata matibabu ya SLT ya kudhibiti shinikizo la maji ya macho na wasio na pumu. Waliwekwa kwenye moja ya makundi mawili bila ya kuchagua kwa uwiano wa 1:1, kundi moja walipewa dawa ya matone ya timolol 0·5% ambayo walitumia mara mbili kwa siku na kundi la pili walifanyiwa matibabu ya SLT ya kudhibiti shinikizo la maji ya jicho. Matokeo ya makuu yalikuwa ni uwiano kati ya macho ya wale waliopatiwa tiba kuonyesha mafanikio miezi 12 baada ya kuingia kwenye utafiti, ambapo vigezo vya ufanisi zilikuwa ni shinikizo la maji ya macho chini au sawasawa na lengo lililowekwa kutokana na uharabifu uliosababishwa na ugonjwa. Kurudiwa tena kutoa maelekezo ya matumizi sahihi ya dawa za matone au kurudiwa kwa matibabu ya SLT iliruhusiwa mara moja tu. Uchambuzi wa awali ulikuwa na nia ya kufanya matibabu kwa kutumia vifaa na wale ambao hawakufuatilia matibabu waliondolewa. Uwiano wa jumla wa makadirio ulitumiwa kurekebisha uwiano kati ya macho. Jaribio hili liliandikishwa kwa Msajili wa Majaribio ya Kliniki ya Afrika (Pan African Clinical trial registry) kwa namba PACTR201508001235339.

**Matokeo**

Washiriki 201 (macho stahiki 382) waliandikishwa kutokana na wagonjwa 840 waliochunguzwa kati ya 31 Mei 2015 na 12 Mei 2017 ; watu 100 (50% ya washiriki, macho 191) bila mpangilio walipewa dawa ya macho ya timolol, na wengine 101 (50%, macho 191) walifanyiwa matibabu ya SLT.

Baada ya mwaka mmoja macho 339 yalifanyiwa utafiti (89%). Matibabu yalionyesha mafanikio kwenye macho 55/176 (31%) kwenye kundi la matone ya timolol, (macho 16/55 [29%] yalihitaji ushauri nasaha kwa mara ya pili kuhusu matumizi ya dawa) na macho 99/163 (61%) kwenye kundi la SLT (macho 33/99 [33%] yalihitajika kurudia SLT); odds ratio 3·37 (95% CI 1·96-5·80, p<0·0001). Madhara (yasiyohusu macho) yalitokea kwa washiriki 10 (10·%) waliokuwa kwenye kundi la dawa za matone ya timolol na nane (8%) waliokuwa kwenye kundi la SLT (p=0·61).

**Tafsiri**

SLT ilionesha ubora kuliko dawa ya matone ya timolol katika kudhibiti wagonjwa wenye shinikizo la maji ya macho kwa muda wa mwaka mmoja nchini Tanzania. Imeonyesha pia uwezo wa kubadilisha udhibiti wa shinikizo la maji ya macho kwenye mazingira ya Afrika Kusini mwa Sahara, hasa ambapo ugonjwa huu umeenea zaidi.



**Ufadhili**

CBM, Seeing is Believing Innovation Fund, na Wellcome Trust (207472/Z/17/Z).

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# Trabéculoplastie sélective au laser versus 0·5% timolol en gouttes ophtalmiques pour le traitement du glaucome en Tanzanie : un essai contrôlé randomisé


## *Sommaire*

**Contexte**

Le glaucome est une cause majeure de perte de la vue dans le monde entier ; la plus haute prévalence et incidence régionales ont été rapportées en Afrique. Le traitement à faible coût le plus couramment utilisé pour contrôler le glaucome est l'application à long terme du collyre timolol. Cependant, le manque d'observation du traitement par le patient constitue un défi majeur. Notre objectif consistait à déterminer si la trabéculoplastie sélective au laser (SLT) était supérieure aux gouttes ophtalmiques de timolol pour contrôler la pression intraoculaire (PIO) chez les patients atteints de glaucome à angle ouvert.

**Méthodes**

Nous avons réalisé un essai contrôlé et randomisé dans deux groupes, en mode parallèle et en simple insu, au service ophtalmique du Kilimanjaro Christian Medical Centre, à Moshi, en Tanzanie. Les participants éligibles (âgés de ≥18 ans) avaient un glaucome à angle ouvert et une PIO supérieure à 21 mm Hg. Ils ne souffraient pas d'asthme et n'avaient pas d'antécédents de chirurgie du glaucome ou de laser. Les participants ont été choisis au hasard (1 : 1) à recevoir soit des gouttes ophtalmiques de timolol 0·5% à administrer deux fois par jour, soit à recevoir une SLT. Le résultat principal était la proportion d'yeux traités avec succès dans chaque groupe ; le succès étant défini comme une PIO inférieure ou égale à la pression cible selon la gravité du glaucome, 12 mois après la randomisation. Une ré-explication de l'application des gouttes ophtalmiques ou une répétition de la SLT était autorisée une fois.

L'analyse primaire a été réalisée en intention de traiter modifiée, en excluant les participants perdus de vue, à l'aide d'une régression logistique ; des équations d'estimation généralisées ont été utilisées pour ajuster la corrélation entre les yeux. Cet essai a été enregistré dans le registre panafricain des essais cliniques, sous le numéro PACTR201508001235339.

**Résultats**

201 participants (382 yeux éligibles) ont été inclus parmi 840 patients dépistés entre le 31/08/2015 et le 12/05/2017 ; 100 personnes (191 yeux) ont été choisies de manière aléatoire pour le traitement timolol et 101 (191 yeux) pour la SLT. La PIO moyenne de départ était de 26·7mmHg (SD 6·9mmHg), 162 yeux avaient un glaucome modéré et 220 yeux avaient un glaucome avancé.

Après un an, 339 yeux ont été analysés (89%). Le traitement a été couronné de succès dans 55/176 yeux (31·3%) dans le groupe timolol (16/55 yeux ont nécessité une nouvelle consultation) et dans 99/163 yeux (60·7%) dans le groupe SLT (33/99 yeux ont nécessité une nouvelle SLT) ; odds ratio 3·37 (95% CI 1·96-5·80, p<0·0001). Des événements indésirables sont survenus chez 10 (10·0%) participants dans le groupe timolol et 8 (7·9%) dans le groupe SLT (p=0·61).

**Interprétation**

Dans la prise en charge des patients en Tanzanie atteints de glaucome à angle ouvert à haute pression intraoculaire, la SLT était supérieure aux gouttes ophtalmiques de timolol sur une période d'un an.

La SLT a le potentiel de transformer la prise en charge du glaucome en Afrique subsaharienne, même là où la prévalence du glaucome avancé est élevée.



**Financement**

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# Trabeculoplastia laser selectiva versus 0·5% de colírio de timolol para o tratamento do glaucoma na Tanzânia: um ensaio aleatório controlado


## *Resumo*

**Contexto**

O glaucoma é uma das principais causas de perda de visão em todo o mundo, com a maior prevalência e incidência regional relatada em África. O tratamento de baixo custo mais comumente utilizado para controlar o glaucoma é o colírio de timolol a longo prazo. No entanto, a baixa aderência à terapêutica é um grande desafio. O nosso objectivo consistiu em investigar se a trabeculoplastia laser selectiva (TLS) era superior ao colírio de timolol para controlo da pressão intra-ocular (PIO) em doentes com glaucoma de ângulo aberto.

**Métodos**

Efectuou-se um ensaio clinico randomizado controlado de dois braços, cego, em grupo paralelo, no Departamento de Oftalmologia do Kilimanjaro Christian Medical Centre, Moshi, Tanzânia. Os participantes elegíveis (com idade ≥18 anos) tinham glaucoma de ângulo aberto e uma PIO acima de 21 mm Hg, e não tinham asma ou historial de cirurgia de glaucoma ou laser. Os participantes foram distribuídos aleatoriamente (1:1) para receberem 0·5% de colírio de timolol com administração duas vezes por dia ou para receberem TLS.

O resultado principal correspondeu à proporção de olhos de ambos os grupos com sucesso de tratamento, definida como uma PIO abaixo ou igual à pressão alvo, de acordo com a gravidade do glaucoma, 12 meses após a aleatorização. Permitiu-se a repetição da explicação da aplicação de gotas oftálmicas ou uma repetição do TLS, uma vez. A análise principal foi feita por intenção de tratamento modificada, excluindo os participantes perdidos para acompanhamento, usando regressão logística; foram usadas equações de estimativa generalizada para ajustar a correlação entre os olhos.

Este ensaio foi registado no Pan African Clinical Trials Registry, número PACTR201508001235339.

**Resultados**

840 pacientes foram examinados para elegibilidade, dos quais 201 (24%) participantes (382 olhos elegíveis) foram inscritos entre 31 de Agosto de 2015, e 12 de Maio de 2017. 100 (50%) dos participantes (191 olhos) foram distribuídos aleatoriamente pelo grupo timolol e 101 (50%; 191 olhos) pelo grupo SLT. Após 1 ano, foram analisados 339 (89%) de 382 olhos. O tratamento foi bem sucedido em 55 (31%) de 176 olhos no grupo do timolol (16 [29%] de 55 olhos requereram aconselhamento de administração repetida) e em 99 (61%) de 163 olhos no grupo do TLS (33 [33%] de 99 olhos requereram TLS repetida; odds ratio 3-37 [95% CI 1·96-5·80]; p<0·0001). Eventos adversos (na sua maioria não relacionados com eventos oculares) ocorreram em dez (10%) participantes do grupo timolol e em oito (8%) participantes do grupo TLS (p=0·61).

**Interpretação**

O TLS apresentou resultados superiores às gotas oftálmicas de timolol na gestão de pacientes com glaucoma de alta pressão de ângulo aberto durante 1 ano na Tanzânia. O TLS pode potencialmente transformar a gestão do glaucoma na África subsaariana, mesmo em locais onde a prevalência de glaucoma avançado é elevada.



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# Supplementary appendix 4

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Philippin H, Matayan E, Knoll KM, et al. Selective laser trabeculoplasty versus 0·5% timolol eye drops for the treatment of glaucoma in Tanzania: a randomised controlled trial. *Lancet Glob Health* 2021; published online Oct 13. http://dx.doi.org/10.1016/S2214-109X(21)00348-X.

# Selective laser trabeculoplasty versus 0·5% timolol eye drops for the treatment of glaucoma in Tanzania: a randomised controlled trial

*Kilimanjaro Glaucoma Intervention Programme (KiGIP) – SLT trial*

## Supplementary appendix


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# Exclusion Criteria

Table A1: List of exclusion criteria

| List of exclusion criteria |
| --- |
| **Related to the eyes of the participant** |
| • Opaque cornea or anterior chamber which inhibits to visualise the chamber angle or to do SLT<br>• Narrow or closed chamber angle (less than Shaffer II in two out of four quadrants)<br>• No perception of light<br>• History of previous glaucoma surgery including other laser treatments<br>• History of previous uveitis<br>• Neovascular glaucoma<br>• Traumatic glaucoma<br>• Corneal irregularities affecting tonometry (e.g. advanced pterygium, astigmatism > 3dpt)<br>• Pseudophakic patients will be excluded if the chamber angle is blocked or the anterior segment shows signs of inflammation. |
| **Related to the participant** |
| • Inability to provide informed consent<br>• Unwillingness to return for regular follow-up visits (baseline + 4 follow-up visits, patients should come preferably from Arusha or Kilimanjaro Regions)<br>• Physical inability to administer topical treatment<br>• Age below 18 years.<br>• Pregnant women<br>• History of asthma, bradycardia, previous heart failure, hypersensitivity to beta-blockers |

# Screening Results

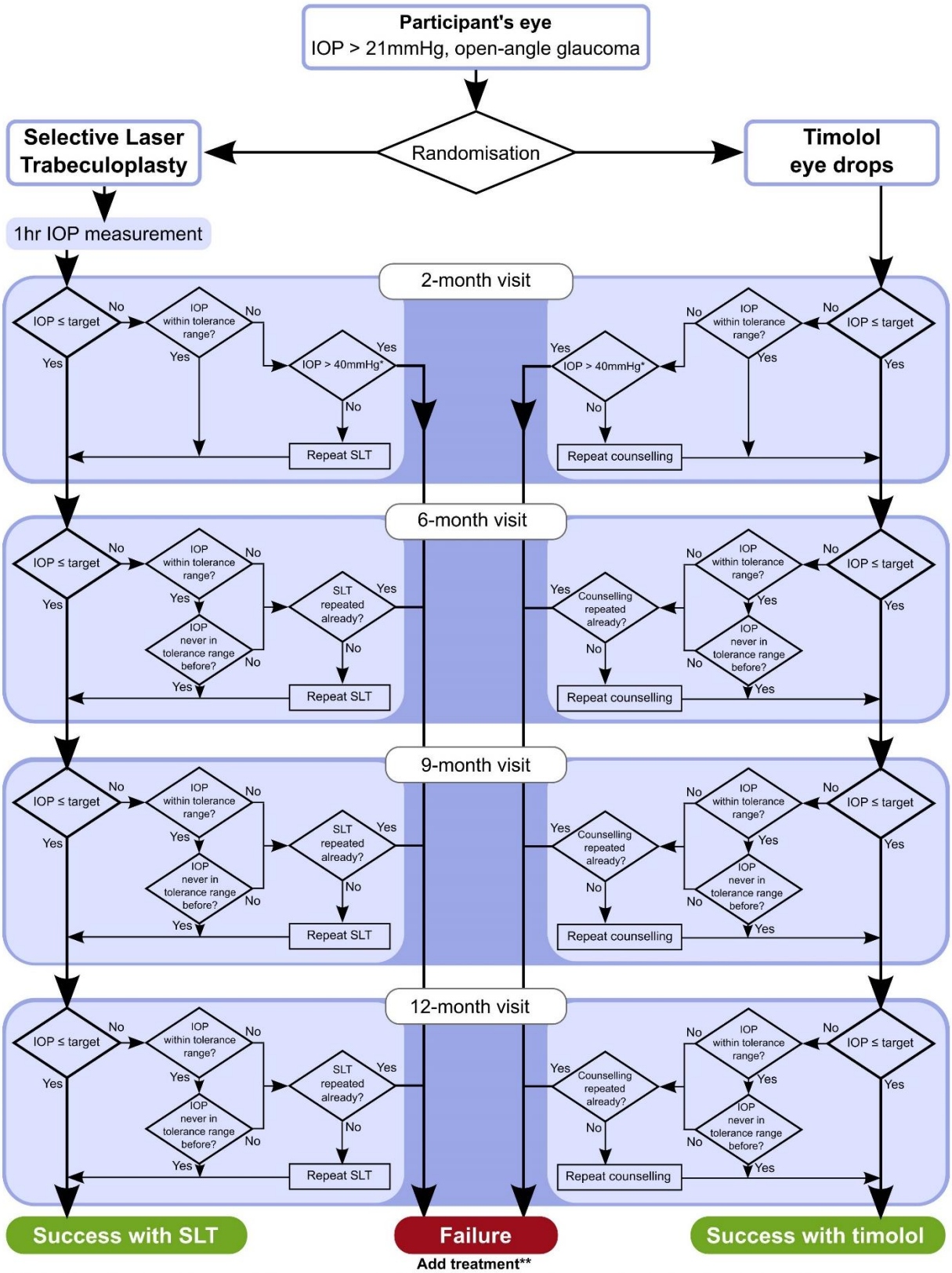
Table A2: Examination findings of all 840 patients with glaucoma screened for inclusion in this trial

| | | Total N=840 |
|---|---|---|
| Age | Mean (SD) | 65·28 (14·65) |
| Sex | Female | 351 (41·8%) |
| | Male | 489 (58·2%) |
| Detailed screening results | Enrolled in trial | 201 (23·9%) |
| | Had cyclophotocoagulation | 22 (2·6%) |
| | Had selective laser trabeculoplasty | 33 (3·9%) |
| | Had trabeculectomy | 103 (12·3%) |
| | Had other glaucoma surgery | 2 (0·2%) |
| | Secondary glaucoma | 102 (12·1%) |
| | IOP ≤ 21mmHg | 110 (13·1%) |
| | Ocular hypertension | 8 (1·0%) |
| | Needs immediate surgery (e.g. trabeculectomy) | 64 (7·6%) |
| | Narrow angle | 10 (1·2%) |
| | Opaque cornea | 19 (2·3%) |
| | Dense cataract | 13 (1·5%) |
| | No perception of light | 101 (12·0%) |
| | Has asthma | 9 (1·1%) |
| | Didn't return for enrolment | 8 (1·0%) |
| | Unable to return for regular follow-up | 21 (2·5%) |
| | Refused to participate | 13 (1·5%) |
| | Deceased before enrolment | 1 (0·1%) |

Data are presented as mean (SD) for continuous measures, and n (%) for categorical measures.

# Treatment Algorithm

Figure A1: Treatment decision algorithm at follow-up examinations




* IOP > 40mmHg at any follow-up visit is an immediate failure. For simplicity, the respective decision is only shown for the 2-month visit.
**Additional treatment will not be part of the trial and will be given according to clinical judgement of the treating ophthalmologist. However, standard additional treatment in the timolol group will be SLT and vice versa. Other addtional treatment options include latanoprost eye drops and trabeculectomy among others.

# Intraocular Pressure Results

Table A3: Absolute IOP and relative IOP reductions at baseline, 2-month visit and study exit

| | Timolol | | SLT | | All | |
|---|---|---|---|---|---|---|
| **Visit** | **n** | **mean (sd) / Δ (sd)** | **n** | **mean (sd) / Δ (sd)** | **n** | **mean (sd) / Δ (sd)** |
| Baseline | 191 | 27·0 (7·5) | 191 | 26·4 (6·3) | 382 | 26·7 (6·9) |
| 2-month | 182 | 23·6 (7·4) /-3·2 (7·5) | 181 | 20·0 (5·5) /-6·3 (6·1) | 363 | 21·8 (6·8) /-4·7 (7·0) |
| Study exit | 191 | 25·4 (7·8) /-1·5 (7·5) | 191 | 20·1 (5·1) /-6·3 (6·4) | 382 | 22·8 (7·1) /-3·9 (7·4) |
| Failure | 121 | 28·5 (7·5) /-0·7 (8·9) | 64 | 23·9 (4·6) /-5·5 (7·2) | 185 | 26·9 (7·0) /-2·4 (8·6) |
| Loss to FU | 15 | 25·5 (6·9) /-1·7 (2·7) | 28 | 21·5 (6·5) /-3·1 (4·5) | 43 | 22·9 (6·9) /-2·6 (4·0) |
| Success | 55 | 18·6 (3·0) /-3·3 (4·1) | 99 | 17·3 (2·7) /-7·7 (6·0) | 154 | 17·8 (2·9) /-6·1 (5·8) |

IOP - Intraocular pressure measurements (mmHg) at baseline and differences relative to baseline measurements at 2-month visits, failure visits, visits prior to loss to follow up or success visits at 1 year. Δ - delta or difference; SLT=selective laser trabeculoplasty; sd=standard deviation; FU=follow-up.

Table A4: Changes of intraocular pressure (%)

| | Timolol | | SLT | | All | |
|---|---|---|---|---|---|---|
| **Visit** | **n** | **mean (sd) %** | **n** | **mean (sd)** | **n** | **mean % (sd)** |
| 2-month | 182 | -9·2 (25·4) | 181 | -22·0 (18·8) | 363 | -15·6 (23·2) |
| Study exit | 191 | -2·8 (30·6) | 191 | -21·4 (20·0) | 382 | -12·1 (27·4) |
| Failure | 121 | 2·6 (35·5) | 64 | -15·4 (20·8) | 185 | -3·6 (32·3) |
| Loss to FU | 15 | -6·2 (9·9) | 28 | -12·2 (17·1) | 43 | -10·1 (15·1) |
| Success | 55 | -13·6 (16·8) | 99 | -27·8 (18·0) | 154 | -22·7 (18·8) |

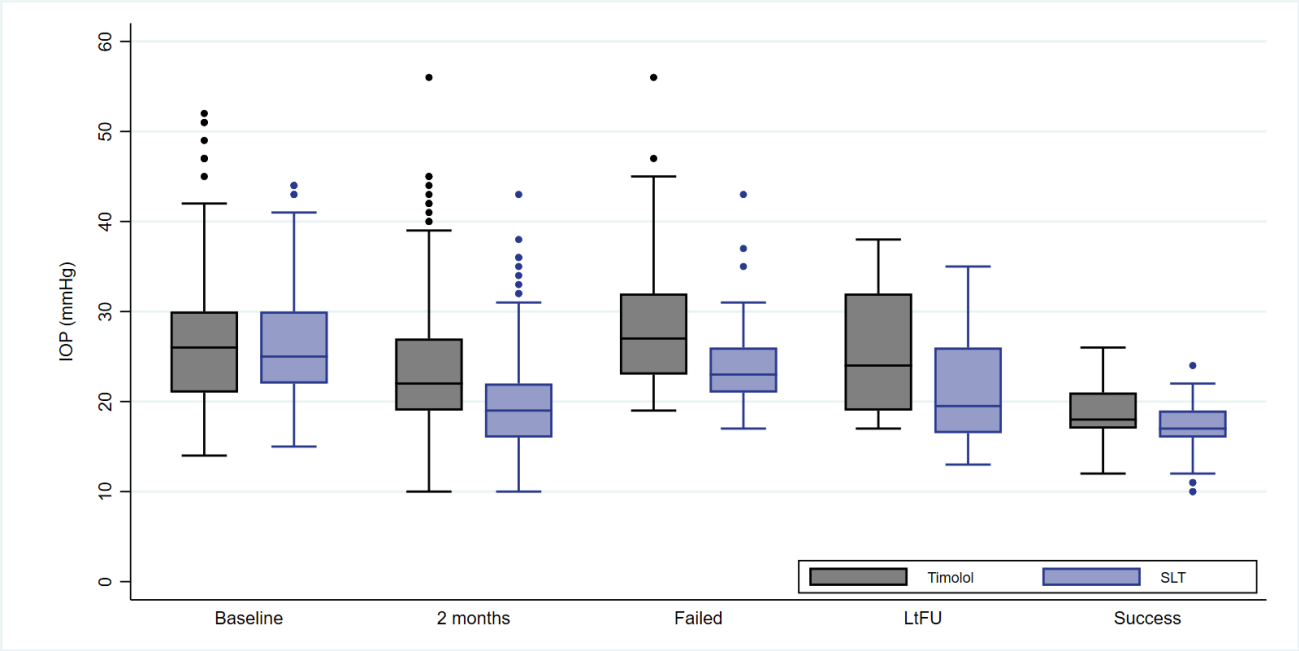
Changes of intraocular pressure (%) relative to baseline measurements at 2-month visits; failure visits, visits prior to loss to follow up or success visits at 1 year. SLT=selective laser trabeculoplasty, sd=standard deviation, FU=follow-up.

Table A5: Intraocular pressure results at follow-up visits

| | Timolol | | SLT | | All | |
|---|---|---|---|---|---|---|
| **Visit** | **n** | **mean (sd)** | **n** | **mean (sd)** | **n** | **mean (sd)** |
| Baseline | 191 | 27·0 (7·5) | 191 | 26·4 (6·3) | 382 | 26·7 (6·9) |
| 2-month | 182 | 23·6 (7·4) | 181 | 20·0 (5·5) | 363 | 21·8 (6·8) |
| 6-month | 170 | 23·6 (7·1) | 174 | 20·5 (4·4) | 344 | 22·0 (6·1) |
| 9-month | 96 | 21·1 (3·8) | 134 | 18·8 (3·5) | 230 | 19·8 (3·8) |
| 12-month | 71 | 19·8 (4·0) | 113 | 17·7 (2·9) | 184 | 18·5 (3·5) |

Intraocular pressure measurements of eyes (mmHg) at baseline and 2-month, 6-month, 9-month and 12-month visits including the respective study exit visit (failure, last visit before loss to follow-up or success at 12 months). SLT=selective laser trabeculoplasty, sd=standard deviation.

Figure A2: Boxplots of intraocular pressure results




Boxplots of intraocular pressure measurements of the two treatment arms at baseline, 2-month, failure, before loss to follow-up, and success (at 12 months) visits. A box shows median, upper, and lower quartiles. Whiskers represent scores outside the middle 50%. Outliers are presented as individual dots. LtFU - loss to follow-up.

# Predicted Probabilities of Success

Table A6: Predicted probabilities of success from the most parsimonious multivariable model

| Explanatory variables and levels | | | Timolol | | | SLT | | |
|---|---|---|---|---|---|---|---|---|
| | | | Eyes n | Probability of success (95% CI) | p-value | Eyes n | Probability of success (95% CI) | p-value |
| Stage of glaucoma | IOP at baseline | XFG | | | | | | |
| Moderate | <25 | No | 41 | 0·72 (0·61, 0·84) | <0·001 | 44 | 0·93 (0·89, 0·98) | <0·001 |
| | | Yes | 3 | 0·29 (0·05, 0·53) | 0·016 | 3 | 0·69 (0·44, 0·93) | <0·001 |
| | ≥25 | No | 23 | 0·47 (0·32, 0·62) | <0·001 | 23 | 0·82 (0·73, 0·92) | <0·001 |
| | | Yes | 4 | 0·12 (0·00, 0·24) | 0·053 | 4 | 0·42 (0·15, 0·69) | 0·002 |
| Advanced | <25 | No | 28 | 0·22 (0·11, 0·33) | <0·001 | 27 | 0·61 (0·46, 0·75) | <0·001 |
| | | Yes | 5 | 0·04 (0·00, 0·09) | 0·106 | 2 | 0·19 (0·01, 0·38) | 0·039 |
| | ≥25 | No | 62 | 0·09 (0·04, 0·14) | 0·001 | 49 | 0·34 (0·22, 0·46) | <0·001 |
| | | Yes | 10 | 0·01 (0·00, 0·03) | 0·114 | 11 | 0·07 (0·00, 0·15) | 0·059 |

Predicted probabilities of success derived from the most parsimonious multivariable model. XFG=exfoliation glaucoma. IOP=intraocular pressure, SLT=selective laser trabeculoplasty.

The probabilities of success as derived from the odds ratios of the multivariable model (see table 2 in the main manuscript) are shown in table A6. For example, eyes treated with SLT which had moderate glaucoma, a baseline IOP <25mmHg, and no exfoliation glaucoma had a higher probability of success (0·93, 95% CI 0·89-0·98, p<0.001) than eyes in the SLT arm affected by advanced glaucoma, a baseline IOP <25mmHg, and no exfoliation glaucoma (probability for success 0·61, 95% CI 0·46-0·75, p<0.001).

# Interaction Plots

Figure A3: Interaction plot for intervention and stage of glaucoma

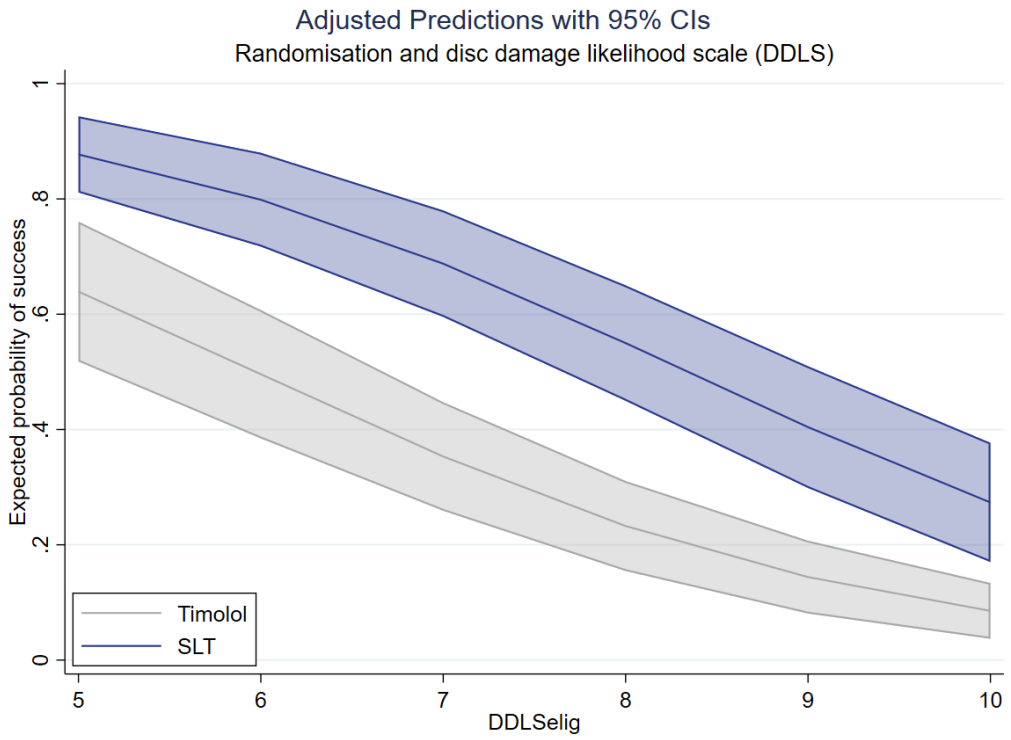
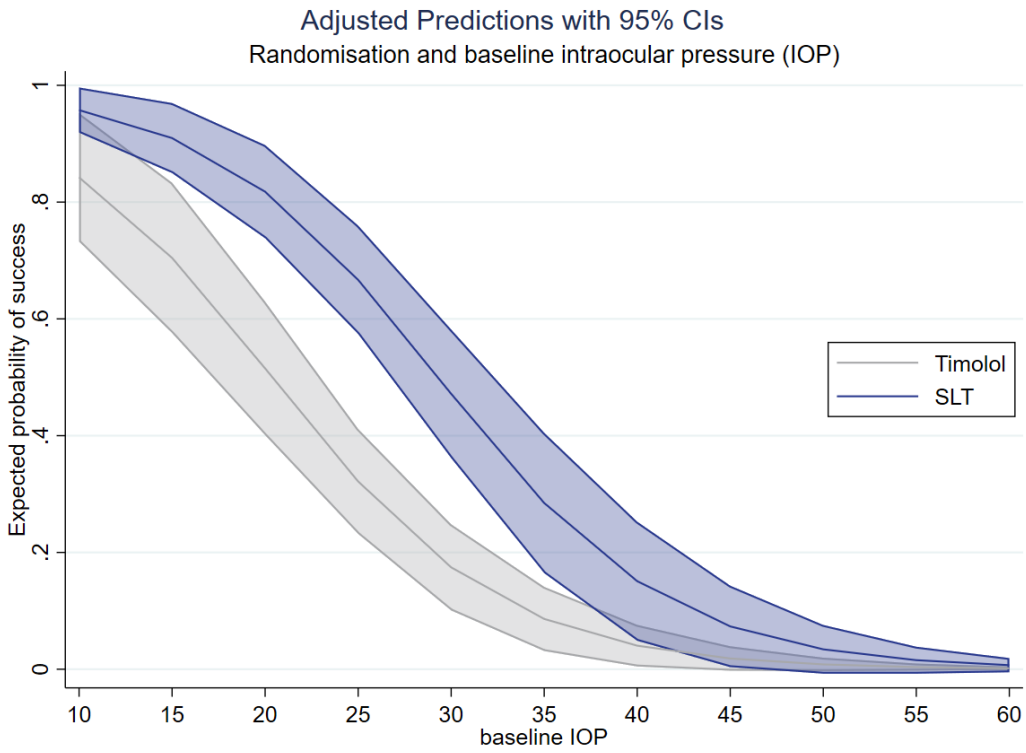



Figure A4: Interaction plot for intervention and baseline intraocular pressure



# SLT Procedures: Transient Events

Table A7: Transient events during and shortly after SLT procedures

| Transient event | | Baseline SLT N=191 | Repeat SLT N=104 |
|---|---|---|---|
| Pain during SLT procedure* | no pain | 69 (36·7%) | 44 (44·0%) |
| | mild pain | 103 (54·8%) | 50 (50·0%) |
| | moderate pain | 15 (8·0%) | 6 (6·0%) |
| | severe pain | 1 (0·5%) | 0 (0%) |
| Cells in anterior chamber* | 0·5+ (1-5) | 49 (26·2%) | 39 (38·6%) |
| | 1+ (6-15) | 129 (69·0%) | 61 (60·4%) |
| | 2+ (16-25) | 9 (4·8%) | 1(1·0%) |
| Endothelial changes** | No | 114 (59·7%) | 60 (58·3%) |
| | Translucent nummuli | 77 (40·3%) | 43 (41·7%) |
| IOP spike >5mmHg*** | No | 188 (100·0%) | 99 (98·0%) |
| | Yes | 0 (0·0%) | 2 (2·0%) |

Transient events during and after SLT procedures (within 1 hour), unit of reporting are eyes. Data are presented as n (%). Data missing for *seven eyes, **one eye, and ***six eyes. SLT=selective laser trabeculoplasty, IOP=intraocular pressure.

# Cost Analysis

*Offering SLT treatment – the eye care provider's perspective*

Table A8: Assumptions, sources and measured parameters. All costs are reported in US Dollars

| **Assumptions and measurements** | | | |
|---|---|---|---|
| *Item* | *Amount* | *Unit* | *Source* |
| Monthly ophthalmologist's salary | 1600 | $ | Serje et al [1] |
| Working hours per month | 160 | hours | Gazzard et al [2] |
| SLT procedures done per hour (including preparations) | 5 | 1/h | Data collected during trial |
| Price of brimonidine 0.2% eye drops (one bottle of 5ml) | 5 | $ | KCMC Eye Department |
| Price of prednisolone 1% eye drops (one bottle of 5ml) | 3 | $ | KCMC Eye Department |
| Price of amethocaine eye drops (one bottle of 5ml) | 3 | $ | KCMC Eye Department |
| Number of eye drops in a 5ml bottle (approx.) | 100 | drops | Data collected during trial |
| No of preop. eye drops per SLT treatment (approx.) | 4 | drops | Data collected during trial |
| Annual rent (shared) and other fixed cost | 700 | $ | Assumption |
| Maximum power consumption of SLT laser per hour | 0·24 | kWh | Operator manual [3] |
| Cost of 1 kWh | 0·2 | $ | Assumption |
| Price of laser including contact glass and shipping | 36000 | $ | CBM UK Finance Dept |
| Uninterruptible power supply (UPS), two replacement batteries | 1200 | $ | Assumption |
| Lifespan of SLT laser | 10 | years | Gazzard et al [2] |
| Maintenance annual cost | 300 | $ | Assumption |
| Repair cost including shipping of SLT laser | 1500 | $ | Assumption |
| Maintenance interval[2] | 1 | year | Operator manual |

We assumed that a sub-contracted local technician does the annual maintenance and for repairs the laser would need to be sent abroad. We assumed two repairs to be necessary during the expected life span of the SLT laser device of 10 years. Tanzanian Shilling (TZS) were converted to US$ using an average rate of 2,200 for the years 2015-2018. Duration of SLT treatment, average number of drops in an eye drop bottle and other parameters were determined as part of the study.

Table A9: Calculated cost items

| | **A) Variable cost per procedure** | |
|---|---|---|
| *Item* | *Calculation* | *Cost (US$)* |
| Ophthalmologist's time | =($1600/ 160 hours) / 5 procedures per hour | 2·0 |
| Brimonidine eye drops | =($5 per bottle / 100 drops) * 4 drops | 0·2 |
| Prednisolone eye drops | =($3 per bottle / 100 drops) * 4 drops | 0·12 |
| Amethocaine eye drops | =($3 per bottle / 100 drops) * 8 drops | 0·24 |
| Power | =(240/1000 kWh * $0·2) / 5 procedures per hour | 0·01 |
| | **Total** | **2·57** |

| | **B) Fixed annual cost** | |
|---|---|---|
| *Item* | *Calculation* | *Cost (US$)* |
| SLT laser depreciation | =$36000 / 10 years | 3,600 |
| SLT laser maintenance | =$300 * 8 / 10 years | 240 |
| SLT laser repair | =$ 1500 *2 / 10 years | 300 |
| UPS | =$ 1200 / 10 years | 120 |
| Other (rent etc.) | =$ 700 | 700 |
| | **Total** | **4,960** |

Table A10: Total cost of a single SLT laser treatment for eight different hypothetical scenarios.

| | Hypothetical annual number of treatments (n) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 300 | 400 | 500 | 600 | 700 | 800 | 900 | 1000 |
| Variable cost (US$) | 2·57 | 2·57 | 2·57 | 2·57 | 2·57 | 2·57 | 2·57 | 2·57 |
| Fixed cost (US$) | 16·53 | 12·40 | 9·92 | 8·27 | 7·09 | 6·20 | 5·51 | 4·96 |
| **Total cost per treatment (US$)** | **19·10** | **14·97** | **12·49** | **10·84** | **9·66** | **8·77** | **8·08** | **7·53** |

Fixed cost per treatment calculated as total fixed annual cost/number of hypothetical annual treatments = 4,960/n US$.

### *Annual treatment cost for patients or health insurance companies*

A) Timolol eye drops

The price per bottle of timolol (5ml) in Tanzania is approximately US$1·36. With 12 bottles per eye per year, the annual treatment cost amount to US$16·32. The cost of a 5ml timolol eye drop bottle was determined using the median of 3 prices at pharmacies across Tanzania in 2019.

B) SLT laser procedure

Assuming a hypothetical quantity of 500 eyes treated per year, the cost of a single SLT treatment is US$ 12·49 (table A4). According to this trial, an average of 1·33 SLT treatments is required for an eye to achieve successful IOP reduction. The resulting average treatment cost per year and per eye would be US$ 16·61 which is comparable to a supply of timolol eye drops for one year.

## Affordability of Timolol Eye Drops and SLT Laser Procedure

Affordability describes whether a person has sufficient income to pay for health care services (or treatment costs). [4] It can be estimated using the average annual income of a person in need for treatment and an affordability threshold in relation to the cost of the treatment.[5,6]

We used the annual gross domestic product per capita as a surrogate for income and an affordability threshold of 2·5%.[5,6] The annual GDP per capita in Tanzania in 2019 was reported as US$1,122.12, so any annual treatment cost below US$28.05 should be considered affordable.[7]

Thus, the annual treatment cost of timolol and SLT for one eye are below this threshold (assuming 500 procedures per year in an eye health unit). For SLT, the treatment costs for two eyes can also be considered affordable for the majority of patients as 66/99 eyes (67%) only required one treatment to achieve a successful outcome (annual treatment cost for two eyes of US$24.98).

# Counselling of Patients Who Receive Timolol Eye Drops

## *Purpose*

This standard Operating Procedure) specifies the counselling of patients who are assigned to the conservative treatment arm with Timolol eye drops.

Adherence to topical treatment plays a pivotal role for the conservative management of glaucoma. Explaining the necessity of treatment and other means of motivation of patients can considerably improve adherence.[8,9]

## *Procedure*

### *Overall Instructions*

The talk will take place in a quiet environment and performed by a native Swahili speaker

### *Content*

- Enquire about the level of knowledge and attitude
    - What do you know about your disease?
    - Which experience with any medical treatment do you have already? If any, what are the challenges for you (Cost? Side effects? Application? Understanding of mechanism?)
    - What are your concerns related to glaucoma and its treatment?
- Emphasize that treatment helps to prevent (further) loss of sight
- Mention known side effects of timolol eye drops: reduced libido, stinging, bradycardia, trouble breathing
- Explain application technique of eye drops or confirm who will apply eye drops (see below)

*How to use and instil your own eye drops*

1) How to open your eye drop bottle. ***Jinsi ya kufungua chupa yako ya matone ya macho.***

- Tight your bottle cap to the maximum end. ***Kaza chupa yako yenye matone mpaka mwisho kabisa.***
- Open and gently try to squeeze out a drop to see of the cap has punched a hole into the bottle tip. ***Taratibu fungua ili uone kama kifuniko kimetengeneza tundu kwenye mdomo wa chupa.***
- Use the same eye drop bottle for about one month before opening another one (in case you were given several bottles). ***Tumia chupa hiyo hiyo ya matone kwa kadri ya mwezi mmoja kabla ya kufungua nyingine. (ikiwa unazo chupa za ziada)***

2) How to instil your own eye drops **Jinsi ya kuweka matone kwenye macho yako.**

- Combine drop application time with your daily routine activities **Ambatanisha uwekaji wa matone na shughuli zako za kila siku, mfano; Kabla ya chai au chakula cha jioni**
- Sit or lie down with your head supported. As your skill develops you may eventually manage to instil your eye drops while standing. **Keti au lala na egemeza kichwa, kadri unavyotumia utazoea kuweka matone ukiwa umesimama.**
- Use your dominant hand to hold the bottle. **Shika chupa kwa mkono unaoutumia (kushoto au kulia)**
- With the index finger of your other hand, hold a clean piece of tissue or cotton wool (if available), and gently pull down the lower eyelid to form a 'pocket'. **Tumia kidole cha shahada kwa mkono mwingine na kitambaa kisafi,tishu au pamba kufungua jicho kwa chini**
- Hold the bottle between your thumb and forefinger, and place the 'heel' of your hand (where the wrist meets the hand) on your cheek. This will help to steady shaky hands. **Shika chupa yako kwa dole gumba na shahada, egemeza mkono juu ya uso kuzulia usitikisike.**
- Make sure there is a short distance of about an inch (2.5cm, the width of two fingers) between your eye and the end of the bottle. Be careful – the tip must not touch any part of the eye or eyelids. **Hakikisha unaacha nafasi kama inchi 2.5 kati ya vidole na uso na chupa ili usigusishe chupa yenye dawa na jicho lako au kope zako.**
- Look up or to the side. Do not look directly at the bottle. **Angalia juu au pembeni. Usiangalie chupa yenye matone.**
- Squeeze the bottle – allow one drop to fall into the lid pocket. **Binya chupa – hakikisha tone moja linaingia kwenye jicho ulilolifungua kwa kitambaa safi, tishu au pamba**
- Slowly let go of the lower lid. Gently close your eyes; try not to shut them tightly as this will squeeze the drop out of your eye. **Taratibu acha tone lisambae ndani ya jicho, funga jicho taratibu, usikaze jicho ili dawa isitoke nje.**
- Dab your closed eye with the tissue or cotton wool to remove any excess. **Ukiwa umefumba macho yako futa matone au machozi yaliyomwagika nje au pembeni ya macho kwa kitambaa safi, tishu au pamba**
- Put gentle pressure on the inside corner of your eye and count to 60, very slowly. This prevents the medicine from draining out of your eye before it is absorbed. **Kandamiza upande wa macho yako karibu na pua kwa dakika 1 au 2 ili kuzuia dawa kushuka kwenye koo lako na kubaki kwenye macho yako.**

(adapted from *Instilling your own eye drops.* Community Eye Health Journal. 2012; **79 & 80**: 79)

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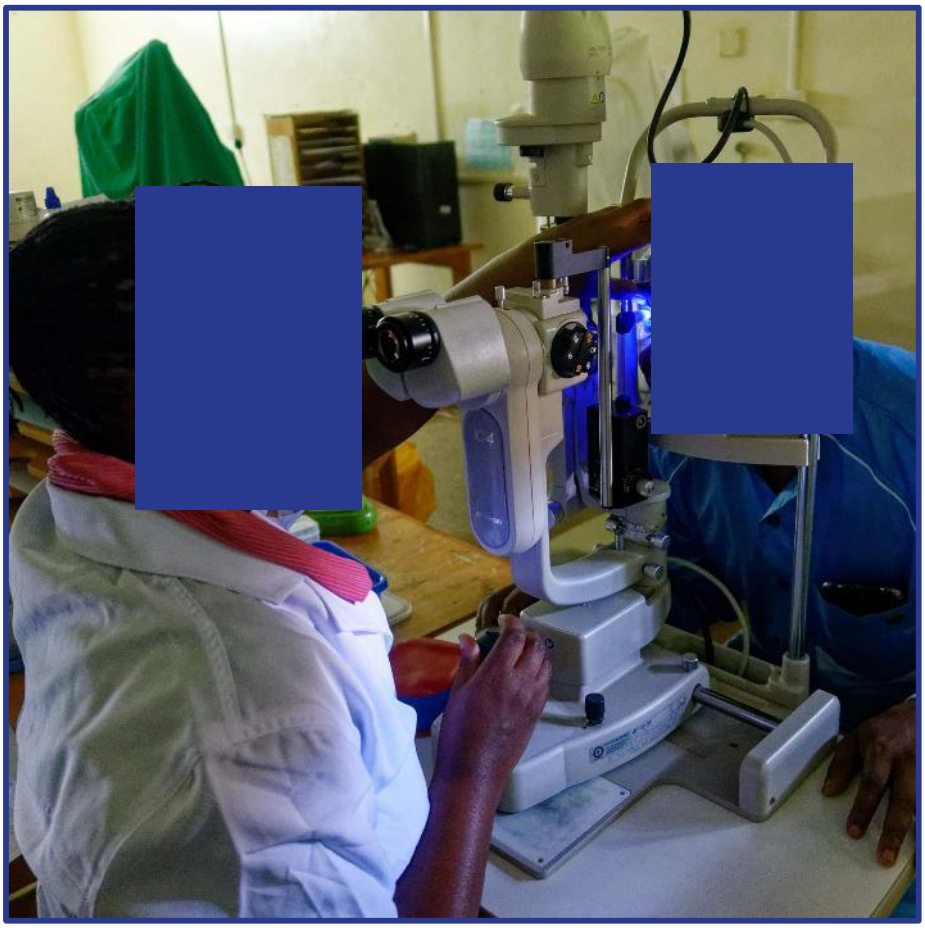
# 6 Intraocular pressure responses after primary and repeat selective laser trabeculoplasty in Tanzania



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| **Principal Supervisor** | Matthew Burton |
| **Thesis Title** | Selective laser trabeculoplasty versus 0.5% timolol eye drops for the treatment of glaucoma in Tanzania: a randomised controlled trial |

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Literature research, trial design, data collection, data verification, statistical analysis, interpretation of results, writing first draft and review of manuscript.

**Student Signature:** [redacted] **Date:** April 15, 2022

**Supervisor Signature:** [redacted] **Date:** 23/04/2022

# Intraocular pressure responses after primary and repeat selective laser trabeculoplasty in Tanzania

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# Abstract

**Background**

Selective laser trabeculoplasty (SLT) has been shown to effectively reduce intraocular pressure (IOP). We investigated the associations of IOP responses after primary and repeat SLT, between treated fellow eyes and predictors of IOP reduction after SLT.

**Methods**

Post hoc analysis of the SLT group of a two arm, single masked, randomised controlled trial comparing SLT and 0.5% timolol eye drops at the eye department of Kilimanjaro Christian Medical Centre, Moshi, Tanzania. Patients received SLT at baseline, in some this was repeated following an IOP threshold algorithm. Main outcomes were early IOP changes after 2 or 3 months respectively with a response defined as an IOP reduction of 2mmHg or more. We compared responses in different groups using Pearson's chi-squared test, and linear regression models with generalised estimating equations to examine associations between predictors and absolute IOP changes with the eye as the unit of analysis.

**Results**

We enrolled 201 participants (382 eyes), mean baseline IOP 26.7 (SD 6.9) mmHg, 162 eyes had moderate (DDLS 5-7), and 220 eyes had advanced (DDLS 8-10) glaucoma. We randomised 191 eyes to primary SLT, and re-examined 181/191 eyes after 2 months; 146 (81%) showed an IOP response and 35 (19%) had no response after primary SLT. Among non-responders, 70% responsed and 30% showed no response after repeat SLT (p=0.872). SLT treatment response was correlated between eyes: primary SLT in 85 pairs, chi-squared=18.07 (p<0.001), after repeat SLT in 47 pairs 3.68 (p=0.055). The most parsimonious model of absolute IOP reduction after primary SLT included age <70 years, no timolol eye drops before enrolment, IOP ≥25mmHg and a minimum height of the trabecular meshwork of >1/2 of the laser spot size as predictors, and only IOP ≥25mmHg for the model after repeat SLT.

**Discussion**

These findings support repeat SLT including after a primary SLT with no IOP response. Responses in fellow eyes were correlated and a high IOP prior to the SLT procedures was the strongest predictor of absolute IOP-lowering which may be helpful in treatment planning including in eyes with advanced glaucoma.

# Introduction

Lowering intraocular pressure (IOP) is currently the main glaucoma treatment approach and remains the only proven intervention to prevent irreversible vision loss.[1–3] The glaucomas are the most common cause of irreversible blindness worldwide, with the highest prevalence of blindness due to glaucoma found in the Africa region.[4] The continent also has the highest prevalence of glaucoma, which is estimated to be 4.8%.[5] Most glaucoma treatments in Africa is based on eye drops or incisional surgery. However, high long-term costs, patchy availability, erratic adherence, and side-effects limit the feasibility of eye drops.[6,7] Incisional surgery has shown good IOP lowering results in Africa. However, low acceptance rates in some populations, insufficient numbers of well trained eye surgeons and the risk of complications are reducing coverage rates.[7,8]

The third treatment approach to lowering IOP using laser therapies has been explored in only a few studies across Africa. Several laser treatments have been tried with promising IOP lowering results and few complications, including selective laser trabeculoplasty (SLT).[9–12] SLT was based on studies by Latina and Park in 1995 on selectively targeting pigmented trabecular meshwork cells without producing collateral damage to adjacent non-pigmented cells or structures.[13]

The Kilimanjaro Glaucoma Intervention Programme (KiGIP) SLT trial was the first randomised controlled trial in Africa comparing selective laser trabeculoplasty with timolol 0.5% eye drops for patients with open-angle glaucoma. Using eye-specific target IOPs as success criteria, the estimated odds for success after one year were 3.37 times higher in the SLT group than the odds for success using timolol 0.5% eye drops. A repeat SLT was permitted following predefined criteria.[14] Enrolled participants mostly had advanced glaucoma, which reflects the typical stage at presentation in this region, and about which there is less evidence compared to earlier disease stages. The purpose of this subsidiary report from the KiGIP SLT trial was to investigate responses after the primary and repeat SLT procedures as well as the response in the fellow eye. We also report associations between predictive factors and the absolute IOP change following SLT treatment.

# Methods

## Study design

We conducted a two-arm, parallel-group, single-masked randomised controlled trial at the Eye Department of Kilimanjaro Christian Medical Centre (KCMC), Moshi, Tanzania. A patient steering group gave input and feedback on the study methods. An independent data and safety monitoring board was appointed by the trial steering committee. Ethical approval was obtained from the research ethics review committees of the National Institute for Medical Research in Dar es Salaam, Tanzania (NIMR/HQ/R.8a/Vol IX/1929), the Kilimanjaro Christian Medical University College in Moshi, Tanzania (number 800), and the London School of Hygiene & Tropical Medicine in London, UK (LSHTM Ethics Ref 7166). The KiGIP SLT trial was conducted in accordance with Good Clinical Practice guidelines and adhered to the tenets of the Declaration of Helsinki. It was registered with the Pan African Clinical Trials Registry (PACTR201508001235339). This subsidiary study was a post hoc analysis of the KiGIP SLT trial, the design, primary and most secondary outcomes at 1 year have been described.[14]

## Participants

The main inclusion criteria were open-angle glaucoma with an increased IOP >21mmHg and a combination of structural changes (≥5 on Disc Damage Likelihood Scale (DDLS) or cup/disc ratio ≥0.7 or cup/disc ratio asymmetry between two eyes ≥0.2) and functional changes (glaucomatous visual field defect). High-risk glaucoma suspects or high-risk ocular hypertension were also permitted. Eye related exclusion criteria included a narrow chamber angle (<Shaffer grade II in two quadrants), an opaque cornea, no perception of light, previous glaucoma surgery or laser treatment, previous uveitis, neovascular, or traumatic glaucoma. Patient related exclusion criteria included an age <18 years, history of bradycardia or asthma. The purpose and details of the trial were explained to eligible patients in Kiswahili. and they were invited for the baseline examination on a separate day. Potential participants who self-reported using eye drops or tablets to lower IOP underwent a four-week washout period beginning on the day they self-reported last using eye drops or tablets.

## Trial flow and treatment decisions

The trial team obtained written informed consent during the baseline assessment. Intraocular pressures were measured following a standard operating procedure which included two measurements within 5 minutes using a calibrated Goldmann Applanation Tonometer (Haag Streit, Koeniz, Switzerland). The mean IOP was recorded in case of a difference ≤2mmHg between the first two measurements. If the difference was >2mmHg, a third measurement was obtained and the

median was noted.[15] The repeatability coefficient of Goldmann Tonometry was described by Tonnu et al. as approximately 2.5 mm Hg.[16] The baseline examination also included a detailed history and slitlamp examination, a static visual field and pachymetry. More details are described elsewhere.[14] Patients were then randomised to timolol 0.5% eye drops or selective laser trabeculoplasty (1:1), with both eyes receiving identical treatment when enrolled. The respective treatment was repeated if an eye-specific IOP threshold was exceeded. The IOP threshold was determined by the level of glaucomatous optic nerve head damage (Disc Damage Likelihood Scale results) with 21mmHg for eyes with moderate (DDLS 5-7) and 18mmHg for eyes with advanced glaucomatous changes (DDLS 8-10). If the threshold was exceeded for the second time, it was considered a treatment failure and the eye was exited from the trial and received additional treatment. In addition, if the IOP was >40mmHg at any follow-up visit, the eye was exited from the trial immediately. Furthermore, one IOP measurement of up to 2mmg above threshold IOP was allowed on a single follow-up visit without triggering a decision to reflect the repeatability coefficient of Goldmann tonometry[16] and clinical practice which usually includes a repeat measurement before a treatment decision is made. Follow-up visits were scheduled after 2, 6, 9, and 12 months and included history, a slit-lamp examination with IOP measurement following the same protocol as described above. Clinicians who examined IOP were masked to the treatment group of a patient, the IOP threshold and previous IOP measurements of the individual eye, and were not involved in any other aspects of the trial.

## Selective Laser Trabeculoplasty

About 15 minutes prior to the selective laser trabeculoplasty, eyes received amethocaine for topical anaesthesia, 0.2% brimonidine eye drops for IOP spike prevention, and topical 1.0% prednisolone to reduce the inflammatory response. A Latina goniolens visualised the chamber angle. Covering 360° of the trabecular meshwork, approximately 100 laser spots were applied with the SLT laser (Lumenis Selecta II Lumenis, Yokneam, Israel) by one ophthalmologist (HP). He was trained in the procedure at University Hospitals Birmingham by PS and had completed around 100 SLT procedures before starting the trial. Energy level was started at 0.6mJ and continuously titrated in steps of 0.1mJ up or down until cavitation bubbles appeared in about every third laser spot application. The height of the trabecular meshwork was estimated in relation to the laser spot diameter of 400µm starting from the 84$^{th}$ enrolled patient as new descriptor. About one hour after the procedure the eye was examined including an IOP measurement.

## Outcomes

For the purpose of this post hoc analysis, we reported the absolute IOP values at the time of the primary or repeat SLT, at the first follow-up visit afterwards (2-month or 3-month visit), and the difference of the two measurements. A dichotomous response variable was defined as an intraocular pressure reduction of 2mmHg or more and no response as a reduction of less than 2 mmHg following the repeatability coefficient of Tonnu et al.[16]

## Statistical methods

The unit of analysis was the eye. Means and standard deviation were calculated for absolute IOPs before and after the interventions as well as their difference. Eyes which responded to the SLT treatment were compared to eyes which did not respond using Pearson's chi-squared test. The test was also used to compare responses after the primary and repeat SLT procedures in the same eye. The association between different descriptors and the outcome variable absolute change in IOP was analysed by using linear regression models with generalised estimating equations to consider correlation between the two eyes of a participant. Unadjusted models provided a raw result of an association. The fully adjusted analysis included initially all predictors with $p<0.2$ and backward stepwise selection identified the most parsimonious model.

## Results

The 201 participants (382 eyes) who were enrolled in the study had a mean age of 66.3 (SD 11.6) years and 83 (41%) participants were female. Mean baseline IOP was 26.7 (SD 6.9) mmHg, 162 eyes had moderate (DDLS 5-7), and 220 eyes advanced (DDLS 8-10) glaucoma. 101 participants (50%; 191 eyes) were randomly assigned to the SLT treatment group, all of whom received the initial SLT treatment (table 1).

We examined 181 eyes of 96 people randomised to SLT at the 2-month follow-up visit; 5 patients (10 eyes) were lost to follow-up. Out of the 181 examined eyes, 146 eyes (81%) showed an IOP reduction of at least 2mmHg and 35 eyes (19%) showed no IOP reduction response (Figure 1). Following the KiGIP trial treatment escalation algorithm, 104 eyes exceeded the individual IOP threshold and required repeat SLT at one of the follow-up visits, and 102 of these eyes were followed up at the immediate visit. One patient (2 eyes) moved away and was lost to follow-up (Figure 1). Out of the 102 eyes examined after a second SLT treatment, 75 eyes had belonged to the group of initial responders and 27 eyes to the group of initial non-responders after the primary SLT treatment. Out of the 75 eyes with an initial response, 54 (72%) showed a response and 21 (28%) showed no response after the second SLT. Out of the 27 eyes with no response after the primary SLT treatment, 19 eyes (70%) showed a response whereas 8 (30%) showed no response after the second SLT procedure ($\chi$2-test p=0.872) (Figure 1). The responses of fellow eyes in people who had both eyes treated are shown in table 4 (primary SLT) and table A1 of the appendix (repeat SLT).

Mean intraocular pressure of 191 eyes at baseline visit before the first selective laser trabeculoplasty was 26.4 (SD 6.3) mmHg which was reduced by 6.3 (SD 6.1) mmHg to 20.0 (SD 5.5) mmHg at the 2-month visit (181 eyes).[14] Following the study protocol, 104 eyes required a repeat SLT treatment after exceeding the individual IOP threshold, and 102 were followed up. These had a mean IOP of 25.0 (SD 4.3) mmHg before the repeat intervention which was reduced by 3.7 (SD 4.2) mmHg to 21.3 (SD 4.4) mmHg at the next follow-up visit. Table 2 describes the IOP results before and after the primary and repeat SLT procedures for different potential predictors of IOP change.

The analyses of potential predictors are shown in table 3 for the primary SLT treatment and in the appendix (table A2) for the repeat SLT procedure. All models were also adjusted for IOP before the respective SLT procedure which had the strongest association with absolute IOP reduction after primary and repeat interventions. The most parsimonious model for the primary SLT procedure contained age <70 years, no timolol eye drops before enrolment, IOP ≥ 25mmHg and a minimum

height of the trabecular meshwork of >1/2 of the laser spot size (approx. 200-400µm) as predictors of a stronger IOP reduction (table 3). For the repeat SLT procedure, the most parsimonious model only contained IOP before the repeat SLT treatment as a significant predictor (appendix table A2).

# Tables

## Table 1: Patient and ocular characteristics.

| **Patient characteristics (number of patients)** | | **Total N=101** | |
|---|---|---|---|
| Sex | Female | 37 | (36.6%) |
| | Male | 64 | (63.4%) |
| Age group | < 70 years | 59 | (58.4) |
| | ≥ 70 years | 42 | (41.6) |
| Education | < Secondary level | 63 | (62.4%) |
| | ≥ Secondary level | 38 | (37.6%) |
| Ethnic group | Chagga | 57 | (56.4%) |
| | Pare | 23 | (22.8%) |
| | Meru | 4 | (4.0%) |
| | Maasai | 1 | (1.0%) |
| | Sambaa | 2 | (2.0%) |
| | Other | 14 | (13.9%) |
| Financial resources | ≤ 2 US$/day | 32 | (38.2%) |
| | > 2 US$/day | 69 | (61.8%) |
| Travel distance | < 50 km | 54 | (52.2%) |
| | ≥ 50 km | 47 | (47.8%) |
| Family history of glaucoma | No | 77 | (76.2%) |
| | Yes | 24 | (23.8%) |
| **Ocular characteristics at baseline before primary SLT procedure (number of eyes)** | | **Total N=191** | |
| Visual acuity, WHO categories, ICD-11 | No vision impairment (VA≥6/12) | 115 | (60.2%) |
| | Mild vision impairment (6/18≤VA<6/12) | 30 | (15.7%) |
| | Moderate vision impairment (6/60≤VA<6/18) | 22 | (11.5%) |
| | Severe vision impairment (3/60≤VA<6/60) | 1 | (0.5%) |
| | Blindness (1/60≤VA<3/60) | 1 | (0.5%) |
| | Blindness (PL≤VA<1/60) | 22 | (11.5%) |
| Vision impairment | no vision impairment (VA≥6/12) | 115 | (60.2%) |
| | vision impairment (VA<6/12) | 76 | (39.8%) |
| Functional stage of glaucoma (GSS) | early/moderate/advanced | 100 | (52.4%) |
| | severe/end-stage | 91 | (47.6%) |
| Structural stage of glaucoma | Moderate (DDLS 5-7) | 83 | (43.5%) |
| | Advanced (DDLS 8-10 | 108 | (56.5%) |
| Exfoliation glaucoma | No | 166 | (86.9%) |
| | Yes | 25 | (13.1%) |
| Central corneal thickness* | < 520 µm | 97 | (53.0%) |
| | ≥ 520 µm | 86 | (47.0%) |
| Prior glaucoma eye drops** | No | 82 | (42.9%) |
| | Yes | 109 | (57.1%) |
| Prior timolol eye drops** | No | 91 | (47.6%) |
| | Yes | 100 | (52.4%) |
| Pseudophakia | No | 177 | (92.7%) |
| | Yes | 14 | (7.3%) |
| Chamber angle width (mean Spaeth) | ≤30° | 38 | (19.9%) |
| | >30° | 153 | (80.1%) |
| Angle pigmentation | light pigmentation | 161 | (84.3%) |
| | strong pigmentation | 30 | (15.7%) |
| Intraocular pressure, mmHg | mean (standard deviation) | 26.4 | (6.3) |
| Intraocular pressure categories | IOP <25mmHg | 91 | (47.6%) |
| | IOP ≥25mmHg | 100 | (52.4%) |
| SLT laser, total energy | Total energy < 85mJ | 96 | (50.3%) |
| | Total energy ≥ 85mJ | 95 | (49.7%) |
| Cavitation bubbles*** | Plenty | 62 | (48.4%) |
| | Few | 66 | (51.6%) |
| Trabecular meshwork height, minimum*** | ≤1/2 of laser spot diameter | 30 | (28.8%) |
| | >1/2 of laser spot diameter | 74 | (71.2%) |
| **Ocular characteristics before repeat SLT procedures** | | **Total N=104** | |
| IOP at baseline, mmHg | mean (standard deviation) | 28.1 | (6.4) |
| IOP prior to repeat SLT, mmHg | mean (standard deviation) | 24.9 | (4.3) |
| IOP at baseline, categories | IOP <25mmHg | 40 | (38.5%) |
| | IOP ≥25mmHg | 64 | (61.5%) |
| IOP prior to repeat SLT, categories | IOP <25mmHg | 58 | (55.8%) |
| | IOP ≥25mmHg | 46 | (44.2%) |
| Total energy of SLT | Total energy < 85mJ | 43 | (41.3%) |
| | Total energy ≥ 85mJ | 61 | (58.7%) |
| Cavitation bubbles*** | Plenty | 22 | (25.9%) |
| | Few | 63 | (74%) |
| Minimum trabecular meshwork height*** | ≤1/2 of laser spot diameter | 28 | (35%) |
| | >1/2 of laser spot diameter | 51 | (65%) |

*Data are mean (standard deviation) or n (%). * Central corneal thickness measurements missing in 8 eyes due to temporary failure of the pachymeter. ** Based on patient history. *** Missing data for cavitation bubbles and minimum trabecular meshwork height as they were introduced after the start of the trial, but were recorded consecutively thereafter*.

***Table 2: Intraocular pressures (mean(sd)) before the primary and repeat SLT treatment and at the immediate follow-up visit.***

| Explanatory variable and levels | Primary selective laser trabeculoplasty | | | | | Repeat selective laser trabeculoplasty | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline IOP (mmHg) | | 2-month IOP (mmHg) | | Δ IOP (mmHg) | IOP prior repeat SLT (mmHg) | | IOP post repeat SLT (mmHg) | | Δ IOP (mmHg) |
| | N | mean (sd) | N | mean(sd) | mean (sd) | N | mean (sd) | N | mean (sd) | mean (sd) |
| **All** | 191 | 26.4 (6.3) | 181 | 20.0 (5.5) | -6.3 (6.1) | 104 | 24.9 (4.2) | 102 | 21.3 (4.4) | -3.7 (4.2) |
| Sex | | | | | | | | | | |
| Female | 70 | 25.7 (6.8) | 66 | 19.4 (5.4) | -6.2 (6.7) | 34 | 25.9 (4.9) | 34 | 21.8 (5.4) | -4.1 (4.5) |
| Male | 121 | 26.8 (6.0) | 115 | 20.3 (5.6) | -6.3 (5.8) | 70 | 24.4 (3.8) | 68 | 21.0 (3.8) | -3.5 (4.1) |
| Age group | | | | | | | | | | |
| <70 years | 112 | 27.6 (6.7) | 106 | 19.2 (5.0) | -8.1 (6.6) | 54 | 25.0 (4.1) | 52 | 21.0 (4.5) | -4.2 (4.3) |
| ≥70 years | 79 | 24.7 (5.3) | 75 | 21.1 (6.0) | -3.7 (4.2) | 50 | 24.8 (4.4) | 50 | 21.5 (4.3) | -3.3 (4.2) |
| Education | | | | | | | | | | |
| < Secondary level | 117 | 26.4 (6.2) | 107 | 20.2 (5.5) | -6.0 (6.3) | 64 | 24.9 (4.2) | 64 | 20.9 (4.0) | -4.0 (4.1) |
| ≥ Secondary level | 74 | 26.4 (6.4) | 74 | 19.7 (5.5) | -6.7 (5.9) | 40 | 24.9 (4.4) | 38 | 21.9 (4.9) | -3.2 (4.5) |
| Ethnic group | | | | | | | | | | |
| Chagga | 106 | 26.1 (6.0) | 98 | 19.7 (5.6) | -6.3 (6.6) | 55 | 24.9 (4.5) | 55 | 20.6 (4.1) | -4.3 (4.4) |
| Pare | 45 | 26.5 (6.7) | 43 | 20.5 (5.4) | -5.7 (4.9) | 27 | 24.3 (3.6) | 25 | 22.2 (5.5) | -2.3 (3.6) |
| Meru | 7 | 25.9 (4.3) | 7 | 18.7 (5.6) | -7.1 (6.8) | 2 | 27.5 (4.9) | 2 | 22.0 (2.8) | -5.5 (7.8) |
| Maasai | 2 | 34.5 (2.1) | 2 | 27.5 (3.5) | -7.0 (1.4) | 2 | 27.5 (3.5) | 2 | 21.5 (0.7) | -6.0 (2.8) |
| Sambaa | 4 | 30.3 (2.8) | 4 | 22.8 (8.5) | -7.5 (8.7) | 2 | 30.0 (2.8) | 2 | 23.0 (4.2) | -7.0 (1.4) |
| Other | 27 | 26.3 (7.2) | 27 | 19.5 (4.8) | -6.8 (6.4) | 16 | 24.6 (4.5) | 16 | 21.6 (3.9) | -3.0 (4.0) |
| Financial resources | | | | | | | | | | |
| ≤ 2 US$/day | 61 | 26.5 (5.9) | 57 | 21.4 (5.1) | -5.2 (5.9) | 39 | 25.0 (4.2) | 39 | 21.3 (3.6) | -3.7 (3.4) |
| > 2 US$/day | 130 | 26.3 (6.5) | 124 | 19.4 (5.6) | -6.8 (6.2) | 65 | 24.8 (4.3) | 63 | 21.3 (4.8) | -3.7 (4.7) |
| Travel distance | | | | | | | | | | |
| < 50 km | 104 | 25.6 (5.6) | 100 | 19.3 (5.4) | -6.3 (5.9) | 54 | 24.7 (4.6) | 54 | 21.0 (4.3) | -3.7 (4.1) |
| ≥ 50 km | 87 | 27.4 (6.9) | 81 | 20.9 (5.5) | -6.3 (6.4) | 50 | 25.1 (3.9) | 48 | 21.5 (4.5) | -3.8 (4.4) |
| Family history of glaucoma | | | | | | | | | | |
| No | 145 | 26.4 (6.0) | 135 | 19.7 (5.5) | -6.6 (6.2) | 77 | 24.8 (4.2) | 75 | 21.2 (4.2) | -3.7 (4.1) |
| Yes | 46 | 26.3 (7.2) | 46 | 20.9 (5.5) | -5.4 (5.7) | 27 | 25.3 (4.3) | 27 | 21.4 (5.0) | -3.9 (4.6) |
| Vision impairment | | | | | | | | | | |
| No (VA≥6/12) | 115 | 25.8 (6.2) | 110 | 18.8 (4.8) | -6.7 (6.4) | 53 | 24.6 (4.3) | 52 | 21.0 (5.0) | -3.7 (4.1) |
| Yes (VA<6/12) | 76 | 27.3 (6.3) | 71 | 21.9 (6.0) | -5.6 (5.6) | 51 | 25.2 (4.2) | 50 | 21.6 (3.7) | -3.7 (4.4) |
| Stage of glaucoma (GSS) | | | | | | | | | | |
| early/moderate/advanced | 100 | 24.3 (5.0) | 95 | 18.7 (4.3) | -5.5 (4.9) | 41 | 24.9 (3.7) | 40 | 20.9 (4.2) | -4.0 (4.1) |
| severe/end-stage | 91 | 28.6 (6.8) | 86 | 21.4 (6.3) | -7.1 (7.2) | 63 | 24.9 (4.6) | 62 | 21.5 (4.5) | -3.5 (4.4) |
| Stage of glaucoma | | | | | | | | | | |
| Moderate (DDLS 5-7) | 83 | 24.0 (5.0) | 82 | 18.9 (4.9) | -4.9 (5.1) | 27 | 27.1 (4.3) | 27 | 22.3 (4.6) | -4.9 (3.6) |
| Advanced (DDLS 8-10) | 108 | 28.2 (6.5) | 99 | 20.9 (5.8) | -7.4 (6.7) | 77 | 24.1 (4.0) | 75 | 20.9 (4.3) | -3.3 (4.4) |
| Exfoliation glaucoma | | | | | | | | | | |
| No | 166 | 26.0 (6.1) | 156 | 19.1 (4.5) | -6.7 (6.0) | 83 | 24.2 (3.7) | 81 | 20.8 (4.2) | -3.4 (4.4) |
| Yes | 25 | 28.8 (7.0) | 25 | 25.4 (7.7) | -3.4 (6.5) | 21 | 27.8 (5.2) | 21 | 22.9 (4.9) | -4.9 (3.6) |
| Central corneal thickness* | | | | | | | | | | |
| < 520 µm | 97 | 26.8 (6.5) | 95 | 20.5 (6.1) | -6.2 (6.2) | 56 | 25.2 (4.3) | 56 | 20.9 (3.8) | -4.4 (4.0) |
| ≥ 520 µm | 86 | 26.0 (6.2) | 82 | 19.7 (4.7) | -6.4 (6.2) | 48 | 24.5 (4.2) | 46 | 21.7 (5.0) | -2.9 (4.4) |
| Prior timolol treatment | | | | | | | | | | |
| No | 91 | 27.4 (6.1) | 87 | 18.9 (4.8) | -8.2 (6.7) | 47 | 24.4 (4.1) | 47 | 21.1 (4.5) | -3.4 (3.3) |
| Yes | 100 | 25.5 (6.4) | 94 | 21.0 (5.9) | -4.5 (4.9) | 57 | 25.3 (4.3) | 55 | 21.4 (4.3) | -4.0 (4.9) |
| Pseudophakia | | | | | | | | | | |
| No | 177 | 26.5 (6.4) | 168 | 19.9 (5.6) | -6.5 (6.2) | 94 | 25.1 (4.4) | 92 | 21.5 (4.6) | -3.7 (4.4) |
| Yes | 14 | 24.3 (4.6) | 13 | 20.8 (3.6) | -3.9 (4.9) | 10 | 23.0 (2.4) | 10 | 19.4 (1.2) | -3.6 (2.2) |
| Chamber angle width | | | | | | | | | | |
| Mean Spaeth ≤ 30° | 38 | 25.6 (5.8) | 36 | 22.0 (6.4) | -3.3 (4.2) | 24 | 27.5 (4.4) | 24 | 23.1 (5.0) | -4.4 (5.1) |
| Mean Spaeth > 30° | 153 | 26.6 (6.4) | 145 | 19.5 (5.1) | -7.0 (6.3) | 80 | 24.1 (3.9) | 78 | 20.7 (4.1) | -3.5 (3.9) |
| Angle pigmentation | | | | | | | | | | |
| light pigmentation | 161 | 26.5 (6.4) | 153 | 19.9 (5.4) | -6.5 (6.1) | 89 | 24.6 (4.3) | 88 | 21.2 (4.5) | -3.5 (4.3) |
| strong pigmentation | 30 | 26.0 (5.7) | 28 | 20.6 (6.0) | -5.4 (6.2) | 15 | 26.5 (3.7) | 14 | 21.9 (3.9) | -4.9 (3.6) |
| IOP at baseline | | | | | | | | | | |
| IOP <25 | 91 | 21.4 (2.3) | 89 | 18.1 (3.3) | -3.3 (3.1) | 40 | 23.1 (3.2) | 38 | 20.1 (3.3) | -3.0 (4.4) |
| IOP ≥25 | 100 | 30.9 (5.2) | 92 | 21.8 (6.5) | -9.2 (6.9) | 64 | 26.1 (4.5) | 64 | 21.9 (4.8) | -4.1 (4.1) |
| IOP prior to repeat SLT | | | | | | | | | | |
| IOP <25 | | | | | | 58 | 21.8 (1.4) | 56 | 19.5 (3.2) | -2.3 (3.2) |
| IOP ≥25 | | | | | | 46 | 28.8 (3.4) | 46 | 23.4 (4.8) | -5.4 (4.7) |
| Total energy of SLT | | | | | | | | | | |
| Total energy < 85mJ | 96 | 26.5 (6.5) | 88 | 20.3 (5.4) | -6.2 (6.5) | 43 | 25.0 (4.3) | 41 | 21.5 (4.8) | -3.6 (4.7) |
| Total energy ≥ 85mJ | 95 | 26.3 (6.1) | 93 | 19.8 (5.6) | -6.4 (5.8) | 61 | 24.9 (4.2) | 61 | 21.1 (4.1) | -3.8 (4.0) |
| Cavitation bubbles** | | | | | | | | | | |
| Plenty | 62 | 26.0 (6.0) | 58 | 19.6 (5.5) | -6.4 (6.0) | 22 | 25.0 (4.0) | 21 | 21.7 (3.6) | -3.5 (4.7) |
| Few | 66 | 25.0 (6.1) | 66 | 20.4 (5.7) | -4.6 (4.7) | 63 | 24.9 (4.4) | 62 | 20.9 (4.5) | -4.0 (4.2) |
| Minimum TM height** | | | | | | | | | | |
| ≤1/2 of laser spot diameter | 30 | 24.4 (4.6) | 28 | 21.0 (5.4) | -2.6 (4.0) | 28 | 25.5 (4.7) | 28 | 20.7 (3.9) | -4.8 (4.0) |
| >1/2 of laser spot diameter | 74 | 25.8 (6.0) | 72 | 19.8 (5.3) | -6.2 (5.5) | 51 | 24.6 (4.3) | 49 | 21.3 (4.3) | -3.4 (4.3) |

**Missing data for central corneal thickness due to temporary failure of the pachymeter. ** Missing data for cavitation bubbles and minimum trabecular meshwork height as they were introduced after the start of the trial, but were recorded consecutively thereafter.*

***Table 3: Unadjusted, adjusted for baseline IOP and fully adjusted regression analyses of predictors for change of intraocular pressure after primary selective laser trabeculoplasty.***

| | | Primary selective laser trabeculoplasty | | | | | |
|---|---|---|---|---|---|---|---|
| **Explanatory variable** | | **unadjusted** | | **adjusted for baseline IOP** | | **fully adjusted analysis** | |
| | N | coef. (95% CI) | p-value | coef. (95% CI) | p-value | coef. (95% CI) | p-value |
| Sex | | | | | | | |
| Female | 66 | 0 (ref) | | 0 (ref) | | | |
| Male | 115 | -0.27 (-2.67-2.14) | 0.83 | 0.20 (-1.91-2.31) | 0.85 | | |
| Age group | | | | | | | |
| <70 years | 106 | 0 (ref) | | 0 (ref) | | 0.00 (ref) | |
| ≥70 years | 75 | 4.33 (2.15-6.51) | 0.00010 | 3.89 (1.98-5.80) | 0.00006 | 2.51 (0.53-4.50) | 0.013 |
| Education | | | | | | | |
| < Secondary level | 107 | 0 (ref) | | 0 (ref) | | | |
| ≥ Secondary level | 74 | -0.75 (-3.12-1.61) | 0.53 | -0.94 (-3.00-1.12) | 0.37 | | |
| Ethnic group | | | | | | | |
| Chagga | 98 | 0 (ref) | | 0 (ref) | | | |
| Pare | 43 | 0.51 (-2.36-3.38) | 0.73 | 0.60 (-1.90-3.10) | 0.64 | | |
| Meru | 7 | 0.39 (-5.54-6.31) | 0.90 | 1.93 (-3.28-7.14) | 0.47 | | |
| Maasai | 2 | -0.78 (-12.15-10.59) | 0.89 | 1.40 (-8.52-11.33) | 0.78 | | |
| Sambaa | 4 | -1.28 (-9.40-6.83) | 0.76 | 0.90 (-6.20-8.01) | 0.80 | | |
| Other | 27 | -0.54 (-3.94-2.86) | 0.76 | -0.86 (-3.83-2.10) | 0.57 | | |
| Financial resources | | | | | | | |
| ≤ 2 US$/day | 57 | 0 (ref) | | 0 (ref) | | | |
| > 2 US$/day | 124 | -1.51 (-3.99-0.96) | 0.23 | -1.94 (-4.08-0.20) | 0.075 | | |
| Travel distance | | | | | | | |
| < 50 km | 100 | 0 (ref) | | 0 (ref) | | | |
| ≥ 50 km | 81 | 0.01 (-2.32-2.34) | 0.99 | 0.03 (-2.01-2.06) | 0.98 | | |
| Family history of glaucoma | | | | | | | |
| No | 135 | 0 (ref) | | 0 (ref) | | | |
| Yes | 46 | 0.89 (-1.77-3.55) | 0.51 | 0.79 (-1.53-3.11) | 0.51 | | |
| Vision impairment | | | | | | | |
| No (VA≥6/12) | 110 | 0 (ref) | | 0 (ref) | | | |
| Yes (VA<6/12) | 71 | -0.13 (-1.43-1.18) | 0.85 | 0.60 (-0.71-1.91) | 0.37 | | |
| Stage of glaucoma (GSS) | | | | | | | |
| early/moderate/advanced | 95 | 0 (ref) | | 0 (ref) | | | |
| severe/end-stage | 86 | -1.40 (-2.71- -0.09) | 0.04 | -0.63 (-1.96-0.69) | 0.35 | | |
| Stage of glaucoma | | | | | | | |
| Moderate (DDLS 5-7) | 82 | 0 (ref) | | 0 (ref) | | | |
| Advanced (DDLS 8-10) | 99 | -1.88 (-3.26- -0.51) | 0.0074 | -1.28 (-2.64-0.09) | 0.067 | | |
| Exfoliation glaucoma | | | | | | | |
| No | 156 | 0 (ref) | | 0 (ref) | | | |
| Yes | 25 | 1.65 (-0.77-4.07) | 0.18 | 3.26 (0.98-5.55) | 0.0050 | | |
| Central corneal thickness | | | | | | | |
| < 520 µm | 95 | 0 (ref) | | 0 (ref) | | | |
| ≥ 520 µm | 82 | 0.63 (-1.33-2.60) | 0.53 | 0.59 (-1.22-2.40) | 0.52 | | |
| Prior timolol eye drops | | | | | | | |
| No | 87 | 0 (ref) | | 0 (ref) | | 0 (ref) | |
| Yes | 94 | 3.22 (1.10-5.34) | 0.0029 | 2.77 (0.90-4.65) | 0.0038 | 4.70 (2.77-6.62) | <0.0001 |
| Pseudophakia | | | | | | | |
| No | 168 | 0 (ref) | | 0 (ref) | | | |
| Yes | 13 | -0.23 (-3.60-3.14) | 0.89 | 1.25 (-1.94-4.43) | 0.44 | | |
| Chamber angle width | | | | | | | |
| Mean Spaeth ≤30° | 36 | 0 (ref) | | 0 (ref) | | | |
| Mean Spaeth >30° | 145 | -3.30 (-5.69--0.90) | 0.0069 | -3.28 (-5.46--1.10) | 0.0032 | | |
| Angle pigmentation | | | | | | | |
| light pigmentation | 153 | 0 (ref) | | 0 (ref) | | | |
| strong pigmentation | 28 | 0.16 (-2.67-2.99) | 0.91 | 0.17 (-2.39-2.73) | 0.89 | | |
| IOP at baseline | | | | | | | |
| IOP < 25 mmHg | 89 | 0 (ref) | | | | 0 (ref) | |
| IOP ≥ 25 mmHg | 92 | -4.06 (-5.57- -2.55) | <0.0001 | N/A | | -4.06 (-5.71- -2.40) | <0.0001 |
| Total energy of SLT | | | | | | | |
| Total energy < 85mJ | 88 | 0 (ref) | | 0 (ref) | | | |
| Total energy ≥ 85mJ | 93 | -0.07 (-1.62-1.48) | 0.93 | -0.14 (-1.63-1.35) | 0.86 | | |
| Cavitation bubbles | | | | | | | |
| Plenty | 58 | 0 (ref) | | 0 (ref) | | | |
| Few | 66 | 2.55 (0.45-4.65) | 0.017 | 2.65 (0.72-4.58) | 0.0072 | | |
| Minimum TM height | | | | | | | |
| ≤1/2 of laser spot diameter | 28 | 0 (ref) | | 0 (ref) | | 0 (ref) | |
| >1/2 of laser spot diameter | 72 | -3.20 (-5.53- -0.87) | 0.0071 | -2.46 (-4.57- -0.36) | 0.022 | -2.86 (-4.72- -0.99) | 0.003 |

*Generalised estimating equations were used to account for the absence of independence between eyes of a patient. Potential predictors with p<0.2 were included in the fully adjusted analysis and backward stepwise selection identified the most parsimonious model.*

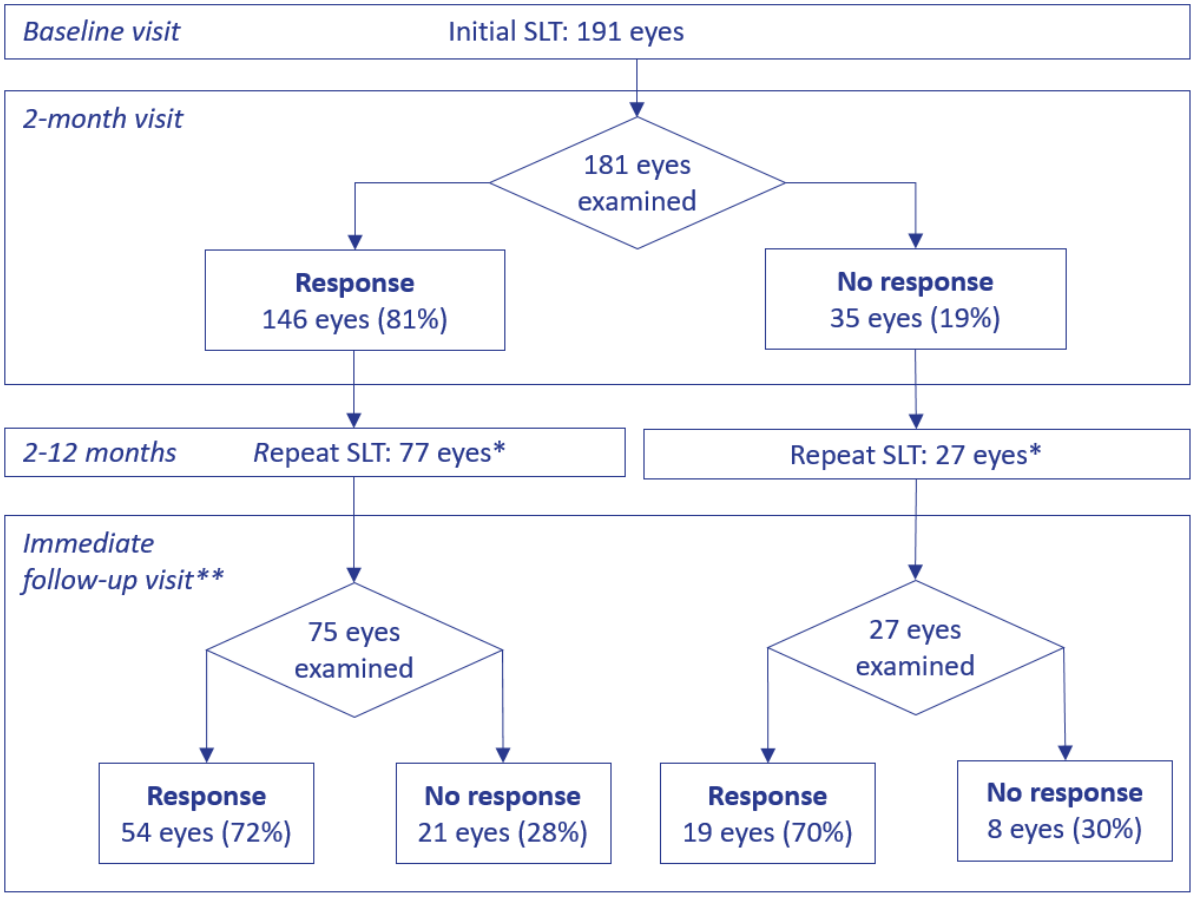
***Table 4: Intraocular pressure responses in fellow eyes following primary SLT procedures.***

| | **Left eyes** | | |
|---|---|---|---|
| **Right eyes** | No response | Response | Total |
| No response | 9 (56%) | 7 (10%) | 16 (19%) |
| Response | 7 (44%) | 62 (90%) | 69 (81%) |
| Total | 16 (100%) | 69 (100%) | 85 (100%) |

*Pearson $chi^2$ = 18.07, p<0.001. Response = intraocular pressure reduction of 2mmHg or more, no response = reduction of less than 2mmHg following the primary SLT procedure. 90 patients (180 eyes) received bilateral SLT, five patients (10 eyes) were lost to follow up before the 2-month visit.*

# Figure

***Figure 1: Intraocular pressure responses following primary and repeat SLT procedures***




*Response was defined as an intraocular pressure reduction of 2mmHg or more and no response as a reduction of less than 2mmHg after the SLT procedure. Following the primary SLT procedure, 5 patients (10 eyes) were lost to follow-up before the 2-month visit and 1 patient (2 eyes) between the repeat SLT and next follow-up visit. *Repeat SLTs were done between the 2-month and 12-month visits if the IOP exceeded an individual IOP threshold as defined in the KiGIP SLT trial protocol. ** IOP was measured at the follow-up visit immediately following the repeat SLT procedure, typically after 3 months. SLT=selective laser trabeculoplasty*

## Discussion

This post hoc analysis of the KiGIP SLT trial indicates a low association between the absolute IOP reduction after primary and repeat SLT treatments: 70% of eyes which did not respond after the primary SLT did so following the repeat SLT, and 28% of eyes which responded to the primary SLT did not respond to the repeat SLT. Polat et al. reported a retrospective review of 38 eyes of 38 patients who had undergone two successive 360° SLT treatments. Repeat SLT safely re-established IOP control with comparable IOPs after primary and repeat SLT.[17] Garg et al. conducted a post hoc mixed-model analysis of the LiGHT trial and revealed a significantly greater absolute IOP reduction after the repeat SLT in comparison to the initial SLT after adjusting for pre-treatment IOPs.[18] Our results confirmed the efficacy of repeat SLT in a study population of more advanced glaucoma. These findings of different responses after primary and repeat SLT in the same eye suggest that predictors of absolute IOP reduction after SLT may not be strongly associated with anatomical characteristics of the eye.

Our analysis showed a strong association of post treatment responses in fellow eyes which may be considered when counselling patients and planning glaucoma management after treating the first eye.

The most parsimonious model for predicting absolute IOP reduction after primary SLT included pre-SLT IOP, age, absence of timolol eye drops before enrolment and a minimum height of the trabecular meshwork of >1/2 laser spot diameter. Following repeat SLT, only pre-SLT IOP was a significant covariate.

Therefore, our analysis indicates that a higher pre-treatment IOP is the strongest predictor of IOP reduction after SLT. This has also been described in several other studies.[18–20] Khawaja et al. found a strong association between treatment success and a baseline IOP > 21 mmHg versus ≤ 21 mmHg (hazard ratio 0.67, 95% CI 0.57-0.80; p<0.001) in a retrospective observational study of electronic medical records of 831 SLT-treated eyes. [20]

Eyes which were treated with timolol eye drops before enrolment showed a smaller response compared to treatment-naïve eyes after primary SLT. McIlraith et al. [21] reported from a prospective, nonrandomized trial clinical outcomes in 87 eyes who underwent a washout period of prior topical glaucoma medication (79 eyes (91%) latanoprost) for a minimum of 4 weeks before SLT. IOP reduction after SLT was significantly less compared to the treatment-naïve group of 74 eyes with an average IOP reduction of 8.1 versus 6.4 mmHg (P<0.001). The authors stated that the 4-week washout period might have been insufficient to achieve a true baseline at the start of the study resulting in a lower IOP prior to

the SLT intervention and the appearance of a blunted effect of SLT.[21] Alternatively they suggested that SLT could be more efficacious as primary treatment. In our study, the majority of patients who underwent a washout period had been on timolol eye drops. However, most of the patients had run out of drops at the time of the eligibility visit and the name of the eye drops as well as the date when the bottles had finished were based on patient's history. We estimated the 4-week wash-out period from this information which might have led partly to an insufficient wash-out period as described by McIlraith et al.[21] This was also supported by our results of repeat SLT procedures which showed no association between pre-SLT timolol treatment and absolute IOP reduction.

The minimum height of the trabecular meshwork of more than half of the SLT laser spot diameter was significantly associated with IOP reduction after the primary SLT in the most parsimonious model. There was no significant association with repeat SLT which might be due to the smaller sample size and a selection bias of eyes which required a repeat SLT. We believe that this feature has not been previously analysed. It might play a limited role in identifying eyes more likely to respond to SLT, and further studies are necessary to evaluate this.

This study has several limitations. SLT was repeated when an eye failed the individual IOP threshold algorithm[14] which lead to different group sizes of eyes receiving primary and repeat SLT and a biased selection of eyes which received the repeat SLT, similar to other studies.[18] The analysis was based on the 1-year follow-up data and focuses on early responses which are relevant in clinical practice and are less affected by patients lost to follow-up or exiting the trial due to a failure but long-term effects on IOP lowering are not captured.

In conclusion, this report indicates the efficacy of repeat SLT and extends the existing evidence for advanced stages of glaucoma. There is a strong association between SLT responses of fellow eyes, which could be used for counselling and developing an individual treatment plan. Pre-SLT IOP was a strong predictor for the absolute IOP reduction after primary and repeat SLT. This provides additional evidence that SLT can be used repeatedly, including in advanced disease, which has a strong impact on vision and related quality of life.[22]

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# Appendices

***Table A1: Intraocular pressure responses in partner eyes following the repeat SLT procedures**.*

| | **Left eyes** | | |
|---|---|---|---|
| **Right eyes** | No response | Response | Total |
| No response | 10 (56%) | 8 (28%) | 18 (19%) |
| Response | 8 (44%) | 21 (72%) | 29 (81%) |
| Total | 18 (100%) | 29 (100%) | 47 (100%) |

*Pearson chi2 = 3.68, p=0.055. Response = intraocular pressure reduction of 2mmHg or more, no response = reduction of less than 2mmHg following the repeat SLT procedure. 48 patients (96 eyes) received bilateral repeat SLT, one patient (2 eyes) was lost to follow up before the next follow-up visit.*

**Table A2: Unadjusted and adjusted regression analyses of predictors for change of intraocular pressure after repeat selective laser trabeculoplasty**

| Explanatory variable | Repeat selective laser trabeculoplasty | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Unadjusted analysis | | Adjusted for IOP prior to repeat SLT | | Fully adjusted analysis | |
| | N | coef. (95% CI) | p-value | coef. (95% CI) | p-value | coef. (95% CI) | p-value |
| Sex | | | | | | | |
| Female | 34 | 0.00 (ref) | | 0 (ref) | | | |
| Male | 68 | 0.77 (-1.20-2.74) | 0.44 | 0.38 (-1.50-2.26) | 0.698 | | |
| Age group | | | | | | | |
| <70 years | 52 | 0.00 (ref) | | 0 (ref) | | | |
| ≥70 years | 50 | 0.60 (-1.25-2.44) | 0.53 | 0.61 (-1.14-2.35) | 0.50 | | |
| Education | | | | | | | |
| < Secondary level | 64 | 0.00 (ref) | | 0 (ref) | | | |
| ≥ Secondary level | 38 | 0.90 (-1.02-2.82) | 0.36 | 1.29 (-0.52-3.10) | 0.16 | | |
| Ethnic group | | | | | | | |
| Chagga | 55 | 0.00 (ref) | | 0 (ref) | | | |
| Pare | 25 | 1.98 (-0.19-4.15) | 0.074 | 1.95 (-0.11-4.01) | 0.063 | | |
| Meru | 2 | -1.13 (-6.91-4.64) | 0.70 | -0.96 (-6.38-4.46) | 0.73 | | |
| Maasai | 2 | -1.63 (-8.46-5.19) | 0.64 | 0.16 (-6.42-6.73) | 0.96 | | |
| Sambaa | 2 | -2.63 (-9.46-4.19) | 0.45 | -0.84 (-7.42-5.73) | 0.80 | | |
| Other | 16 | 1.44 (-1.13-4.00) | 0.27 | 0.72 (-1.74-3.19) | 0.56 | | |
| Financial resources | | | | | | | |
| ≤ 2 US$/day | 39 | 0.00 (ref) | | 0 (ref) | | | |
| > 2 US$/day | 63 | -0.15 (-2.07-1.78) | 0.88 | -0.08 (-1.90-1.74) | 0.93 | | |
| Travel distance | | | | | | | |
| < 50 km | 54 | 0.00 (ref) | | 0 (ref) | | | |
| ≥ 50 km | 48 | -0.25 (-2.12-1.62) | 0.79 | 0.23 (-1.55-2.01) | 0.80 | | |
| Family history of glaucoma | | | | | | | |
| No | 75 | 0.00 (ref) | | 0 (ref) | | | |
| Yes | 27 | -0.09 (-2.24-2.07) | 0.94 | 0.04 (-2.01-2.09) | 0.97 | | |
| Vision impairment | | | | | | | |
| No (VA≥6/12) | 52 | 0 (ref) | | 0 (ref) | | | |
| Yes (VA<6/12) | 50 | -0.68 (-2.26-0.89) | 0.40 | -0.15 (-1.63-1.32) | 0.84 | | |
| Stage of glaucoma (GSS) | | | | | | | |
| early/moderate/adv. | 40 | 0 (ref) | | 0 (ref) | | | |
| severe/end-stage | 62 | 0.05 (-1.60-1.69) | 0.95 | 0.27 (-1.24-1.78) | 0.73 | | |
| Stage of glaucoma | | | | | | | |
| Moderate (DDLS 5-7) | 27 | 0 (ref) | | 0 (ref) | | | |
| Advanced (DDLS 8-10) | 75 | 1.11 (-0.72-2.95) | 0.23 | 0.55 (-1.16-2.25) | 0.53 | | |
| Exfoliation glaucoma | | | | | | | |
| No | 81 | 0.00 (ref) | | 0 (ref) | | | |
| Yes | 21 | -0.98 (-3.07-1.10) | 0.36 | 0.13 (-1.87-2.12) | 0.90 | | |
| Central corneal thickness | | | | | | | |
| < 520 µm | 56 | 0.00 (ref) | | 0 (ref) | | | |
| ≥ 520 µm | 46 | 1.19 (-0.59-2.97) | 0.19 | 1.17 (-0.50-2.85) | 0.17 | | |
| Prior timolol eye drops | | | | | | | |
| No | 47 | 0 (ref) | | 0 (ref) | | | |
| Yes | 55 | -0.59 (-2.45-1.27) | 0.53 | -0.47 (-2.23-1.30) | 0.60 | | |
| Pseudophakia | | | | | | | |
| No | 92 | 0.00 (ref) | | 0 (ref) | | | |
| Yes | 10 | 0.29 (-2.77-3.35) | 0.85 | 0.09 (-2.80-2.99) | 0.95 | | |
| Chamber angle width | | | | | | | |
| Mean Spaeth ≤30° | 24 | 0.00 (ref) | | 0 (ref) | | | |
| Mean Spaeth >30° | 78 | 0.98 (-1.13-3.08) | 0.36 | -0.49 (-2.58-1.59) | 0.64 | | |
| Angle pigmentation | | | | | | | |
| light pigmentation | 88 | 0.00 (ref) | | 0 (ref) | | | |
| strong pigmentation | 14 | -1.33 (-4.02-1.36) | 0.33 | -0.32 (-2.92-2.28) | 0.81 | | |
| IOP at baseline | | | | | | | |
| IOP < 25 mmHg | 38 | 0 (ref) | | 0 (ref) | | | |
| IOP ≥ 25 mmHg | 64 | -0.67 (-2.41-1.07) | 0.45 | 0.11 (-1.53-1.76) | 0.89 | | |
| IOP prior to repeat SLT | | | | | | | |
| IOP < 25 mmHg | 56 | 0.00 (ref) | | N/A | | | |
| IOP ≥ 25 mmHg | 46 | -3.37 (-4.88--1.86) | <0.0001 | | | -3.37 (-4.88--1.86) | <0.0001 |
| Total energy of SLT | | | | | | | |
| Total energy < 85mJ | 41 | 0.00 (ref) | | 0 (ref) | | | |
| Total energy ≥ 85mJ | 61 | -0.18 (-1.81-1.44) | 0.83 | -0.17 (-1.66-1.31) | 0.82 | | |
| Cavitation bubbles | | | | | | | |
| Plenty | 21 | 0.00 (ref) | | 0 (ref) | | | |
| Few | 62 | -0.86 (-3.18-1.45) | 0.46 | -0.67 (-2.78-1.43) | 0.53 | | |
| Minimum TM height | | | | | | | |
| ≤1/2 of laser spot diameter | 28 | 0.00 (ref) | | 0 (ref) | | | |
| >1/2 of laser spot diameter | 49 | 1.75 (-0.25-3.74) | 0.086 | 1.05 (-0.75-2.86) | 0.25 | | |

*Regression analyses were using generalised estimating equations to account for the absence of independence between eyes of a patient. Potential predictors with p<0.2 were included in the adjusted analysis and backward stepwise selection identified the most parsimonious model. This model included baseline IOP before the repeat SLT treatment.*

# 7 Discussion


*A research assistant listens to experiences and questions of a participant.*

## Overview

The aim of this research was to test the hypothesis that selective laser trabeculoplasty is superior to timolol eye drops for reducing IOP of patients with glaucoma, and that the laser treatment is comparable concerning safety, acceptance among patients, preservation of visual acuity, change in vision-related quality of life, and cost in Tanzania one year after starting the treatment. It is hoped that what we have learned will contribute to the development of strategies for more effective services for people with glaucoma in Tanzania and the wider region (Figure 14).

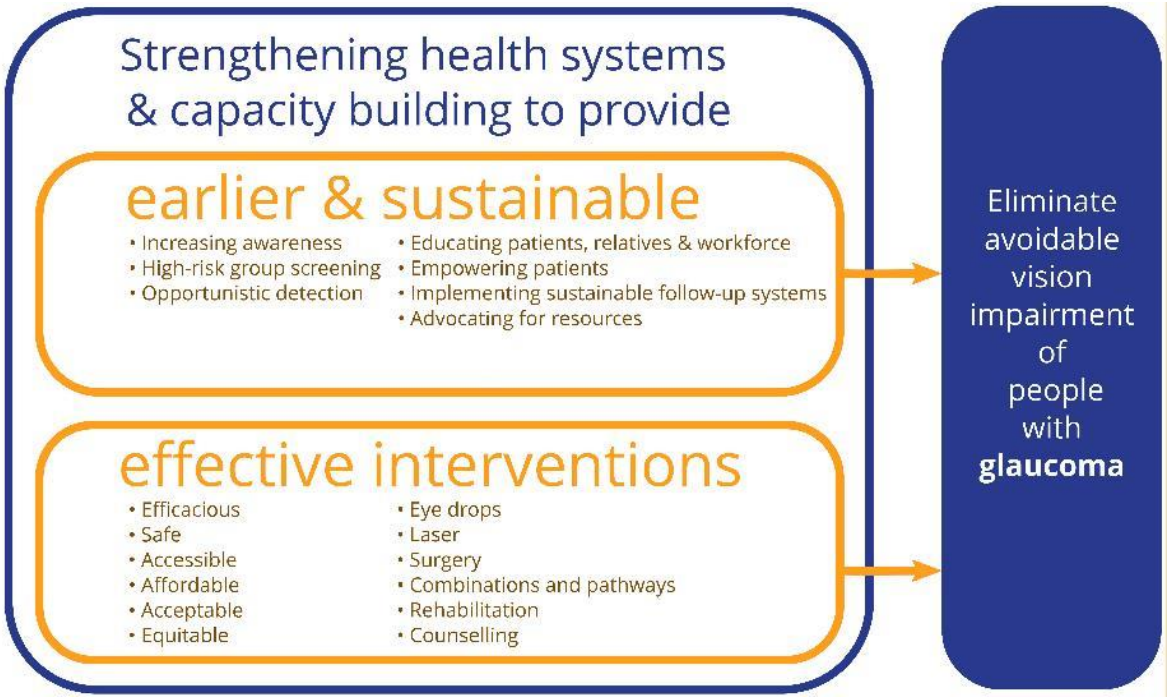



***Figure 14: Strategy to reduce the number of people suffering from glaucoma impairment.***

## The relevance of optic nerve head descriptors

Most participants had advanced stages of glaucoma at their recruitment into the trial. We showed that the disc damage likelihood scale (DDLS, see Table 15, page 47) and cup/disc ratio (CDR) are reliable low-cost methods for describing and discriminating structural changes, including for late stages of glaucoma. DDLS (compared to CDR) had a larger area under the receiver operating characteristics curve and provided more categories to differentiate stages of glaucomatous optic nerve damage. Both methods are robust and can be applied in many different settings without the need for expensive technology. These staging systems may be considered sustainable strategies to detect glaucoma earlier and communicate the stage of glaucomatous damage within a referral

network. Reliable and robust documentation can play an important role in a larger strategy to reduce avoidable vision impairment of people with glaucoma (Figure 14, page 143).

### Trial outcomes in the context of other research

Another essential component of the strategy shown in Figure 14 is the evaluation of interventions which have the potential to improve treatment of patients with glaucoma in African countries. This was the main rationale for this study (see chapter 2.2, page 59). Our randomised controlled trial which compared the standard treatment in the region, 0.5% timolol eye drops[59], with selective laser trabeculoplasty showed an odds ratio for success of 3.37 in favour of selective laser trabeculoplasty (95% CI 1·96-5·80, p<0·0001) after one year.[189] In the timolol group, treatment was successful in 55 (31%) of 176 eyes (16 [29%] of 55 eyes required repeat administration of counselling). In the SLT group, 99 (61%) of 163 eyes were successfully treated (33 [33%] of 99 eyes required repeat SLT). Safety, acceptance of treatment, vision-related quality of life, and preservation of visual acuity were comparable in both groups after one year. An eye care unit in the region which purchases a SLT laser and maintains it for 10 years would need to treat around 500 eyes per year with the laser to cover the cost if charging an amount similar to a year's supply of timolol eye drops.[189]

The timolol group showed an absolute IOP lowering of 3.2 mmHg (SD 7.5) at the first follow-up visit after 2 months which is similar to the results reported from a systematic review of 3.70 mmHg (95% CI 3.16-4.24) (see table 5, page 27).[48] In the SLT group, the IOP was reduced by 6.28 mmHg (SD 6.1) after 2 months. The LiGHT trial (see table 10, page 36) reported a mean initial IOP lowering at 2 months of 6.5 mmHg (SD 4.3) in eyes with open-angle glaucoma.[95] In summary, the KiGIP SLT trial in Tanzania with eyes affected predominantly by advanced glaucoma showed similar results to the literature which is based on trials in other world regions, typically evaluating a spectrum of earlier stages of glaucoma.

### Predictors of outcomes

We reported predictors of success in the main trial report (chapter 5, page 87) and predictors of absolute IOP reduction in a separate manuscript describing absolute IOP outcomes (chapter 6, page 121). A high baseline IOP before selective laser trabeculoplasty was the strongest predictor for absolute IOP lowering but it was also associated with a decreased probability of success.[189] This can be explained with the success criteria of our trial which required an IOP of 18mmHg or less for

advanced and 21mmHg or less for moderate glaucoma. Hence, success was more difficult to achieve for advanced glaucoma. Thus, despite the baseline IOP being higher in the group of eyes with advanced glaucoma and therefore achieving a stronger IOP reduction, achieving success was still less likely compared to eyes with moderate glaucoma.

Elevated baseline intraocular pressure was also the most consistently reported factor associated with success in the literature.[78,82,190,191] However, comparing predictors of success between studies is difficult as multiple variations exist within studies.[78] A commonly used definition of success is an IOP reduction of ≥20% which can be misleading as even an IOP reduction of 20% might still not be low enough to prevent progression. So it is preferable to give the individualised absolute target IOP a higher priority than a certain amount of absolute or relative IOP reduction when aiming to prevent glaucoma progression.[78] See also chapter Target intraocular pressure , page 51. A retrospective review of 72 treatment-naïve subjects with electronic Shiøtz tonographic outflow facility (TOF) measurements before selective laser trabeculoplasty aimed to investigate the predictive role of TOF. Still, the only variable associated with success was baseline intraocular pressure.[191] The authors suggested that TOF may be reflecting post-trabecular meshwork pathology which probably is not targeted by SLT.

Advanced glaucoma was also associated with a decreased probability of success in both treatment groups of our trial. But advanced glaucoma was also associated with an increased intraocular pressure (see table 2, chapter 6) and it was associated with a stronger IOP reduction compared to moderate glaucoma after the primary SLT (see table 3, chapter 6), even after adjusting the linear regression model for IOP at baseline. However, after the repeat SLT the difference in IOP reduction was not significantly associated with the stage of glaucoma. In summary, SLT achieves a similar or even stronger IOP reduction in advanced glaucoma versus moderate glaucoma but it might less successfully prevent progression in many eyes. So far only very few studies evaluated SLT treatment in advanced glaucoma. Schlote et al. demonstrated in a retrospective analysis that SLT provided a successful IOP-lowering effect (defined as a >20% IOP reduction of the baseline IOP and IOP ≤ 21 mm Hg) in 63% of patients with early glaucoma and 59% of patients with advanced glaucoma. Patients with advanced glaucoma in this study had a mean ± SD IOP of 14.8 ± 2.4mmHg 12 months after treatment, with 50% achieving an IOP < 18 mm Hg and ≤ 30% reduction.[192]

Our trial also included 49 eyes with exfoliation glaucoma (see Figure 2, page 19), a secondary open-angle glaucoma which typically carries a poorer long-term prognosis than primary open-angle glaucoma.[193] So far the effect of selective laser trabeculoplasty on eyes with exfoliation glaucoma was studied only in a few clinical studies with small sample sizes which have shown inconclusive results concerning the association of IOP lowering through SLT treatment and exfoliation glaucoma.[193–196] In this trial, the presence of exfoliation glaucoma was an independent predictor of a lower success rate compared to eyes with no exfoliation glaucoma (odds ratio for success 0.16 (95% CI 0.05-0.46, p=0.0009).[189] However, the probability of success in the SLT group was still higher than in the timolol group (see table A6, appendix 4, chapter 5). The absolute IOP reduction was lower in eyes with exfoliation glaucoma compared to eyes with no exfoliation glaucoma in the SLT group. The regression analysis estimated a difference in IOP reduction of 1.65 mmHg (95% CI -0.77 – 4.07, p=0.18) between the two groups. After adjusting for the different baseline IOPs in the two groups, the difference was statistically significant and increased to 3.26 mmHg (95% CI 0.98 – 5.55, p=0.005). Exfoliation glaucoma has a particularly high prevalence in some regions in Africa including blindness related to XFG, see also chapter Exfoliation syndrome and exfoliation glaucoma, page 19.[29]

We also evaluated the SLT laser-specific factors: total energy and amount of cavitation bubbles which are temporarily generated by the procedure. Chamber angle descriptors which we tested for an association with IOP lowering were chamber angle width (Spaeth), angle pigmentation, and minimum height of the trabecular meshwork. The height of the trabecular meshwork was estimated by relating the distance between the scleral spur and Schwalbe's line in relation to the fixed laser spot diameter of 400µm. The lowest height of the four quadrants of the chamber angle was used for the evaluation and showed an association with IOP lowering after primary SLT but not after repeat SLT. The chamber angle width (mean Spaeth angle ≤30° versus >30°) showed the same pattern of associations after primary and repeat SLT (see table 3 and table A2 in chapter 6). The difference between primary and repeat SLT might be due to the biased selection of eyes which underwent repeat SLT and the smaller sample of eyes which underwent repeat SLT. Alternatively, the parameters might have a limited relevance for predicting IOP lowering. To our knowledge the height of the trabecular meshwork in relation to the SLT aiming beam diameter has not been previously described and further research is needed to evaluate its relevance.

### Repeat selective laser trabeculoplasty

The study protocol provided for repeat SLT if the individual IOP threshold was exceeded. The protocol was also followed if the primary SLT didn't show a response. Out of the 181 examined eyes, 146 eyes (81%) showed an IOP reduction of at least 2mmHg and 35 eyes (19%) showed no IOP reduction response after SLT (Figure 1, chapter 6). Out of the eyes with an initial response, 72% showed a response and 28% showed no response after the repeat SLT. But out of the eyes with no response after the primary SLT treatment, 70% still showed a response after repeat SLT whereas 30% showed no response after the second SLT procedure. So far there is only limited evidence for repeat SLT after primary SLT with no response. Khouri et al. published a retrospective analysis of 45 eyes of 25 participants with open-angle glaucoma treated with repeat 360-degree SLT a mean of 28.3 (SD ± 12.7) months after initial SLT.[197] Patients receiving repeat SLT were included regardless of their initial response to SLT. At 24 months after repeat treatment, 29% of patients achieved an IOP reduction of at least 20% and 39% of eyes achieved an IOP reduction of at least 15%, which was not significantly different from the 24-month success rates of the initial SLT treatment.[197]

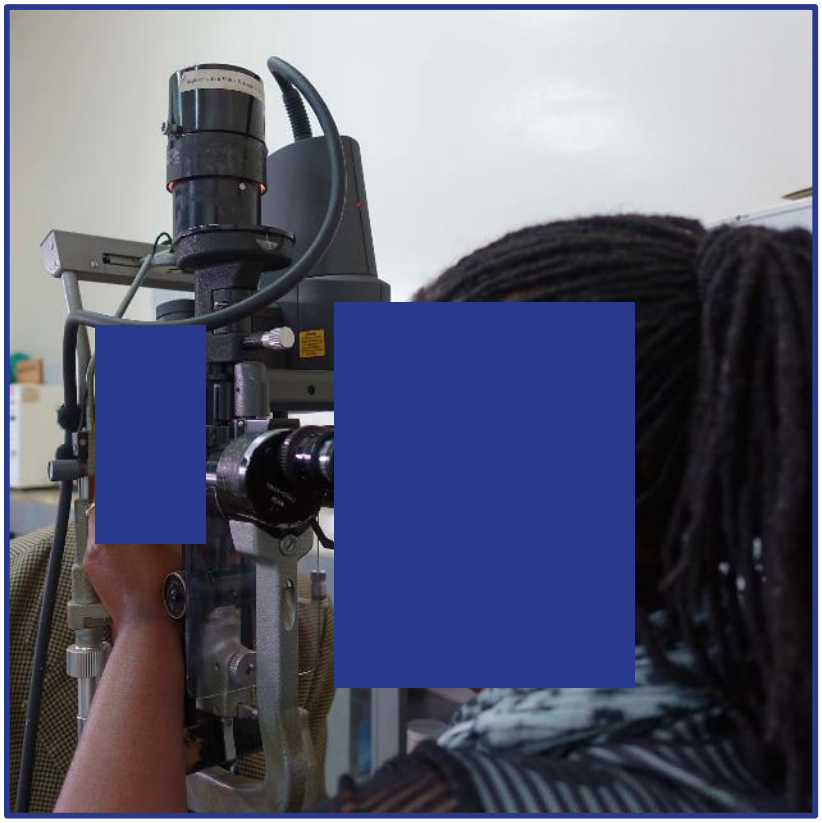
### Using selective laser trabeculoplasty in public eye health

The results suggest that SLT could be used instead of timolol eye drops as initial treatment or in combination if glaucoma still progresses. For some patients this might be a sufficient treatment option for a long period of time. However, even if a trabeculectomy is necessary early, SLT treatment can provide a stronger IOP reduction in case the patient would like more time to decide about surgery. In a consensus meeting of 22 eye health care professionals from throughout Tanzania in 2017 many felt that offering surgery at an initial visit would discourage patients from returning to the centre and few centres offer this option. In addition, a fear of surgery was felt to exist in both patient and surgeons.[59] A study from Nigeria reported that fewer than 5% of people offered surgery (trabeculectomy) returned for the procedure.[121] Laser treatment might have a higher acceptance rate which was similar to timolol eye drops in our study.

The high initial financial investment for the SLT laser and ongoing maintenance and repairs when necessary are factors which need to be considered when planning to implement SLT laser treatment in a region. Our cost calculation based on figures in Tanzania showed that by completing around 500 SLT procedures per year over 10 years the initial investment and subsequent expenses can be covered without charging patients more than a 1-year supply of timolol eye drops.[189] Depending on the setting, introducing the SLT laser may need to go hand in hand with strengthening of the eye health system.

A referral network around a larger eye unit equipped with the SLT laser which links the community with glaucoma services could be one model.

# 8 Future research



*Following this new evidence for more effective treatment of patients with glaucoma in Africa it is equally important to develop ways for an earlier detection and improved follow-up of glaucoma.*

This work has focused on the 1-year results of the randomised controlled trial comparing selective laser trabeculoplasty with 0.5% timolol eye drops for the treatment of glaucoma in Tanzania. Future work is planned or has started already:

- A detailed analysis of quality of life of patients with glaucoma in Tanzania using the WHO / Prevention of Blindness and Deafness 20-item Visual Functioning Questionnaire (WHO/PBD VF20, see chapter 10.7, page 168) as well as a comparison with the results of the glaucoma patient outcome and experience measure (POEM, see *table 14*, page 45).
- There is a large volume of literature on timolol eye drops but there is only very limited information on the efficacy of timolol eye drops in our region even though it is the most common treatment option for glaucoma in many African countries. Additional analyses are planned of the group of patients treated with timolol eye drops and related absolute IOP changes including a regression analysis to estimate predictive factors of IOP changes.
- Changes of secondary outcomes such as vision-related quality of life, visual acuity and visual field measurements as well as optic nerve head appearance descriptors might only become apparent after more than one year of follow-up. We therefore applied for funding to continue with follow-up of patients who continue to fulfil the success criteria. Additional funding was provided by Christian Blind Mission to continue with the follow-up of enrolled patients up to five years. A 3-year and 5-year analysis is planned using the same primary and secondary outcomes and with additional analyses of visual field data to determine progression of glaucomatous damage.
- We have developed proposals and are currently applying for funding of similar trials in other African countries to confirm and expand the results and evaluate additional treatments and treatment pathways.
- Following this new evidence for more effective treatment of patients with glaucoma in Africa it is equally important to develop ways for an earlier detection of glaucoma. These new tools and systems need to be evaluated for their reliability, cost-effectiveness, acceptability in compatibility with other systems of health care. We have started a study to scrutinize a collection of innovative tools.

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# 10 Appendices

## 10.1 Glaucoma history questionnaire

Interviewer: Date:
Patient names: KCMC No: Trial ID:

### Glaucoma History

| H 1 | Current and Past History | *Hali ya sasa tangu kipimo kilichopita* |
|---|---|---|
| H 1.1 | Did you notice any change of your vision recently (e.g. during the last 3 months since the last visit)? E.g. transient visual loss **(specify eye)** or visual hallucinations?<br>*Je, umeona mabadiliko yeyote katika kuona?* | |
| H 1.2 | Do you have any other (new) ocular complaint? If yes, specify<br>*Je, una tatizo jipya la macho?* | |
| H 1.3 | Do you have any other (new) general complaint? If yes, specify<br>J*e, una tatizo jingine lolote la afya?* | |
| H 1.4 | Do you take any new eye drops or tablets? If yes, specify<br>*Je unatumia matone mengine ya macho au vidonge?* | |
| H 1.5 | Do you have any comment or question?<br>Je, una maswali au maoni yeyote?<br>*For patients on timolol eye drops:*<br>1) Who gives the eyedrops?<br>2) In the past 2 weeks – did you use timolol<br>a) every day?<br>b) all days except 1 or 2 days?<br>c) not, I couldn't take/forgot it on >2 days?<br>3) When did you take the last eye drop? | |

## 10.2 Annual glaucoma history and cost questionnaire

| **H 1** | **General Data *Habari kwa ujumla*** |
|---|---|
| H 1.1 First Name *Jina*: | |
| H 1.1 Middle (Father's) Name | |
| H 1.1 Family Name *Jina*: | |
| H 1.2 KCMC No: | |
| E 1.4 BIMA Yes/No | |
| H 1.3 Date of Birth *DD/MM/YYYY* *Tarehe ya kuzaliwa* | / / / |
| H 1.4 Phone numbers (specify phone holder) *Namba ya simu (mmiliki)* | *1) No:* *Name:*<br>*2) No:* *Name:*<br>*3) No:* *Name:* |
| H 1.5 Trial ID | |
| H 1.6 Preferred language *Lugha pendekezi* | ① Swahili, ② English, ③ Chagga, ④ Massai ⑤ Other (specify) |
| H 1.7 Place of living *Mahali (Kijiji na wilaya)* | *Village:*<br>*District:* |
| H 1.8 How far is your home from the next main bus stop *Unaishi umbali gani kutoka kituo cha basi (muda au km, kutembea au pikipiki)* | *Time (min):*<br>*Distance (km):*<br>*Means (Walking, Motorcycle):* |
| H 1.9 Religion *Dini* | ① *Christian,* ② *Muslim,* ③ *Hindu,* ④ *None,* ⑤ *Other (specify)* |
| H 1.10 Occupation *Kazi* ***(always specify!)*** | ① *Peasant/Elementary works*<br>② *Associate Professional*<br>③ *Professional*<br>④ *other* |
| H 1.11 Tribe *Kabila* | ① *Chagga* ② *Pare* ③ *Meru* ④ *Massai* ⑤ *Mwarusha*<br>⑥ *Sambaa* ⑦ *other (specify)* |
| H 1.12 Education *Elimu* | ① *No formal education,* ② *Some primary,* ③ *Completed primary,*<br>④ *Some secondary,* ⑤ *Completed secondary,* ⑥ *College and University* |
| H 1.13 How many (grand) children do you have? How many live at your home? Age and gender? *Una watoto wangapi? Unaishi na wangapi nyumbani? Umri wao* | |
| H 1.14 How many people live at home? (e.g. spouse, children, parents etc.) *Wategemezi ni wangapi? (mwenza, watoto, ndugu, wazazi n.k.)* | |

| | F | M | Living at home | Age of oldest and youngest |
|---|---|---|---|---|
| Children | | | | |
| Grandchildren | | | | |

| | Spouse | Children | Parents | Other relatives | Helper | Other, specify |
|---|---|---|---|---|---|---|
| No | | | | | | |

## 10.3 History of glaucoma at entry into the trial

| H 2 | History of Glaucoma<br>*Taarifa ya ugonjwa wa shinikizo la maji ya macho* | | |
|---|---|---|---|
| H 2.1 | Which symptoms do you have? Je, *unapata dalili zipi?* | **Visual** No ◯ Yes ◯ , specify character, eye, and starting time:<br>**Pain** No ◯ Yes ◯ , specify eye, location and starting time:<br>**Other** No ◯ Yes ◯ , specify (eye and symptom): | |
| H 2.2 | When and where did you seek help for glaucoma for the first time?<br>Lini na wapi uligundulika na ugonjwa wa shinikizo la maji ya macho? | Date:<br>Place: | |
| H 2.3 | When and where was the diagnosis of glaucoma made?<br>Lini na wapi uligundulika na ugonjwa wa shinikizo la maji ya macho? | Date:<br>Place: | |
| H 2.4 | Do you remember your first eye pressure (or any IOP before treatment)?<br>*Je, unakumbuka shinikizo la maji ya jicho la kwanza (au kabla ya matibabu)* | No ◯<br>Yes ◯ , RE: mmHg LE: mmHg, date estimate:<br>RE: mmHg LE: mmHg, date estimate: | |
| H 2.5 | Was any treatment started so far?<br>If you received eyedrops, where did you buy them?<br>*Je, umeanza matibabu yeyote? Je, unanunua wapi matone?* | No ◯ Yes ◯ , if yes, specify type of treatment-surgical- laser-drops<br>If laser or surgery, specify place and date:<br>If already on eye drops, specify name(s):<br>Bought at ① Pharmacy ② Hospital ③ Don't know<br>④ Other (specify) | |
| H 2.6 | Which alternative ways of treatment did you use or consult so far?<br>*Njia zipi mbadala unatumia kwa mfano waganga, viongozi wa dini, dawa za mitishamba, maombi etc* | **Traditional medicine** No ◯ Yes ◯ , specify:<br>**Traditional healer** No ◯ Yes ◯ , specify:<br>**Prayer at church/mosque** No ◯ Yes ◯ , specify,<br>**Other** No ◯ Yes ◯ , specify:<br>If any yes, did it help? No ◯ Yes ◯ , specify: | |
| H 2.7 | Who referred you to KCMC?<br>*Nani alikupa rufaa ya kuja KCMC? 1) Mwenyewe, 2) hospitali nyingine au daktari?* | ① Self-referral<br>② Other hospital or doctor (specify)? | |
| H 2.8 | Do you know of glaucoma in your family?<br>*Unafahamu kama kunamtu yoyote kwenye familia yenu ana ugonjwa wa shinikizo la maji ya macho?* | No ◯ Yes ◯ If yes, who has glaucoma?<br>① Parent<br>② Sibling<br>③ Other, specify | |
| H 2.9 | Did you have uveitis in the past (red painful eye for several weeks)? *Je umekuwa na macho mekundu yenye maumivu kwa wiki chache* | No ◯ Yes ◯ If yes when | |
| H 2.10 | Did you have any other eye problems in the past? *Je umekuwa na matatizo mengine ya macho kabla* | No ◯ Yes ◯ If yes specify | |
| H 2.11 | Do you have asthma, bradycardia (slow heart beat), previous heart failure (swollen legs, trouble breathing)? *Je una matatizo ya pumu, bradycadia(Mapigo ya chini ya moyo) moyo kushindwa kufanya kazi( miguu kuvimba, kushindwa kupumua)* | No ◯<br>Yes ◯ | |
| H 2.12 | Do you have any other general diseases or complaints? *Je una matatizo mengine ya afya?* | No ◯ Yes ◯ If yes specify | |
| H 2.13 | Did you use beta-blockers (for high blood pressure) or did you experience a hypersensitity to beta-blockers (fast heartbeat and feeling hot after taking beta-blocker tablets)? *Je unatibia presha ya kupanda, na unajisikia kuweweseka unapotumia dawa kama moyo kwenda kasi na joto?* | No ◯<br>Yes ◯ | |
| H 2.14 | Do you take any other tablets? *Je unatumia vidonge vyovyote*? | No ◯ Yes ◯ If yes specify | |
| H 2.15 | Are you possibly pregnant? *Je una ujauzito?* | No ◯<br>Yes ◯ | |

## 10.4 Cost of transport questionnaire

| H 3 | Cost of Transport Gharama za usafiri | |
|---|---|---|
| H 3.1 | Where did you start your journey to the hospital? *Safari yako ilianzia wapi kuja hospitalini?* | ① Home as indicated in 1.7?<br>② Other, specify |
| H 3.2 | At which day and time did you start your journey to the hospital and at what time did you arrive? *Ulianza lini safari ya kuja hospitalini?* | Date and time of start:<br>Date and time of arrival: |
| H 3.3 | What type(s) of transport did you use? (one way) *Je, unatumia usafiri wa aina gani?*<br>1) Walking,<br>2) Motorcycle,<br>3) Dalladalla,<br>4) Bus,<br>5) other | |

| Type No | Place start | Place end | Distance (km) | Cost (TZS) | Time (min or h) | Comments |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

| | | |
|---|---|---|
| H 3.4 | How much did you or will you pay for food during your travel? (TZS) *Je, unalipa kiasi gani kwa chakula cha mchana?* | TZS |
| H 3.5 | Did you come with a family member or a helper? If yes, what is he/she usually doing? *Ulikuja na mtu wa familia yako au msaidizi? Kama ndiyo, huwa anajishughulisha na nini?* | No ◯ Yes ◯<br>Occcupation (categories see H 1.10): |
| H 3.6 | Do you have to stay overnight? *Je unapaswa kulala? Kama ndiyo, wapi? Kwa gharama zipi?* | No ◯ Yes ◯<br>Where? Extra Cost: |

## 10.5 Situation at home questionnaire

| H 4 | Situation at Home *Hali ya nyumbani* | |
|---|---|---|
| H 4.1 | What are you doing most of the time (at work or at home)? *Muda mwingi hua unafanya nini nyumbani? (see H 1.10)* | |
| H 4.2 | Are you earning money? *Unafanya shughuli gani kujipatia kipato? Tafadhali fafanua* | No ◯ Yes ◯<br>If yes, what kind of work? |
| H 4.3 | In total, how much money do you **spend** per month? *Kwa jumla, unatumia kiasi gani cha fedha kwa mwezi?* | ① ≤ 30,000 TZS per month (≤1,000 per day)<br>② >30-150,000 per month (>1,000 – 5,000 per day)<br>③ >150,000-600,000 per month (>5,000 – 20,000 per day)<br>④ >600,000-1.2 Million per month (>20,000 – 40,000 per day)<br>⑤ > 1.2 Million TZS per month (> 40,000 per day) |
| H 4.4 | Do you have help at home? *Je, una msaidizi nyumbani? Kama ndiyo, je anaweza kukuwekea matone? Anajishughulisha na nini?* | No ◯ Yes ◯ If yes, who could give you eyedrops?<br>① Self ② Spouse ③ Children ④ Relatives ⑤ Neighbours ⑥ Other (specify)<br>If yes, what is the helper doing otherwise? (categories see H 1.10) |

## 10.6 Willingness-to-pay questionnaire

| H 5 | **Willingness-to-pay *Utayari wa kulipa*** | |
|---|---|---|
| H 5.1 | If you could buy full vision how much would you be willing to pay? *Kama ungetakiwa kulipa ili uweze kuona, ni kiasi gani cha fedha ungeweza kulipa?* | 1) 100% 2) 75% 3) 50% 4) 25% 5) 0% of monthly income?<br>◯ I don't know |
| Do you have any other questions or comments concerning this interview?<br><br>*Je, una maswali* au mawazo yeyote kuhusu usahili huu? | | |

## 10.7 WHO/PBD VF20 Questionnaire

Interviewer: Date: Start time: End time:

Interviewee Names: Hospital No: Trial ID:

I would like to ask you questions concerning your eyes and the ability to see. The first questions will be dealing with your visual capability. There will be five options of answers then you can select one.
*Ningependa kukuuliza maswali kuhusu macho yako na kuona kwako. Maswali ya kwanza yanahusiana na uwezo wako kuona kijumla. Nitakusomea orodha ya majibu matano kwa kila swali na utachagua jibu linaloeleza hali yako muafaka.*

| | **1. Very good *vizuri sana*** **2. Good *vizuri*** **3. Moderate *wastani*** **4. Bad *vibaya*** **5. Very bad *vibaya sana*** | |
|---|---|---|
| 1 | Overall, how would you rate your eyesight using both eyes – with glasses or contact lenses if you wear them?<br>*Kwa jumla, unaonaje uwezo wako wa kuona kwa macho yote mawili (ukiwa umevaa miwani)* | |
| | **1. None *hapana*** **2. Mild *maumivu kidogo*** **3. Moderate *wastani*** **4. Severe *maumivu makali*** **5. Extreme *maumivu makali sana*** | |
| 2 | How much pain or discomfort do you have in your eyes (e.g. burning, itching, aching)?<br>*Unamaumivu kiasi gani kwenye macho yako mfano kuumwa, kuwashwa, kuchomwa* | |
| (NOTE: If the responses were "Very good" and "None" to the above two questions, END the interview.)<br>Kama majibu ni **vizuri sana** na **hapana** kwa maswali hayo mawili usiendelee na maswali mengine | | |

| | **1. None *hapana*** **2. Mild- *kidogo*** **3. Moderate *wastani*** **4. Severe *sana*** **5. Extreme *siwezi kabisa*** | |
|---|---|---|
| 3 | Because of your eyesight, how much difficulty do you have in going down steps or stairs?<br>*Kulingana na uono wako unapata shida kiasi gani unapopanda au kushuka ngazi?* | |
| 4 | How much difficulty do you have in noticing obstacles while you are walking alone (e.g. animals or vehicles)?<br>*Unapata shida kiasi gani kutambua/kuona vizuizi unapotembea peke yako? Mfano wanyama, magari* | |
| 5 | How much difficulty do you have in seeing because of glare from bright lights?<br>*Kulingana na uono wako unapata ugumu kiasi gani kwenye mwanga mkali?* | |
| 6 | Because of your eyesight, how much difficulty do you have in searching for something on a crowed shelf?<br>*Kulingana na uono wako unapata ugumu kiasi gani kutafuta kitu kwenye kabati lenye vitu vingi?* | |
| 7 | How much difficulty do you have in seeing differences in colours?<br>*Unapata ugumu kiasi gani kutofautisha rangi?* | |
| 8 | Because of your eyesight, how much difficulty do you have in recognizing the face of a person standing near you?<br>*Unapata ugumu kiasi gani kutambua sura ya mtu aliyesimama mbele yako?* | |
| 9 | How much difficulty do you have in seeing the level in a container when pouring?<br>*Unapata shida kiasi gani kujua ujazo wa kitu unachomimina kwenye chombo?* | |
| 10 | Because of your eyesight, how much difficulty do you have in going to activities outside of the house (e.g. sporting events, shopping, church, mosque)?<br>*Unapata shida kiasi gani kufanya shughuli nje ya nyumbani kwako? Mfano michezo,kwenda dukani, kanisani, msikitini* | |

| **1. None *hapana*** | **2. Mild- *kidogo*** | **3. Moderate *wastani*** | **4. Severe *sana*** | **5. Extreme *siwezi kabisa*** | |
|---|---|---|---|---|---|
| 11 | Because of your eyesight, how much difficulty do you have in recognizing people you know from a distance of 20 metres?<br>*Kulingana na uono wako unapata shida kiasi gani kumtambua mtu unayemjua kwa umbali wa mita 20?* | | | | |
| 12 | How much difficulty do you have in seeing close objects (e.g. making out differences in coins or notes, reading newsprint) with your reading glasses (if you use them)?<br>*Unapata ugumu kiasi gani kuona vitu vilivyo karibu? Mfano kusoma, kutofautisha sarafu* | | | | |
| 13 | How much difficulty do you have in seeing irregularities in the path when walking (e.g. potholes)?<br>U*napata shida kiasi gani kutembea kwenye njia yenye mabonde au mandimbwi?* | | | | |
| 14 | How much difficulty do you have in seeing when coming inside after being in bright sunlight? *Unapata shida kiasi gani kuona unapotoka kwenye mwanga mkali na kuingia* ndani? | | | | |
| 15 | How much difficulty do you have in doing activities that require you to see well close up (e.g. sewing, using hand tools)?<br>*Unapata ugumu kiasi gani unapofanya shughuli zinazohitaji kuona kwa ukaribu mfano kufuma vitambaa, kutumia vifaa vya mkono?* | | | | |
| 16 | Because of your eyesight, how much difficulty do you have in carrying out your usual work?<br>*Unapata ugumu kiasi gani kuendelea na shughuli zako za kila siku?* | | | | |

| **1. Never *sijawahi*** | **2. Rarely *kwa nadra*** | **3. Sometimes *mara chache*** | **4. Often *mara kwa mara*** | **5. Very often *mara nyingi*** | |
|---|---|---|---|---|---|
| 17 | Because of your eyesight, how often have you been hesitant to participate in social functions?<br>*Kulingana na uono wako kwa kiasi gani unasita kushiriki katika shughuli za kijamii?* | | | | |
| 18 | Because of your eyesight, how often have you found that you are ashamed or embarrassed?<br>*Kwa kiasi gani umedharaulika kuligana na uona wako?* | | | | |
| 19 | Because of your eyesight, how often have you felt that you are a burden on others?<br>*Kulingana na uono wako, kwakiasi gani umejiona ni mzigo kwa wenzako?* | | | | |
| 20 | Because of your eyesight, how often do you worry that you may lose your remaining eyesight?<br>*Kwa kiasi gani umekuwa ukiogopa kupoteza uwezo wako wa kuona uliobaki?* | | | | |

Comments:

## 10.8 How to use and instil your own eye drops

1) How to open your eye drop bottle. ***Jinsi ya kufungua chupa yako ya matone ya macho.***

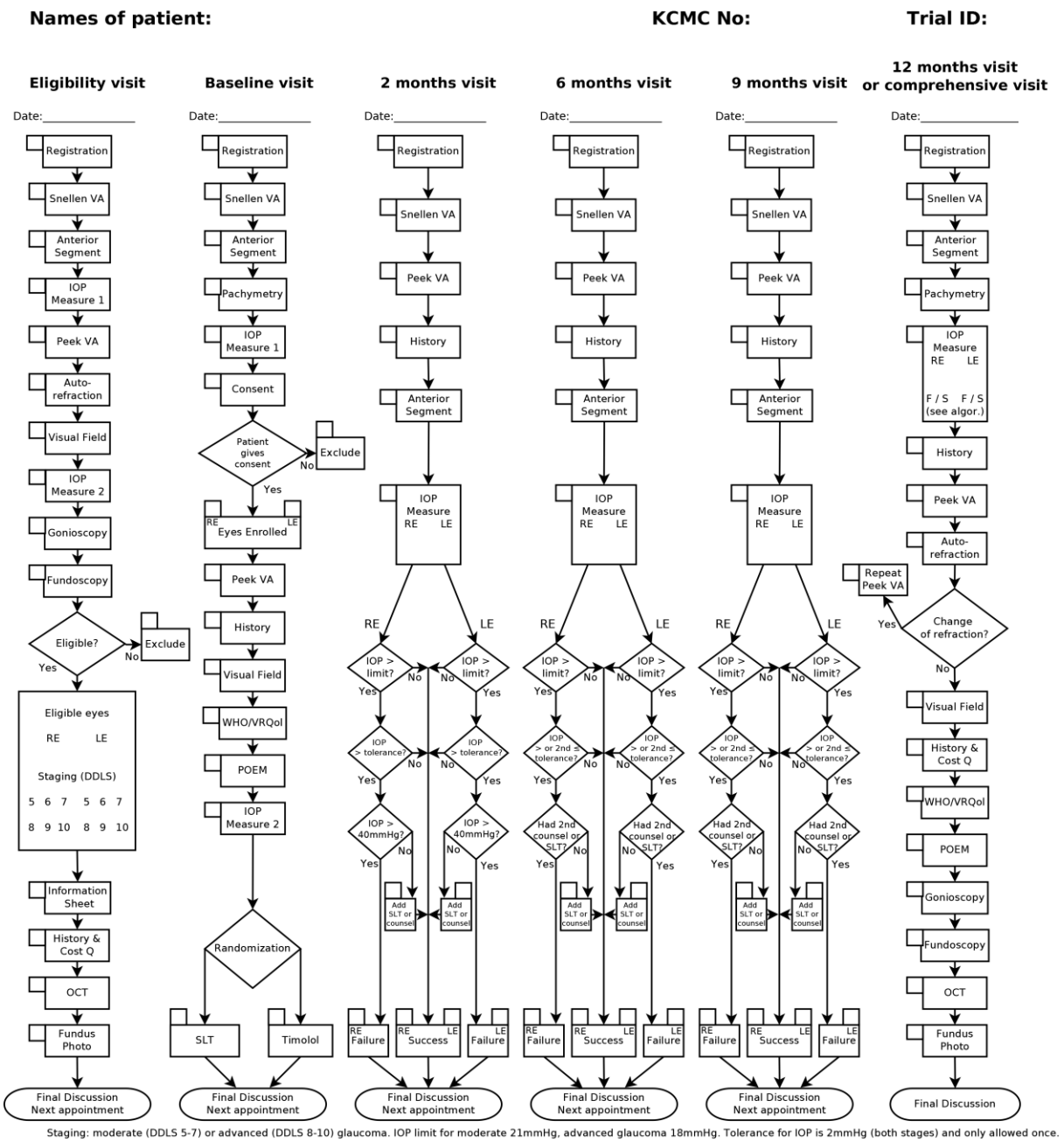
- Tight your bottle cap to the maximum end. ***Kaza chupa yako yenye matone mpaka mwisho kabisa.***
- Open and gently try to squeeze out a drop to see of the cap has punched a hole into the bottle tip. ***Taratibu fungua ili uone kama kifuniko kimetengeneza tundu kwenye mdomo wa chupa.***
- Use the same eye drop bottle for about one month before opening another one (in case you were given several bottles). ***Tumia chupa hiyo hiyo ya matone kwa kadri ya mwezi mmoja kabla ya kufungua nyingine. (ikiwa unazo chupa za ziada)***

2) How to instil your own eye drops **Jinsi ya kuweka matone kwenye macho yako.**

- Combine drop application time with your daily routine activities **Ambatanisha uwekaji wa matone na shughuli zako za kila siku, mfano; Kabla ya chai au chakula cha jioni**
- Sit or lie down with your head supported. As your skill develops you may eventually manage to instil your eye drops while standing. **Keti au lala na egemeza kichwa, kadri unavyotumia utazoea kuweka matone ukiwa umesimama.**
- Use your dominant hand to hold the bottle. **Shika chupa kwa mkono unaoutumia (kushoto au kulia)**
- With the index finger of your other hand, hold a clean piece of tissue or cotton wool (if available), and gently pull down the lower eyelid to form a 'pocket'. **Tumia kidole cha shahada kwa mkono mwingine na kitambaa kisafi, tishu au pamba kufungua jicho kwa chini**
- Hold the bottle between your thumb and forefinger, and place the 'heel' of your hand (where the wrist meets the hand) on your cheek. This will help to steady shaky hands. **Shika chupa yako kwa dole gumba na shahada, egemeza mkono juu ya uso kuzulia usitikisike.**
- Make sure there is a short distance of about an inch (2.5cm, the width of two fingers) between your eye and the end of the bottle. Be careful – the tip must not touch any part of the eye or eyelids. **Hakikisha unaacha nafasi kama inchi 2.5 kati ya vidole na uso na chupa ili usigusishe chupa yenye dawa na jicho lako au kope zako.**
- Look up or to the side. Do not look directly at the bottle. **Angalia juu au pembeni. Usiangalie chupa yenye matone.**
- Squeeze the bottle – allow one drop to fall into the lid pocket. **Binya chupa – hakikisha tone moja linaingia kwenye jicho ulilolifungua kwa kitambaa safi, tishu au pamba**
- Slowly let go of the lower lid. Gently close your eyes; try not to shut them tightly as this will squeeze the drop out of your eye. **Taratibu acha tone lisambae ndani ya jicho, funga jicho taratibu, usikaze jicho ili dawa isitoke nje.**
- Dab your closed eye with the tissue or cotton wool to remove any excess. **Ukiwa umefumba macho yako futa matone au machozi yaliyomwagika nje au pembeni ya macho kwa kitambaa safi, tishu au pamba**
- Put gentle pressure on the inside corner of your eye and count to 60, very slowly. This prevents the medicine from draining out of your eye before it is absorbed. **Kandamiza upande wa macho yako karibu na pua kwa dakika 1 au 2 ili kuzuia dawa kushuka kwenye koo lako na kubaki kwenye macho yako.**

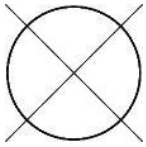
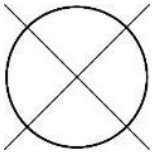
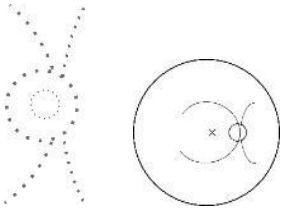
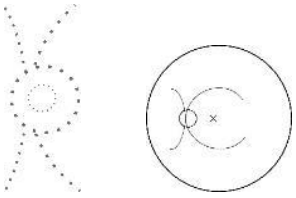
(adapted from *Instilling your own eye drops* (2012) Community Eye Health Journal, Vol 25, 79 & 80, p 79)

## 10.9 Patient flow chart



## 10.10 Data collection tools

### 10.10.1 Eligibility visit

| EV | | RE Examination LE | | | | | |
|---|---|---|---|---|---|---|---|
| EV 1 | Snellen Visual Acuity (Plain/Pinhole/Glasses) | Pl | Ph | Gl | Pl | Ph | Gl |
| EV 2 | PEEK VA (logMAR) (Plain/Pinhole/Glasses) | Pl | Ph | Gl | Pl | Ph | Gl |
| EV 3 | PEEK Contrast (C) and Red Desaturation (RD) | C | RD | | C | RD | |
| EV 4 | Autorefractor | Sph | Cyl | Ax | Sph | Cyl | Ax |
| EV 5 | **IOP** 1 Time: Examiner: | R1 | R2 | (R3) | L1 | L2 | (L3) |
| | **IOP 2** Time: Examiner: | R1 | R2 | (R3) | L1 | L2 | (L3) |
| EV 6 | **Anterior Segment** Lids | | | | | | |
| | Conjunctiva | | | | | | |
| | Cornea | Opacities Kruk Y/N | | | Opacities Kruk Y/N | | |
| | AC[1] | Flare ____ Cells ____ VH ____%/_____ | | | Flare ____ Cells ____ VH ____%/_____ | | |
| | Pupil diameter | _____ mm | | | _____ mm | | |
| | Lens | COR__ PSC ___ NUC ___ XF ____ | | | COR__ PSC ___ NUC ___ XF ____ | | |
| | Other | | | | | | |
| EV 7 | **RAPD** | | | | | | |
| EV 8 | **Gonioscopy** Peripheral iris insertion Angular approach Iris curvature TM pigmentation (@ 12:00) |  | | |  | | |
| EV 9 | **Optic Disc** Size vert/hor | V_____mm H_____mm | | | V_____mm H_____mm | | |
| | Beta Zone | Y / N, if y where? | | | Y / N, if y where? | | |
| | Disc haemorrhages. | Y / N, if y where? | | | Y / N, if y where? | | |
| | Rim notch | Y / N, if y where? | | | Y / N, if y where? | | |
| | Pores↑ lamina cribrosa | Y / N | | | Y / N | | |
| | Narrowest rim/ °/DDLS[2] | / °/ | | | / °/ | | |
| | CD-R vert/hor | / | | | / | | |
| EV 10 | **Posterior Segment** **Sketch** Optic Disc Macula Periphery |  | | |  | | |

### 10.10.2 Baseline visit

| | | RE | | | Examination | | LE | |
|---|---|---|---|---|---|---|---|---|
| BV 1 | Snellen Visual Acuity (Plain/Pinhole/Glasses) | Pl | Ph | Gl | Pl | Ph | Gl | |
| BV 2 | PEEK VA (logMAR) (Plain/Pinhole/Glasses) | Pl | Ph | Gl | Pl | Ph | Gl | |
| BV 3 | PEEK Contrast (C) and Red Desaturation (RD) | C | RD | | C | RD | | |
| BV 4 | **IOP** 1 Time: Examiner: | R1 | R2 | (R3) | L1 | L2 | (L3) | |
| | **IOP 2** Time: Examiner: | R1 | R2 | (R3) | L1 | L2 | (L3) | |
| BV 5 | **Anterior Segment** Lids | | | | | | | |
| | Conjunctiva | | | | | | | |
| | Cornea | Opacities | | Kruk Y/N | Opacities | | Kruk Y/N | |
| | AC[1] | Flare ____ Cells ____ VH ____%/_____ | | | Flare ____ Cells ____ VH ____%/_____ | | | |
| | Pupil diameter | _____ mm | | | _____ mm | | | |
| | Other | | | | | | | |
| BV 6 | **RAPD** | | | | | | | |
| BV 7 | **CCT** avg±sd, min, max | | | | | | | |

### 10.10.3 Two-month visit examination form

| | | RE Examination LE | | | | | |
|---|---|---|---|---|---|---|---|
| 2V 1 | Snellen Visual Acuity (Plain/Pinhole/Glasses) | Pl | Ph | Gl | Pl | Ph | Gl |
| 2V 2 | PEEK VA (logMAR) (Plain/Pinhole/Glasses) | Pl | Ph | Gl | Pl | Ph | Gl |
| 2V 3 | PEEK Contrast (C) and Red Desaturation (RD) | C | RD | | C | RD | |
| 2V 4 | **IOP** Time: Examiner: | R1 | R2 | (R3) | L1 | L2 | (L3) |
| 2V 5 | **Anterior Segment** Lids | | | | | | |
| | Conjunctiva | | | | | | |
| | Cornea | Opacities Kruk Y/N | | | Opacities Kruk Y/N | | |
| | AC[1] | Flare ____ Cells ____ VH ____%/_____ | | | Flare ____ Cells ____ VH ____%/_____ | | |
| | Other | | | | | | |
| 2V 6 | **RAPD** | | | | | | |

[1] VH…van Herrick test, note % and/or stage

The data collection forms of 6-month and 9-month visits followed the format of the 2-month visit and the 12-month visit repeated all examinations of the eligibility and baseline visits.

# 10.11 Ethical clearance certificate: London School of Hygiene & Tropical Medicine

**London School of Hygiene & Tropical Medicine**
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

**www.lshtm.ac.uk**

**Observational / Interventions Research Ethics Committee**

Dr. Heiko Philippin
Research Degree Student
ITD
LSHTM

8 October 2014

Dear Dr. Philippin,

**Study Title: A Randomized Controlled Trial Comparing Selective Laser Trabeculoplasty and Timolol for Treatment of Glaucoma in Tanzania**

**LSHTM Ethics Ref: 7166**

Thank you for your letter of 29 September 2014, responding to the Interventions Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

**Conditions of the favourable opinion**

Approval is dependent on local ethical approval having been received, where relevant.

**Approved documents**

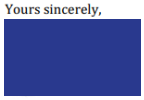
The final list of documents reviewed and approved by the Committee is as follows:

| Document Type | File Name | Date | Version |
|---|---|---|---|
| Protocol / Proposal | KiGIP A 01 Patient Checklist 2014 07 28.pdf | 29/07/2014 | 1.0 |
| Protocol / Proposal | KiGIP A 03 Examination Form.pdf | 29/07/2014 | 1.0 |
| Protocol / Proposal | KiGIP A 04 Interview - History & Cost MJB.pdf | 29/07/2014 | 1.0 |
| Protocol / Proposal | KiGIP A 05 Interview - POEM.pdf | 29/07/2014 | 1.0 |
| Protocol / Proposal | KiGIP A 06 Interview - QoL.pdf | 29/07/2014 | 1.0 |
| Protocol / Proposal | KiGIP A 07 Focus Group Interview Guide.pdf | 29/07/2014 | 1.0 |
| Protocol / Proposal | KiGIP A 08 SAE Form.pdf | 29/07/2014 | 1.0 |
| Advertisements | Participant Recruitment.docx | 31/07/2014 | 1.0 |
| Protocol / Proposal | KiGIP 2014 07 31 Study Protocol.pdf | 31/07/2014 | 1.0 |
| Information Sheet | KiGIP A 02 Patient Information & Consent English 2014 09 30.pdf | 30/09/2014 | v1.2 |

**After ethical review**

Any subsequent changes to the application must be submitted to the Committee via an Amendment form on the ethics online applications website. The Principal Investigator is reminded that all studies are also required to notify the ethics committee of any serious adverse events which occur during the project via an Adverse Event form on the ethics online applications website. An annual report form is required on the anniversary of the approval of the study and should be submitted during the lifetime of the study on the ethics online applications website. At the end of the study, please notify the committee via an End of Study form on the ethics online applications website. Ethics online applications website link: http://leo.lshtm.ac.uk

Yours sincerely,



**Professor John DH Porter**
**Chair**

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

**Improving health worldwide**

Page 1 of 1

## 10.12 Ethical clearance certificate: Kilimanjaro Christian Medical University College

CRERC FORM NO.7

TUMAINI UNIVERSITY MAKUMIRA

KILIMANJARO CHRISTIAN MEDICAL UNIVERSITY COLLEGE
P. O. Box 2240, MOSHI, Tanzania

RESEARCH ETHICAL CLEARANCE CERTIFICATE

No. 800

**Research Proposal No.** 675

**Study Title:** A randomized controlled trial comparing selective laser trabeculoplasty and timolol for treatment of glaucoma.

**Study Area:** Moshi.

**Principal Investigator:** William U. Makupa

**Co-investigator (s):** Elisante Muna, Mathew Burton, Heiko Philippin

**Institution (s):** KCMC and KCMU College

**Funding Agency:** LSHTM

**The Proposal was approved on:** .15th January, 2015

**Duration of Study:** One year

**From:** 15th January,2015 to15th January,2016

*This certificate is valid for one year only*

[redacted]

Beatrice Temba
**Secretary – CRERC**

[redacted]

Prof. Mramba Nyindo
**Chairman – CRERC**

## 10.13 Ethical clearance certificate: National Institute for Medical Research, Tanzania

THE UNITED REPUBLIC OF TANZANIA

National Institute for Medical Research
3 Barack Obama Drive
P.O. Box 9653
11101 Dar es Salaam
Tel: 255 22 2121400
Fax: 255 22 2121360
E-mail: headquarters@nimr.or.tz

NIMR/HQ/R.8a/Vol. IX/1929

Ministry of Health and Social Welfare
6 Samora Machel Avenue
P.O. Box 9083
11478 Dar es Salaam
Tel: 255 22 2120262-7
Fax: 255 22 2110986

23th March 2015

Dr William Makupa
KCMC, Ophthalmology Department
P O Box 3010, MOSHI
Kilimanjaro

**CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA**

This is to certify that the research entitled: A randomized controlled trial comparing Selective Laser Trabeculoplasty and Timolol for treatment of Glaucoma in Tanzania, (Makupa W *et al*), has been granted ethical clearance to be conducted in Tanzania.
The Principal Investigator of the study must ensure that the following conditions are fulfilled:

1. Progress report is submitted to the Ministry of Health and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
2. Permission to publish the results is obtained from National Institute for Medical Research.
3. Copies of final publications are made available to the Ministry of Health & Social Welfare and the National Institute for Medical Research.
4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine. NIMR Act No. 23 of 1979, PART III Section 10(2).
5. Sites: Eye Department, at Kilimanjaro Christian Medical Centre, Moshi .

Approval is for one year: 23rd March 2015 to 22nd March 2016.

**Name: Dr Mwelecele N Malecela**

**Signature** [redacted]
**CHAIRPERSON**
**MEDICAL RESEARCH**
**COORDINATING COMMITTEE**

**Name: Dr Margaret E Mhando**

**Signature** [redacted]
**Ag CHIEF MEDICAL OFFICER**
**MINISTRY OF HEALTH, SOCIAL WELFARE**

**CC:** **RMO**
**DED**
**DMO**

## 10.14 Patient information sheet and consent form (English)

**Patient Information**

**Full Title of Project:** A Randomized Controlled Trial Comparing Selective Laser Trabeculoplasty and Timolol for Treatment of Glaucoma in Tanzania

**Introduction**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read or listen to the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

**What is the study about?**

The study compares two different treatments for glaucoma. One option is selective laser trabeculoplasty, a treatment which has been in use for over 10 years in different countries. But it has not yet been shown to be effective in Sub Saharan Africa. The second option is the standard treatment in this area, timolol eye drops.

**What is glaucoma?**

Glaucoma is caused by an increased eye pressure which causes damage to the nerve connecting the eye to the brain. Normal eye pressure ranges between 9 and 21mmHg. Damaged nerves cannot grow back (cannot heal) and this leads to loss of vision usually starting from the outer sides. But it does not cause complete loss of vision until the last part of the nerve is damaged which then causes blindness. People who are developing glaucoma usually are not aware of it until it is already very advanced. The disease cannot be reversed and doesn't improve on its own.

Treatment of glaucoma starts usually with eye drops. If a patient takes eye drops for glaucoma, it is a long term treatment perhaps throughout life. Other options are eye surgery (called trabeculectomy) or laser treatment known as *trabeculoplasty*.

**Selective Laser Trabeculoplasty and Timolol Eye Drops**

Most glaucoma patients in Tanzania receive eye drops for treatment of glaucoma to reduce their eye pressure. One bottle of eye drops lasts for about one month. But sometimes it can be challenging to buy and take the drops regularly or their effect is not enough. The next step is usually surgery in this region. An alternative treatment could be a **gentle** laser therapy of the front of the eye ("Selective Laser Trabeculoplasty"). As mentioned before, this laser is not new but it is not in use everywhere. And it has not yet been compared with timolol eye drops, the standard treatment in Tanzania (or elsewhere in sub-Saharan Africa) for glaucoma. The laser has been used in many hundreds of thousands of people during the last ten years e.g. in Europe and Northern America. Its effect will probably last for around two years on average and it can be repeated if necessary.

**What will we ask you to do?**

We will tell you if you receive either laser treatment or eye drops. Laser treatment takes around 10 minutes at a slit lamp. After application of numbing eye drops a contact glass will be inserted (the same as for examination of your drainage system (gonioscopy) which you might remember from previous visits). The laser procedure itself is not painful and patients report only mild discomfort. You can leave the hospital one hour after the procedure. The laser can be repeated which we are planning to do if the eye pressure is still too high after the first treatment. If then the effect is still not enough you can either receive eye drops or surgery.

In case we will give you eye drops, we will ask you to take two drops every day, one at breakfast and one at dinner time.

To find out how well the treatment works we will ask you to come back after 2months, 6months, 9months and 12months. These are appointments which we often recommend our glaucoma patients anyway. On each visit we will test your vision and examine your eyes as we always do when you come to the hospital. Some visits will also include a few more examinations related to glaucoma such as an image of your optic nerve. These additional examinations are often part of routine glaucoma visits as well.

We are also interested in your overall experience with glaucoma and taking treatment and will ask you questions about these matters. Information from these interviews will mainly be summarized. But we might use a quote from you without mentioning your name, as an example for a certain piece of knowledge.

**What will happen to all the information about you?**

Relevant examination results will remain in your patient file at KCMC so that in the future they will be available for you and your doctor. These files are kept confidentially. All information which we need to analyse the two treatment options will be anonymised, that is without your name on. A number rather than your name will be used on study records wherever possible.

**Do you have to take part?**

No. To participate in this study is up to you. If you decide to take part, you can still leave the study at any time without giving us a reason. If you do not take part, you will receive regular service.

**What if there is a problem?**

Any complaint will be addressed. Please approach one of the study coordinators who are indicated below.

**Who sponsored this study?**

The study is sponsored by the London School of Hygiene and Tropical Medicine.

**Who has reviewed the study?**

The study has been approved by the ethics committee of the Kilimanjaro Christian Medical University College and the National Institute for Medical Research in Tanzania. It was also approved by the ethics committee of the London School of Hygiene & Tropical Medicine.

**Are there any risks in taking part in the study?**

The laser treatment and eye drops are established treatments for glaucoma in several areas worldwide. The risks are the standard complications which can occur. The laser treatment is rarely associated with a short term rise of eye pressure or a mild inflammation. Both can be treated with eye drops. timolol eye drops can worsen asthma and cause a slow heart rate. Patients with asthma, slow heart rate or previous heart failure will not be enrolled in the study.

**What are possible benefits of taking part in the study?**

You will receive treatment for glaucoma for free for the duration of the study of one year. You will have the opportunity to come for regular follow up visits and receive support for transport expenses. You can contribute to the search for a better treatment option for glaucoma.

**In case of any questions or complaints please contact us**

Edith Macha: +255 xxx, email macha@xxx.xx
Dr. Elisante Muna: T +255 xxx, email: muna@xxx.xx
Dr. Heiko Philippin: T +255 xxx, email: philippin@xxx.xx
Dr. William Makupa: T +255 xxx, email: makupa@xxx.xx

Dr. Matthew Burton: T +44 xxx, email: matthewburton@xxx.xx

National Health Research Ethics Review Committee: T +255 xxx

College Research Ethics Review Committee, KCMUCo: T +255 xxx

**You will be given a copy of the information sheet.**
**Thank you for considering taking the time to read this sheet.**

# Informed Consent Form

**Full Title of Project:** A Randomized Controlled Trial Comparing Selective Laser Trabeculoplasty and Timolol for Treatment of Glaucoma in Tanzania

**Names of Principal Investigators:** Dr. W. Makupa (KCMC), Dr. M. Burton (LSHTM)

| | **Please tick the box** |
|---|---|
| 1. I confirm that I have read and understand the participant information sheet dated ..... (version .....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered fully. | |
| 2. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. | |
| 3. I understand that sections of my medical notes and data collected during the study may be looked at by responsible individuals from the London School of Hygiene & Tropical Medicine, from regulatory authorities or from this hospital, where it is relevant to my taking part in this research. I give permission for these individuals to access my records. | |
| 4. I agree to take part in the above study. | |
| 5 I agree for my photo or quote as explained above to be used in publications or reports released on the study or for teaching in an anonymous way. | |

| Name of Participant | Signature/Thumbprint | Date |
|---|---|---|
| Name of Person taking consent | Signature | Date |
| (Co-)Principal Investigator | Signature | Date |

The participant is unable to read. As a witness, I confirm that all the information about the study was given and the participant consented to taking part.

| Name of Impartial Witness | Signature | Date |
|---|---|---|

**In case of any questions or complaints please contact**

Edith Macha: +255 xxx, email edithmacha@xxx.xx

Dr. Elisante Muna: T +255 xxx, email: elisante.muna@xxx.xx

Dr. Heiko Philippin: T +255 xxx, email: heikophilippin@xxx.xx

Dr. William Makupa: T +255 xxx, email: makupa.uw@xxx.xx

Dr. Matthew Burton: T +44 xxx, email: matthewburton@xxx.xx

National Health Research Ethics Review Committee: T +255 xxx

College Research Ethics Review Committee, KCMUCo: T +255 xxx

### 10.15 Patient information sheet and consent form (Kiswahili)

# Taarifa za Mgonjwa

**Jina la mradi:** Majaribio ya kulinganisha Selective Laser Trabeculoplasty na Timolol kwa ajili ya matibabu ya shinikizo la maji ya jicho Tanzania.

**Utangulizi**

Unakaribishwa kushiriki katika utafiti, kabla haujafanya maamuzi ni muhimu ukafahamu kwa nini utafiti huu unafanywa na utahusisha nini. Tafadhali tumia muda wa kusoma au kusikiliza taarifa ifuatayo kwa umakini. Iwapo ungependa unaweza kuwashirikisha wengine kuhusu utafiti huu. Tuulize kama kuna jambo lolote ambalo hujalielewa au kama unataka taarifa zaidi

**Utafiti huu unahusu nini?**

Utafiti huu unalinganisha aina mbili za matibabu ya shinikizo la maji ya macho, aina ya kwanza ni miale ya taa ambayo imekuwa ikitumika nchi mbalimbali kwa zaidi ya miaka kumi. Ingawa ufanisi wake chini ya jangwa la Sahara haujaonekana, aina ya pili ya tiba ni ya matone ambayo hutumika siku zote

**Shinikizo La Maji Ya Jicho ni nini?**

Ugonjwa washinikizo la maji ya jicho unatokana nakuongezeka kwa maji ya jicho, jambo ambalo husababisha kuharibika kwa mshipa mkuu wa fahamu unaounganisha jicho na ubongo.

Shinikizo la kawaida la maji ya jicho ni kati ya 9 hadi 21 mmHg. Kuchimbika kwa kitovujicho kunasabishwa na kufa kwa vijimishipa vyafahamu vinavyo unganisha jicho na ubongo. Vijimishipa vyafahamu vilivyokufa haviponi tena, jambo linalopunguza upeo wakuona pembeni lakini haudhuru uwezo wakuona hadi kijimshipa cha mwisho kinapokufa na jicho kuwakipofu. Ugonjwa washinikizo la maji ya jicho huwa hauna dalili za maumivu ya aina yoyote yale kwenye jicho, hivyo mgonjwa asijishughulishe na dalili ambazo hawezi kuzitambua. Ugonjwa huu hauponi wenyewe, siyo mafua. Matibabu ya shinikizo ya maji ya jicho kawaida uanza na dawa ya matonye kwa muda mrefu kama sio maisha yake yote. Ila kuna njia nyingine ya upasuaji wa jicho (huitwa Trabeculectomy) au matibabu ya taa inayojulikana kama Trabeculoplasty.

**Matibabu ya taa ya laser ijulikanayo na dawa za matone mfano wa Timolol**

Wagonjwa wengi wa Tanzania wanatumia matone kutibu shinikizo la maji ya macho, chupa moja inakaa kama mwezi mmoja, wakati mwingine ni changamoto kununua na kutumia dawa wakati wote au ufanisi wake hautoshi, hatua ya pili katika eneo hili huwa ni upasuaji.

Tiba mbadala ni miale ya taa **pole** (ambayo ni tofauti na miale ya taa inayotibu vivimbe vya kansa) kama ilivyoelezwa hapo mwanzo tiba hii sio mpya lakini haitumiki kila mahali, Na haijalinganishwa na matone ambayo ndiyo tiba inayotumika Tanzania.Tiba ya miale ya taa imetumika kwa mamia na maelfu ya watu kwa miaka kumi iliyopita,ufanisi wake unaweza kukaa kwa muda wa miaka miwili na inaweza ikarudiwa tena ikihitajika.

**Tunachotaka wewe ufanye ni nini?**

Pasipo upendeleo tutakuweka kwenye kundi la kutibiwa kwa miale ya taa au kwa matone.matibabu ya miale ya taa huchukua kama dakika kumi, kwa ujumla matibabu ya miale ya taa hayana maumivu na unaweza kwenda nyumbani baada ya matibabu.

Kama utapangwa kwenye kundi la matone,utatakiwa kutumia matone mawili kwa siku, asubuhi na jioni. Watakaotibiwa kwa miale ya taa tutarudia miale ya taa kama awamu ya kwanza haitafanya kazi na kama haitafanya kazi tena tutafanya upasuaji ili kujua kama dawa inafanya kazi tutakutaka urudi baada ya miezi miwili, sita,tisa na kumi na mbili.

Hivyo ndivyo ambavyo huwa tunafanya kwa wagojwa wa shinikizo la maji ya macho, kila utakapokuja tutakuwa tunapima uonaji wako na kuyapima macho yako kama ambavyo huwa tunafanya unapokuja hospitalini.

Pia tunajihushisha sana na uzoefu wako wa shinikizo la maji ya macho na utumiaji wa dawa na tutakuwa tukikuuliza maswali kuhusu mambo haya.

Taarifa kutokana na mahojiano haya itawekwa kwenye muhutasari lakini tunaweza kukunukuu bila kukutaja jina kama sehemu ya fundisho.

**Itatokea nini juu ya maelezo yote kutoka kwake?**

Matokeo muhimu ya vipimo yatabaki kwenye faili lako la KCMC ili litumiwe na wewe na daktari siku za usoni. Mafaili yametunzwa kwa siri.Taarifa zote zitakazotumika kwenye utafiti wa tiba hizi mbili hautatumia majina.Kwa kadri itakavyowezekana namba badala ya majina zitatumika.

**Je utachukua nafasi hii?**

Hapana.Kushiriki kwenye utafiti huu ni hiari yako na hata unaposhiriki unaweza kujitoa kwenye utafiti huu wakati wowote, kama haushiriki kwenye utafiti utapata huduma za siku zote.

**Kama itatokea shida yote**

Lalamiko lolote litashughulikiwa tafadhali mwone yeyote kati ya watajwa hapo chini.

**Nani ametoa maswali haya?**

Utafiti huu umedhaminiwa na London School of Hygiene and Tropical Medicine.

**Nani ameangalia maswali haya?**

Utafiti huu umeidhinishwa na kamati ya maadili ya chuo kikuu cha KCMC na taasisi ya utafiti ya Tanzania (NIMR)

**Je kuna shida yo yote juu ya maswali haya?**

Matibabu ya miale ya taa na matone ni matibabu yanayotumika maeneo mengi duniani, tahadhari ni matatizo yanayoeleweka yanayoweza kutokea. Miale ya taa inaweza kusababisha kupanda kwa muda mfupi kwa shinikizo la maji ya macho, matone yanaweza kuzidisha pumu au kupunguza mapigo ya moyo.

Wagojwa wa pumu au historia ya matatizo ya moyo kushindwa kufanya kazi vizuri hawatashirikishwa kwenye utafiti huu.

**Je kuna faida gani juu ya maswali haya?**

Utapewa matibabu ya shinikizo la maji ya macho bure kwa kipindi chote cha utafiti cha mwaka mmoja, utapata wasaa wa kuja hospitalini mara kwa mara na utakuwa ukipewa nauli, utakuwa umeshiriki kwenye utafutwaji wa tiba bora zaidi ya kutibu shinikizo la maji ya macho.

**Kama una maswali au manung'uniko wasiliana nasi kwa anuani ifuatayo**

Edith Macha: +255 xxx, email edithmacha@xxx.xx

Dr. Elisante Muna: T +255 xxx, email: elisante.muna@xxx.xx

Dr. Heiko Philippin: T +255 xxx, email: heikophilippin@xxx.xx

Dr. William Makupa: T +255 xxx, email: makupa.uw@xxx.xx

Dr. Matthew Burton: T +44 xxx, email: matthewburton@xxx.xx

National Health Research Ethics Review Committee: T +255 xxx

College Research Ethics Review Committee, KCMUCo: T +255 xxx

**Tutakupa kopi juu ya maelezo**

**Asante kwa kutujali kujibu maswali yote**

# Fomu ya kukubali kushiriki utafiti

**Jina la mradi:** Majaribio ya kulinganisha Selective Laser Trabeculoplasty na Timolol kwa ajili ya matibabu ya shinikizo la maji ya jicho Tanzania.

Jina la mkuu wa utafiti kwa Tanzania: Dr.William Makupa
Jina la mkuu wa utafiti kwa Uingereza: Dr. Matthew Burton

**Weka alama ya vema (√) kwenye kiboksi**

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|---|---|
| 1. Nathibitisha kuwa nimesoma na kuelewa taarifa ya ushiriki, tarehe…….kwa ajili ya utafiti wa hapo juu.nilipata nafasi ya kutafakari,kuuliza maswali yaliyojibiwa kwa ukamilifu. | |
| 2. Naelewa kwamba ushiriki wangu ni wa hiari na niko tayari kujiondoa wakati wowote,pasipo kutoa sababu yoyote,na jambo hilo halitahatarisha matibabu yangu au haki zangu za kisheria. | |
| 3. Naelewa kwamba taarifa zangu za kitabibu na taarifa zilizokusanywa wakati wa utafiti zitakuwa zikifuatiliwa na watu husika kutoka LSHTM,kutoka mamlaka ya kuthibiti viwango au kutoka katika Hospitali hii ambao wana uhusiano na ushiriki wangu katika utafiti huu | |
| 4. Nakubali kushiriki kwenye utafiti huu. | |
| 5. Nakubali kwa picha yangu au maneno yangu kama ilivyoelezwa hapo juu kutumika kama taarifa ya wazi ili wengine wajifunze. | |

| Jina la mshiriki | Sahihi | Tarehe |
|---|---|---|
| Jina la mtu anayeomba ruhusa | Sahihi | Tarehe |
| Mtafiti mkuu/mwenza | Sahihi | Tarehe |

Mshiriki hawezi kuweka sahihi.Kama shahidi, nathibitisha kwamba taarifa zote kuhusu utafiti zimetolewa na mshiriki amekubali kushiriki.

| Jina la shahidi | Sahihi | Tarehe |
|---|---|---|

**Kama una maswali au manung'uniko wasiliana nasi kwa anuani ifuatayo**

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