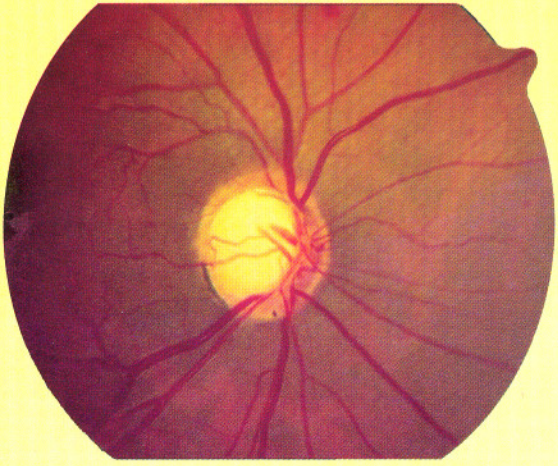
CLINICAL PRACTICE GUIDELINES

FEB 2008

MOH/P/PAK/159.08 (GU)

MANAGEMENT OF PRIMARY OPEN ANGLE GLAUCOMA



MINISTRY OF HEALTH MALAYSIA

ACADEMY OF MEDICINE OF MALAYSIA

This guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

This guideline was issued in 2008 and will be reviewed in 2011 or sooner if new evidence becomes available.

CPG Secretariat
Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia
4th Floor, Block E1, Parcel E
62590, Putrajaya.

Electronic version available on the following website:

http://www.moh.gov.my
http://www.acadmed.org.my

GUIDELINE DEVELOPMENT AND OBJECTIVE

GUIDELINE DEVELOPMENT

Primary Open Angle Glaucoma (POAG) is a chronic disease requiring life long follow-up. It is a disease being continuously researched and new evidences are emerging on various aspects of the disease, ranging from pathophysiology, natural history, risk factors, disease progression, diagnostic criteria and tests, management options and treatment goals, and appropriateness of screening. Anecdotal evidence on patients seen at local hospitals revealed some problems in its diagnosis and management, such as under-diagnosis, over diagnosis and suboptimal treatment and follow-up, leading to undesirable disease progression. In the public hospitals, the cost of treating POAG patients consumes a significant proportion of health care budget, ranging from 70% to 80% of total drug budget given to the Ophthalmology departments in the Ministry of Health. It is thus important to have an evidence based CPG on POAG to help medical officers and ophthalmologists in the management of POAG patients. This guideline is also to guide other health care providers in the screening of POAG amongst the high risk population.

The development group for this guideline comprised of ophthalmologists, a family medicine specialist, and an optometrist from the Ministry of Health, Ministry of Higher Education and private sector.

Literature search was carried out at the following electronic databases: International Health Technology Assessment Website, PUBMED, Cochrane Database of Systemic Reviews (CDSR); Cochrane Controlled Trials Register; Journal full text via OVID search engine; Database of Abstracts of Reviews of Effectiveness; Psychology and Behavioural Sciences Collection and CINAHL via EBSCO search engine. Reference list of all relevant articles retrieved were searched to identify further studies. The search was not restricted to specific language or years of publication. The keywords used in the search included glaucoma; "open angle glaucoma"; "primary open angle glaucoma" AND / (risk OR aetiology) AND screening AND medical management AND (surgical management OR surgical treatment) AND prevention and Trabeculectomy. The keywords used for medication were betaxolol, timolol, dorzolamide, brinzolomide, brimonidine, latanoprost, travoprost, and bimatoprost and their commercial names. Relevant publications were examined for references until no further studies were found.

This guideline is based largely on the findings of systematic reviews and meta-analyses in the literature, taking into consideration local practices. Reference was also made to other guidelines such as Asia Pacific Glaucoma Guideline 2003, Terminology and Guideline for Glaucoma by European Glaucoma Society 2005, American Academy of Ophthalmology (AAO) Preferred Practice Pattern 2005, Finnish Evidence Based Guideline for Open Angle Glaucoma 2003, and Clinical Practice Guideline on Glaucoma October 2005 by Ministry of Health of Singapore.

Assessment of evidence was done independently by individual members and discussed by the committee members of the development before the recommendations were formulated. Where the evidence was insufficient,the recommendations were derived by consensus of the development group.

The articles were graded using the modified version of those used by the Catalonia Agency for Health Technology Assessment and Research (CAHTAR) Spain. While the grading of recommendation in these guidelines was modified from the Scottish Intercollegiate Guidelines Network (SIGN).

The draft guideline was posted on both the Ministry of Health Malaysia and Academy of Medicine, Malaysia websites for comment and feedback. This guideline has also been presented to the Technical Advisory Committee for Clinical Practice Guidelines, and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

OBJECTIVE

The aim of this guideline is to provide evidence based recommendations in the management of POAG.

CLINICAL QUESTIONS

- What is the definition of POAG?
- What are the risk factors for POAG?
- Who should be screened?
- What are the criteria for the diagnosis of POAG?
- What is the management of POAG?
- How should POAG patients be monitored?

TARGET POPULATION

The population targeted are patients with POAG and those who are at risk.

TARGET USER

This guideline is targeted for use by doctors working in ophthalmology units, optometrists and primary care providers.

GUIDELINE DEVELOPMENT COMMITTEE

Chairperson
Dr. Ahmad Mt Saad
Consultant Ophthalmologist
Hospital Sultanah Bahiyah
Alor Setar

Members (in alphabetical order)

Dr Chung Kah Meng
Consultant Optometrist
2-G-45, Ground Floor, Wisma Rampai,
Kuala Lumpur

Dr. Elias Hussein
Consultant Ophthalmologist
Hospital Selayang
Selangor

Dr Fang Seng Kheong
Consultant Ophthalmologist
International Specialist Eye Centre
Kuala Lumpur

Dr. Goh Pik Pin
Consultant Ophthalmologist
Hospital Selayang
Selangor

Dr Linda Teoh Oon Cheng
Consultant Ophthalmologist
Tun Hussein Onn National Eye Hospital
Selangor

Asso. Prof. Dr Mimiwati Zahari
Consultant Ophthalmologist
Universiti Malaya Medical Centre
Kuala Lumpur

Dr Ong Poh Yan
Consultant Ophthalmologist
Hospital Selayang
Selangor

Prof. Ropilah Abdul Rahman
Consultant Ophthalmologist
Medical Faculty
Universiti Kebangsaan Malaysia

Dr R Sukumar
Family Medicine Specialist
Klinik Tanglin
Kuala Lumpur

Coordinators

Dr. Sheamini Sivasampu
Principal Assistant Director
Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia

Dr S. Sivalal
Former Deputy Director
Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia

EXTERNAL REVIEWERS (in alphabetical order)

The following external reviewers provided feedback on the draft

Dr. S Anusiah Selvathurai
Head of Department & Consultant Ophthalmologist
Ophthalmology Department
Hospital Melaka
Melaka

Dr. Choong Yee Fong
Consultant Ophthalmologist
International Specialist Eye Centre
Kuala Lumpur

Dato' Dr. Lee Y C
Consultant Ophthalmologist
Lee Eye Centre
Ipoh, Perak

Prof. Dr. Ravi Thomas
Visiting Professor and Consultant Ophthalmologist
LV Prasad Eye Institute,
Hyderabad, India

Puan Rosminah Mohd Din
Principal Assistant Director
Ministry of Health Drug Formulary
Pharmaceutical Bureau

Dr. Vivian Gong
Clinical Specialist
Ophthalmology Department
Hospital Ipoh
Perak

Dr. Zuraidah Mustari
Head of Department & Consultant Ophthalmologist
Ophthalmology Department
Hospital Sultanah Nur Zahirah
Terengannu

TABLE OF CONTENTS

1. INTRODUCTION

Glaucoma is a sight threatening disease which can cause irreversible blindness. However early detection and treatment can prevent blindness. Glaucoma of all types is the second most common cause of legal blindness in the USA.[1, Level 8] Data from the Malaysian National Eye Survey, 1996 revealed that glaucoma contributed to 1.8% of blindness. Other major causes of blindness were cataract, (39.1%), retinal diseases (24.5%), uncorrected refractive error (4.1%) and corneal disease (3.4%). [2, Level 8]

Based on data extrapolated from the Baltimore Eye Survey, by the year 2000, there will be 66.8 million people with primary glaucoma in the world, with 6.7 million suffering from bilateral blindness.[3, Level 8] Half of them may be unaware that they have glaucoma. [4, Level 8; 5, Level 8; 6, Level 8] The prevalence of primary open angle glaucoma (POAG) varies with geographic area and ethnic origin. (See table 1) Currently, there are no statistics on prevalence of glaucoma in Malaysia.

Table 1. Prevalence of glaucoma according to population based study

Ethnicity	Prevalence of POAG
Barbados of African descent [7, Level 8]	6.8%
African American [5, Level 8]	4.7%
Singaporean Chinese [8, Level 8]	3.2%
Japanese [9, Level 8]	3.1%
Urban South Indian [10, Level 8]	2.6%
Mongolian [8, Level 8]	2.4 %
South Indian [11, Level 8]	1.7%
Caucasian American [5, Level 8]	1.3 %
Rural South Indian [12, Level 8]	1.2%

Definition

POAG is defined as a progressive, chronic optic neuropathy in adults where intraocular pressure (IOP) and other currently unknown factors contribute to damage and in which, in the absence of other identifiable causes, there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This is associated with an anterior chamber angle that is open by gonioscopic appearance.[13, Level 9]

POAG represents a spectrum of disease in adults in which the susceptibility of the optic nerve to damage varies among patients. While many POAG patients present with elevated IOP, a significant minority with otherwise characteristic POAG will not have elevated IOP measurements.[14, Level 8]

2. RISK FACTORS

The identification of risk factors for POAG is important in the determination of its cause and management.

2.1 Elevated Intraocular Pressure

a. Prevalence of POAG [1, *Level 8*; 6, *Level 8*; 7, *Level 8*, 15, *Level 8*; 16, *Level 8*] and incidence of POAG increases as the level of IOP increases. [13, *Level 9*]

b. High IOP is associated with progression of optic nerve damage and progression of ocular hypertension to POAG. [17, *Level 1*; 18, *Level 2*; 19, *Level 2*; 20, *Level 8*; 6, *Level 8*; 21, *Level 8*; 1, *Level 8*]

c. An eye with an IOP of more than 22mmHg is 8.6 times more likely to be glaucomatous than an eye with an IOP of less than 21mmHg. [6, *Level 8*; 1, *Level 8*]

d. Lowering IOP leads to less progression of glaucoma damage. [22, *Level 6*]

e. The diurnal variation of IOP are greater in glaucoma patients. [17, *Level 1*]

f. Asymmetry of IOP of 3 mm or more Hg is associated with POAG. [23, *Level 8*]

g. As there is considerable individual variation in the IOP level that is necessary to cause damage, there is no definite cut off level to indicate risk. [18, *Level 2*]

2.2 Thinner Central Corneal Thickness (CCT)

a. CCT of less than 555 μ had a 3 fold risk of developing POAG compared to patients with CCT of more than 588μ. [19, *Level 2*] However, this does not apply to patients who had trauma or refractive surgery to the cornea.

b. The hazard ratio for glaucoma was 1.71 per 40μ CCT. [19, *Level 2*; 24, *Level 6*]

2.3 Aging

a. Older age is significantly associated with a higher prevalence of glaucoma. [6, *Level 8*; 20, *Level 8*; 25, *Level 8*]

b. There is an exponential increase in prevalence of POAG particularly after the age of 60. [18, *Level 2*]

c. Age is an independent risk factor for the progression of ocular hypertension to POAG [17, *Level 1*] with an increase in relative risk from 8.3 at age 60-69 to 10.0 at age >80. [18, *Level 2*]

2.4 Family History of Glaucoma Among First Degree Relatives (Parents or Siblings)

a. Positive family history of POAG among first-degree relatives doubles the risk of POAG. [18, *Level 2*; 26, *Level 8*]

b. Individuals with a family history of glaucoma among siblings were 4 times more likely to develop glaucoma compared to 2 times for those whose parents had glaucoma. However, individuals whose children had a history of glaucoma were not at risk. [27, *Level 8*]

c. The life time absolute risk of glaucoma at age 80 years was nearly 10 times higher for individuals having relatives with glaucoma compared to control patients. [28, *Level 6*] Thus, the family score was a strong predictor of POAG, independent of IOP.[29, *Level 6*]

d. Though family history of glaucoma increases the risk, its contribution is not as great as non-genetic risk factors (attributable risk of genetic factor is only 16%). [19, *Level 2*] There is also weak evidence of its role in disease progression. [19, *Level 2*]

2.5 Race or Ethnicity

Findings from population based studies demonstrated that individuals of West African, Afro-Caribbean, or Hispanic/Latino ethnicity have a higher prevalence of POAG, [30, *Level 8*; 7, *Level 8*; 15, *Level 8*; 31, *Level 8*; 32, *Level 8*; 33, *Level 8*]. However there are no studies to provide information on the various ethnic groups locally.

2.6 Other possible risk factors

The relationship between diabetes mellitus and POAG is unclear. [34, *Level 8*; 35, *Level 8*; 36, *Level 8*] The association between POAG and factors such as systemic hypertension, [37, *Level 8*; 38, *Level 8*; 39, *Level 8*; 40, *Level 8*] low diastolic perfusion pressure, [41, *Level 8*] migraine headache and peripheral vasospasm, [42, *Level 8*] and myopia [37, *Level 8*; 43, *Level 8*] has not been demonstrated consistently.

Important risk factors are:
• Elevated intraocular pressure **(Grade A)**
• Older age **(Grade B)**
• Family history of glaucoma among first degree relatives (parents/siblings) **(Grade B)**
• Thin central corneal thickness **(Grade B)**

3. SCREENING

A Cochrane systematic review and US Preventive Task Force systematic review, do not recommend a population based screening to be carried out. [46, *Level 1*; 47, *Level 1*] There is insufficient evidence to recommend for or against opportunistic screening for POAG. [48, *Level 9*] Similarly there is insufficient evidence to show that early recognition and treatment of patients with POAG or elevated IOP in asymptomatic patients improve vision-specific functional outcome and health related quality of life. [47, *Level 1*]

However, screening on certain high risk groups, such as older people,[49, *Level 9*] family history of glaucoma [26, *Level 8*; 50, *Level 6*] or specific race, may be justified. [51, *Level 9*; 46, *Level 1*]

In the local context, opportunistic case detection of POAG on any person over 40 years of age and /or those with family history of glaucoma, who seeks ophthalmic attention for any reason, should be carried out by trained health care providers such as primary eye care providers, optometrists and ophthalmologists, provided basic screening equipment such as ophthalmoscope and tonometer are available.

Recommendations for screening
• Population based screening is not recommended. **(Grade A)**
• Opportunistic case detection for high risk groups such as family history of glaucoma may be performed when there are trained health care providers. **(Grade C)**

When should a primary care provider refer a case for an ophthalmologist opinion?

People who have the following features should be referred to an ophthalmologist for further confirmation:

a. IOP > 21mmHg or difference in IOP of both eyes of ≥ 3 mmHg*
b. Cup disc ratio (CDR) of > 0.5 or asymmetry of CDR of > 0.2
c. Other optic disc changes such as disc hemorrhage, undercutting of the neuroretinal rim or thinning of neuroretinal rim in any sector.
d. When in doubt.

**For primary health care providers who have the facility to measure IOP.*

Though these suggestions are not evidence based, they are recommended by the guideline development group.

4. DIAGNOSIS

Patients with POAG do not usually have symptoms. Their visual acuity can also remain normal even at advanced stages of the disease. As such, POAG is most frequently diagnosed during routine visits to eye care professionals when patient may be asymptomatic or have symptoms that are unrelated to glaucoma.[52, *Level 8*]

The diagnosis of POAG is based on the examination of the optic nerve head, nerve fibre layer, visual fields, IOP level and gonioscopy. Confirmation of the diagnosis may require more than one visit. [13, *Level 9*] (e.g. a patient might be identified as having glaucoma on one visit but may return for further evaluation such as visual field assessment and optic nerve head evaluation and documentation)

4. 1 History

4.1.1 Ocular history - history of ocular surgery, ocular trauma, myopia and use of topical steroid. [13, *Level 9*]

4.1.2 Systemic history of diabetes, hypertension, migraine and use of systemic steroid. [13, *Level 9*]

4. 1.3 Family history of glaucoma. [13, *Level 9*]

4.2 Examination

4.2.1 Pupil

The pupils are examined for reactivity and an afferent pupillary defect. [53, *Level 8*; 54, *Level 8*]

4.2.2 Intra-ocular pressure measurement

a. IOP is measured preferably with a Goldmann-type applanation tonometer. [55, *Level 8*] In non ambulatory patients and those who have corneal disease where IOP measurement cannot be obtained from standard Goldmann tonometry, a Tonopen or Perkins tonometer can be used. [56, *Level 8*; 57, *Level 8*]

b. Time of measurement should be recorded as IOP varies at different times of the day, often peak before noon. [58, *Level 8*]

c. Diurnal IOP measurement provides more accurate baseline assessment of IOP. [13, *Level 9*]

d. Central corneal thickness (CCT) affects IOP measurement. Thin CCT may result in falsely low IOP readings and thick CCT in falsely high IOP readings. [59, *Level 1*; 60, *Level 8*; 28, *Level 9*] Measurement of CCT aids the interpretation of IOP measurement results and stratification of patient risk. [19, *Level 8*; 61, *Level 2*; 62, *Level 8*]

Signs suggestive of POAG:

- IOP of more than 21mmHg.[1, Level 8]
- IOP asymmetry of 3 or more mmHg. [23, Level 8]
- IOP difference of 6 mmHg or more in the diurnal recording. [13, Level 9]

4.2.3 Optic Nerve Head and Retinal Nerve Fibre Layer (RNFL) Assessment

Assessment of optic nerve head should be THROUGH A DILATED PUPIL. [13, Level 9] Inability to dilate (or the reason not to dilate) should be documented.The optic disc and nerve fibre layer can be examined by :

a. Slit-lamp biomicroscopy using high power condensing lens is the recommended best clinical method. [63, Level 8; 13, Level 9]
b. Stereoscopic optic disc photography [64, Level 8]
c. Red free illumination may aid in evaluation. [63, Leve l 9; 13 Level 9]
d. Optic nerve head and RNFL imaging such as Optical Coherence Topography (OCT), [65, Level 8; 66, Level 8] Heidelberg Retinal Topography (HRT), [66, Level 8] and scanning laser polarimetry. [67, Level 8; 66, Level 8] However these new technologies are more useful in the monitoring of disease progression. [68, Level 8; 69, Level 6; 70, Level 7; 71, Level 8]
e. Direct ophthalmoscopy only allows optic nerve head assessment. [63, Level 8]

Signs suggestive of POAG:

- Vertical CDR of more than 0.7.[18, Level 2; 20, Level 6; 72, Level 8; 73, Level 8; 74, Level 8; 75, Level 9] Optic disc size is an important parameter to consider because a larger disc has larger cup and smaller disc has smaller cup. [76, Level 1] Asymmetry of CDR of more than 0.2 is significantly associated with POAG. [77, Level 9]
- Thinning and notching of neuroretinal rim (NRR), [63, Level 8] and any variation from the normal neuroretinal rim thickness (ISNT rule)*
- Loss of RNFL [78, Level 8; 79, Level 8] or thinning of RNFL on imaging [66, Level 8]
- Optic nerve head haemorrhage. [80, Level 8; 81, Level 8] It can precede visual field loss and further optic nerve damage. [22 , Level 6; 42, Level 8]
- Peripapillary beta zone atrophy especially those that correspond to the neuroretinal rim thinning and those that progress. [63, Level 8; 82, Level 7]
- Nasalization and bayonetting of retinal vessels. [63, Level 8]
- Laminar dots. [63, Level 8]

*** ISNT rule**

Normally, the thickest to thinnest parts of the neuroretinal rim of the optic disc are Inferior Superior Nasal Temporal (ISNT)

4.2.4 Gonioscopy

An accurate diagnosis of POAG requires a careful evaluation of the anterior chamber to exclude secondary causes of glaucoma. POAG is diagnosed when gonioscopic findings (without indentation) show grade III or IV based on Shaffers classification. Refer Table 2

Table 2. Gonioscopic Chart

Grading system for gonioscopic findings (without indentation)

Grade	0	I	II	III	IV
Shaffer	Closed	10°	20°	30°	40°
Modified Schaffer	Schwalbes line is not visible	Schwalbes line is visible	Anterior TM* is visible	Scleral spur is visible	Ciliary band is visible

Adapted from SEAGIG 2004

* Trabecular meshwork

4.2.5 Visual field testing

Automated perimetry can be done using:

a. Automated static threshold perimetry - This is the current gold standard of visual field assessment. Humphrey perimeter has the best results, with a sensitivity of 97% and specificity of 84% . [84, *Level 8*]

b. Frequency-Doubling Technology (FDT)[85, *Level 8*; 86, Level 8; 87, *Level 8*] has a sensitivity of 87.5% and specificity of 90-95%. [88, *Level 7*]

The shorter testing algorithm such as Swedish Interactive Threshold Algorithm (SITA) based on Humphrey visual field analyzer is the preferred strategy. [89, *Level 8*] Other tests such as Tendency Oriented Perimetry (TOP) programme based on Octopus Perimeter can also be used. Short-Wavelength Automated Perimetery (SWAP) is more sensitive in detecting early visual field loss. [90, *Level 8*]

Visual field defect suggestive of POAG (based on the Humphrey visual field) are:

- Early defects [74, *Level 9*]
  a. Glaucoma hemifield test graded as outside normal limits
  b. A cluster of three contiguous points (non edge points)at the 5% level on the pattern deviation plot
- Classical defects are paracentral scotoma, nasal step, arcuate scotoma and temporal wedge.

There are no generally approved and used criteria to determine glaucomatous visual field defects. [91, *Level 2*; 92, *Level 2*; 93, *Level 6*; 94, *Level 2*; 95, *Level 6*; 96, *Level 2*; 97, *Level 8*]

Visual field defects should be reproducible and correspond to optic nerve and RNFL changes. When the test is repeated, the same examination strategy should be used. [13, *Level 9*]

Summary of diagnosis

In practice, diagnosis of POAG is not always clear cut. Thus the diagnosis of POAG should be made based on combination of both clinical findings and visual field function as shown in Table 3.

Table 3 Features suggestive of POAG - Modified from Finnish Evidence Based POAG guidelines 2003

DIAGNOSIS	ANTERIOR CHAMBER ANGLE	RNFL	OPTIC DISC	VISUAL FIELD	COMMENTS
Definitive diagnosis of POAG	Open	Abnormal	Abnormal	Abnormal	Diagnosis is clear
Diagnosis of POAG	Open	Abnormal	Normal	Abnormal	Probably a small optic disc; e.g. hyperopic disc
*Pre-perimetric glaucoma (suspect)	Open	Abnormal	Normal	Normal	Need to follow-up for progression (need SWAP perimetry or FDT or may have abnormal 8-10 degree visual field)
*Pre-perimetric glaucoma	Open	Abnormal	Abnormal	Normal	Need SWAP perimetry or FDT or may have abnormal 8-10 degree visual field
Glaucoma suspect	Open	Normal	Abnormal	Normal	Large optic disc or optic disc anomaly. Need follow-up and look for progression or FDT
Glaucoma suspect	Open	Normal	Normal	Abnormal	Need to repeat visual field exam. Maybe due to other causes for visual field abnormalities

Notes : *Pre-perimetric glaucoma is a condition, where despite structural abnormalities in the optic disc and RNFL there is a normal visual field.

IOP levels are not necessarily used as a main diagnostic criterion for POAG. However, it is a major risk factor for POAG.

5. TREATMENT

5.1 Goals of Treatment

The aim of treatment is to preserve maximal functional vision throughout a patients lifetime without sacrificing his/her quality of life, and at a sustainable cost. Quality of life is affected by visual function, therapy regimen, side-effects of treatment, financial burden of a treatment and the psychological effect of having a potentially blinding disease. The natural history and progression of glaucoma is shown in Glaucoma Life History Diagram in Appendix 1.

5.2 Target Intraocular Pressure

At present, the only approach proven to be efficient in preventing progression of the disease and preserving vision function is lowering of IOP. [98, *Level 1*] This is supported by major clinical trials as shown in Table 4.

Table 4. Glaucoma Clinical Trials

Clinical trial	Diagnosis	Sample size	Randomization	Follow -up	IOP reduction	% progression (treatment / no treatment)
OHTS [61, *Level 2*]	Ocular hypertension	1636 patients	Medical treatment vs. observation	5 years	20% target	4.4%/9.5% (over 5 years)
EMGT [99, Level 2]	Early POAG	255 patients	Treatment (Argon laser trabeculoplasty + betaxolol) vs. observation	4-9 years	25% target	45%/62% (over 6 years)
CNTGS [100, *Level 2*]	Normal tension glaucoma	140 eyes	Medical treatment and/or surgery vs. observation	7 years	30% target	12%/35% (over 7 years)
CIGTS [101, *Level 2*]	Newly diagnosed POAG	607 patients	Medical treatment vs. surgery	5 years	Medical 38% (average)	No progression at 5 years
					Surgical 46% (average)	No progression at 5 years
AGIS [102, *Level 2*]	Advanced POAG	738 eyes	Argon laser trabeculoplasty vs. surgery	8 years	<18 mmHg at all visits	No progression at 8 years

Notes :

OHTS	Ocular Hypertension Treatment Study
EMGT	Early Manifest Glaucoma Trial
CNTGS	Collaboration Normal Tension Glaucoma Study
CIGTS	Collaboration Initial Glaucoma Treatment Study
AGIS	Advanced Glaucoma Intervention Study

Target IOP, which is an estimate of mean IOP at which further glaucomatous damage is likely to be prevented, should be tailored to individual patients and may vary during the course of the disease.[103, *Level 9*; 104, *Level 9*] Target IOP is set based on the following factors:

a. The pretreatment IOP (mean level, maximum level, diurnal fluctuations)
b. Stage of optic nerve damage and visual field defects
c. Rate of glaucoma progression
d. Age, life expectancy and visual requirements of patient
e. Presence of glaucoma risk factors (e.g. family history, central corneal thickness, diabetes)

Refer to Appendix 2 for further details on target IOP.

Generally a level of 20% to 50% reduction of IOP is required to reduce the risk of disease progression. [19, *Level 2*; *Level 2*; 105, *Level 2*; *101, Level 2*; *102, Level 2*]

The approaches to achieve the desired target IOP include:-

1. Medical management
2. Surgical management including laser
3. Any combinations of the above

5.3 Medical Treatment

Medical therapy is usually the initial treatment of choice in the management of POAG. It includes the use of topical or orally administered agents that increase aqueous outflow or reduce aqueous production or both. The use of topical IOP lowering agents is the cornerstone of glaucoma treatment and its efficacy has been demonstrated by major randomized clinical trials. (Refer to Table 4)

Criteria for prescribing glaucoma medications
• Drug factors (e.g. efficacy, side-effect profiles, dosing regimen, cost and availability of the drug)
• Patient factors (e.g. stage of glaucoma, age, risk factors, coexisting medical conditions , compliance , psychological and socioeconomic status)
• Health care resources

5.3.1 Anti- glaucoma agents

There are 6 main pharmacologic classes of anti-glaucoma agents which can be used as monotherapy or in combination therapy. Features and side effects of anti-glaucoma agents are shown in Appendix 3 and 4. If the target IOP is not reached with first choice monotherapy, switching or adding another drug from a different class is done to achieve the targeted IOP. One eye therapeutic medical trial may be useful but is not always feasible. [104, *Level 9*]

a. Prostaglandin derivatives/ Prostamides

These anti-glaucoma agents have been increasingly used as the first choice monotherapy and have the highest IOP lowering effect of all topical anti-glaucoma drugs. [106, *Level 1*; 107, *Level 1*] It has a lower risk of systemic adverse effects and its once daily dosing enhances compliance.

b. Beta-blockers (adrenergic antagonist)

These anti-glaucoma agents have been the mainstay drug in the treatment of POAG. There are two types of beta-blocker available i.e. selective and non selective agents. (Refer to Appendix 4 for details)

c. Adrenergic agonists

These anti-glaucoma agents act mainly by reducing the aqueous formation and increasing outflow. Their side effects include ocular allergic reactions such as conjunctivitis and uveitis.[108, *Level 8*; 109, *Level 8*]

d. Carbonic anhydrase inhibitors (CAI)

These anti-glaucoma agents are available in topical and systemic forms. Main features of topical CAI are shown Appendix 3 and 4.

The systemic therapy includes:

- Intravenous injection Acetazolamide 500 mg
- Tablet Acetazolamide 250 mg (qid as full dose), 500mg slow-release capsule (bid as full dose)
- Tablet Dichorpenamide 50 mg
- Tablet Methazolamide 50 to100 mg

CAIs are contraindicated in patients with sulfonamide allergy, renal stone/failure, respiratory/metabolic acidosis and hypokalaemia. They may have drug interactions with steroids, diuretics and digoxin and may cause transient myopia. The systemic side-effects consist of fatigue, malaise, anorexia, gastrointestinal discomfort, weight loss, paraesthesia, taste disturbance, Stevens-Johnson syndrome, urticaria, angioedema, blood dyscrasias, renal stones and hypokalaemia.

e. Cholinergic drugs

Pilocarpine eye drops are no longer favoured due to its side effects such as stinging, pupillary constriction and the need for frequent dosing i.e. four times a day.

f. Osmotic agents

These anti-glaucoma agents are only available as systemic therapy. They are the most effective IOP lowering agents and are usually used preoperatively when rapid IOP reduction is desired. It is contraindicated in patients with cardiac and kidney disease as it increases blood volume. It may also alter blood glucose level in diabetic patients. Systemic side-effects include headaches, unpleasant taste, heart failure, pulmonary oedema and death. Commercially available agents are oral glycerol 1.0-1.5 g/kg and intravenous mannitol 1-1.5g/kg.

5.3.2 Adjunctive Therapy

Topical anti-glaucoma drugs can be combined with each other to increase IOP lowering effect. Only drugs from different classes can be used in combination. Fixed drug combinations improved compliance[110, *Level 9*; 111, *Level 8*] because they have simpler dosing regimens, less frequent applications, lessen exposure to preservatives and give a better quality of life. Fixed drug combinations are used as second line treatment. It has similar adverse effects as the individual component drugs do.

Commercially available fixed combined drugs preparations are:

a. Beta-blockers & topical CAI (timolol 0.5% & dorzolamide 2%)
b. Beta-blockers & prostaglandin derivatives (timolol 0.5% & latanoprost 0.005%; timolol 0.5% & travoprost 0.004%)
c. Beta-blockers & adrenergic agonist (timolol 0.5% & brominidine 0.2%)

5.3.3. Compliance with medication

Non compliance to glaucoma medication may lead to blindness. However, when assessing non-compliance drug, interactions and reduced drug tolerance must be taken into consideration.

Poor compliance can be due to the following [104, *Level 9*]

a. Failure to instill eye drops including ineffective technique of self administration
b. Excessive use of eyedrops (extra drops may cause systemic side effects)
c. Self administration of non prescribed eye drops
d. Improper timing of eye drops

Details of topical anti-glaucoma drugs can be found in Appendix 3 and Appendix 4.

General Principles in Medical Management

1.	Determine an appropriate target IOP and readjust, if necessary, throughout the course of disease .
2.	Diagnostic parameters to be considered in deciding on anti-glaucoma agents are : IOP levels and/ or IOP fluctuations, extent of optic disc damage, severity of visual field defects, central corneal thickness • Baseline parameters should be collected prior to initiating treatment • All parameters need to be verified before modifying the therapy
3.	Choose monotherapy that:- • Provides the greatest IOP lowering effect to achieve target IOP • Has the best safety profile e.g. least side-effect and good tolerability • Enhances compliance e.g. simple dosing regimens, minimal disruption to lifestyle and quality of life • Is affordable

4. Treatment:
   - Treatment is considered ***effective*** if percentage of IOP reduction is at least equal to the IOP lowering efficacy of the drug (refer to Appendix 2).
   - If the drug is ***ineffective***, switch to a different class of medication and reassess. Switching within prostaglandin derivatives may be useful. [114, *Level 8*; 115, *Level 3*]
   - IOP reduction is ***adequate*** when it has achieved the target IOP.
   - If IOP reduction is ***inadequate***, adjunctive therapy is used either as a separate drug combination or fixed combination. [110, *Level 9*]
   - Generally, if more than 2 medications are required for the control of IOP, other forms of therapy should be considered. [116, *Level 7*]

5. Patient education:
   - Proper technique of instillation of eye drops (to minimize systemic side-effects and drug wastage)
   - Punctal occlusion and eyelid closure for at least 3 minutes after instillation of eye drops
   - At least 5 minutes interval between instillation of eye drops if multiple topical drugs are used
   - Education on the disease, benefits and risks of the treatment and importance of compliance (following the therapy regimen and follow-up schedule)

Modified from EGS 2003, SEAGIG 2004

Recommendations for medical management
Topical prostaglandin derivatives/ prostamides and beta blockers are the most effective IOP lowering agents in POAG patients. **(Grade A)**
Patient factors such as age, risk factors, coexisting medical illness, compliance, quality of life and cost may need to be taken into consideration when deciding on the first choice therapy. **(Grade C)**

Refer to algorithm on pg 26 and 27

5.4 Surgical Management

POAG is traditionally treated with medical therapy. Surgery is only indicated when the target IOP cannot be reached despite maximal medical therapy [13, *Level 9*] or when the patient is intolerant or non compliant to medical therapy. [104, Level 9; 49, *Level 9*]

Surgical approaches include:

5.4.1 Trabeculectomy

Trabeculectomy is the primary surgery of choice. [102, *Level 2*; 117, *Level 2*; 104, *Level 9*; 118, *Level 3*; 119, *Level 6*] Its IOP lowering effect is as effective as medical therapy.[120, *Level 1*] However, the development of scar tissue under the conjunctiva may lead to inadequate drainage. Thus, anti-scarring or antimetabolites agents such as 5-Fluorouracil (5FU) and Mitomycin C (MMC) are used to improve success rates of surgery. [121, *Level 1*; 13, *Level 9*] But their use may increase the incidence of complications such as bleb leaks, blebitis, endophthalmitis, and hypotony, which is likely to cause maculopathy especially in young myopes. [13, *Level 9*] The risk-benefit ratio of their use in primary filtering surgery is undetermined. [13 *Level 9*] The concentration and duration of application of these agents should be titrated against estimated risk of post-operative scar formation and post- operative complications. [122, *Level 9*; 123, *Level 7*; 124, *Level 3*]

Prompt and early detection of post operative complications is essential in the success of trabeculectomy. [13, Level 9] Refer to Appendix 5 on application of MMC and 5-FU during surgery

Recommendation
Patients who are planned for trabeculectomy should be warned of surgically related complications such as hypotony, visually significant cataract and the risk of bleb infection. **(Grade C)**

5.4.2 Non-penetrating glaucoma surgery

Deep sclerectomy and viscocanalostomy are the types of non-penetrating glaucoma surgery. This surgical approach is less efficient in lowering the IOP in comparison to trabeculectomy and thus is not suitable for patients who need low target IOP. [125, Level 9; 126, Level 3] Its advantages over trabeculectomy include lower risk of postoperative hypotony and bleb infection. [127, Level 1]

5.4.3 Drainage devices implantation

The use of drainage devices such as Molteno, Ahmed, Krupin, Baerveldt, Optimed Model-1014 [128, Level 9] and others is usually indicated in patients who have failed filtering surgery with antimetabolites or for patients whose conjunctiva is so scarred from previous surgery that filtering surgery with antimetabolites is at high risk for failure. [129, Level 8;13, Level 9] The concomitant use of antimetabolites such as MMC and 5-FU did not show any benefit. [130, Level 1]

5.4.4 Laser trabeculoplasty

Laser trabeculoplasty may be used as an adjunct to medical therapy or as primary treatment in patients who are intolerant or non compliant to medical therapy. [131, Level 2] When laser trabeculoplasty is given as primary therapy, approximately half of the patients do not need treatment for 1 to 2 years after treatment. [76, Level 1] However, large clinical studies on laser trabeculoplasty have shown progressive loss of effect over time. [Level 2; 132, Level 6; 133, Level 7; 13, Level 9]

5.4.5. Cyclodestructive surgery

The aim of cyclodestructive surgery is to destroy the ciliary processes and thus decrease production of aqueous humour. It can be done either using laser as in cyclophotocoagulation or using cyclocryotherapy. Because the outcome is less predictable and there are reported risks of serious visual loss, these procedures are generally reserved for refractory glaucoma with poor visual prognosis. [134, Level 8; 135, Level 8]

Recommendations on surgical management
Laser trabeculoplasty is mainly used as an adjunct to medical therapy.(**Grade B)**
Trabeculectomy with or without antimetabolites should be considered in patients who fail medical therapy **(Grade B)**
Drainage devices implantation is indicated in refractory glaucoma **(Grade C)**

Refer to algorithm for Management of POAG on pg 26

6. FOLLOW UP SCHEDULE

Glaucoma is a slow progressive disease where the rates of change to the optic disc, RNFL' and visual field abnormalities vary greatly between patients. It can take several years to detect progression of abnormalities. 100, Level; [105, *Level 2*; 136, Level 2] Glaucoma patients need to be followed up to monitor the effects of treatment, to detect qualitative and quantitative disease progression and any change in health that may affect glaucoma management plan. [13, *Level 9*]

During periodic reevaluation of patient, stability of the IOP, optic nerve and visual fields; patient compliance, side-effects of treatment, and other risk factors need to be assessed. Adjustment on the initial target IOP may be required throughout the course of the disease.

During each review, the following should be elicited:

6.1 History

a. Ocular history
b. Medical history
c. Local or systemic problems with ocular medications
d. General assessment of the impact of visual function on daily living
e. Frequency and time of last IOP lowering medications
f. Verification of compliance

6.2 Physical examination

Recommendation for examination to be done at follow up visits are as follows:

Examination to be done at every visit	Examination to be done when indicated
1. Visual acuity in each eye 2. IOP measurement in each eye 3. Optic nerve head evaluation 4. Slit lamp biomicroscopy	1. Gonioscopy 2. Visual field **3.** Optic disc photography

Follow up intervals are determined by severity of optic disc damage, stage of disease, rate of progression, extent to which the IOP exceeds target pressure, number and significance of other risk factors for damage to the optic nerve head. Sometimes, it is necessary to repeat visual field examination within a short period of time to overcome a learning effect, to clarify a suspicious finding, or to verify progression. [13, Level 9]

The following are recommendations for follow up intervals. [13, Level 9]

Recommendation for follow up intervals			
Target IOP achieved	Progression of Damage	Duration of control (months)	Follow up interval
Yes	No	< 6	Within 6 months
Yes	No	> 6	Within 12 months
Yes	Yes	Not applicable	Within 4 months
No	Not applicable	Not applicable	Within 4 months

7. ADJUSTMENT OF THERAPY

The indications for adjusting therapy are as follows:

- Target IOP is not achieved.
- Patient has progressive optic nerve damage despite achieving the target IOP. The validity of the diagnosis and target pressure should be reassessed.
- Patient is intolerant to the prescribed medical regimen.
- Patient does not adhere to the prescribed medical regimen.
- Development of contraindications to individual medicines.

Downward adjustment of target pressure should be made in the face of progressive optic disc or visual field change. [137, Level 2; 138, Level 8] Upward adjustment of target pressure should be considered:

i) disease is stable

ii) undesired side-effects

iii) patient request for less medication

Modification of treatment justifies a follow up visit at an appropriate interval e.g. after the washout period if a drug is withdrawn or at the period of the maximal effect of an added drug.

Referral to glaucoma specialist

Advanced and complicated POAG cases e.g. those who failed previous surgery, patients who have one seeing eye, and those with advanced visual field loss require referral to glaucoma specialist.

References:

1 Sommer A, Tielsch JM, Katz J, et al., Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol.* 1991; 109(8): 1090-5

2 Zainal M, Ismail SM, Ropilah AR et al., Prevalence of blindness and low vision in Malaysian population: results form the National Eye Survey 1996. *Br J Ophthalmol.* 2002; 86:951- 956.

3 Quigley HA. Number of people with glaucoma worldwide. *Br J Ophthalmol.* 1996; 80:389-393.

4 Quigley HA, Vitale S. Models of open-angle glaucoma prevalence and incidence in the Uunited States. *Investigative &Visual Science.* 1997; 38:83-91.

5 Tielsch JM, Sommer A., Katz J, et al., Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *JAMA.* 1991; 266(3): 369-74. No. 3

6 Mitchell P, Smith W, Attebo K et al., Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1996; 103:1661-9.

7 Leske MC, Connell AM, Schachat AP et al., The Barbados Eye Study. Prevalence of open angle glaucoma. *Arch Ophthalmol* 1994; 112:821-9.

8 Foster P, Oen FT, Machin DS et al., The Prevalence of glaucoma in Chinese residents of Singapore. *Arch Ophthalmol.* 2000; 118:1105 - 1111

9 Iwase A, Suzuki Y, Araie M, et al., The prevalence of primary open-angle glaucoma in Japanese. *Ophthalmology.* 2004; 111: *1641-1648*

10 Dandona L, Dandona R, Srinivas M et al., Open angle glaucoma in an urban population in southern India. The Andhra Pradesh Eye Disease Study. *Ophthalmology.* 2000;107:1702? 1709

11 Ramakrishnan R, Nirmalan PK, Krishnadas R et al., Glaucoma in a rural population of southern India: the Aravind comprehensive eye survey. *Ophthalmology.* 2003; 110(8):1484-90.

12 Vijaya L, George R, Paul PG, Baskaran M, et al., Prevalence of open-angle glaucoma in a rural south Indian population. *Invest Ophthalmol Vis Sci.* 2005 Dec;46(12):4461-7.

13 American Academy of Opthamology. *American Academy of Ophthalmology, Primary Open Angle Glaucoma, Preferred Practice Pattern.* San Francisco, Calif: American Academy of Ophthalmology, 2005

14 Dielemans I, Vingerling JR, Wolfs RC et al., The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. *Ophthalmology* 1994; 101:1851-5.

15 Quigley HA, West SK, Rodriguez J et al., The prevalence of glaucoma in a population based study of Hispanic subjects: Proyecto VER. *Arch Ophthalmol.* 2001;119:1819-26

16 Weih LM, Nanjan M, McCarty CA, et al., Prevalence and predictors of open-angel glaucoma: results form the Visual Impairment Project. *Ophthalmology.* 2001; 108:1966-1972

17 Friedman DS, Wilson MR, Liebmann JM et al., An evidence-based assessment of risk factors for the progression of ocular hypertension and glaucoma. *Am J Ophthalmol.* 2004; 138(3 Suppl): 19-31.

18 Le A, Mukesh BN, McCarty CA, Taylor HR. Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. Invest Ophthalmol Vis Sci. 2003 Sep;44(9):3783-9.

19 Gordon MO, Beiser JA, Brandt JD et al., The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol 2002*; 120:714-20; discussion 829-30.

20 Leske MC, Connell AMS, Wu S et al., Incidence of open-angle glaucoma: The Barbados eye studies. *Arch Ophthalmol.* 2001; 119:289-95

21 Quigley HA, Enger C, Katz J et al., Risk factors for the development of glaucomatous visual field loss in ocular hypertension. *Arch Ophthalmol.* 1994; 112:644-649.

22 Leske MC, Heijl A, Hussein M et al., Factors for glaucoma progression and the Early Manifest Glaucoma Trial. *Arch Ophthalmol.* 2003; 121:48-56.

23 Lee AJ, Rochtchina E, Mitchell P. Intraocular pressure asymmetry and undiagnosed open-angle glaucoma in an older population. *Am J Ophthalmol.* 2004 Feb; 137(2):380-2.

24 Medeiros FA, Sample PA, Zangwill LM et al., "Corneal thickness as a risk factor for visual field loss in patients with preperimetric glaucomatous optic neuropathy. *Am J Ophthalmol.* 2003; 136(5): 805-13.

25 Klein BE, Klein R, Sponsel WE et al., Prevalence of glaucoma. The Beaver Dam Eye Study. *Ophthalmology.* 1992; 10:1499-504.

26 Vistamehr S, Shelsta HN, Palmisano PC et al., Glaucoma screening in a high-risk population. *J Glaucoma.* 2006, Dec; 15(6):534-40.

27 Tielsch JM, Katz J, Sommer A et al., Family History and Risk of Primary Open Angle Glaucoma- The Baltimore Eye Survey. *Arch Ophthalmol.* 1994; 112:69-73

28 Wolfs RCW, Klaver CCW, Ramrattan RS et al., Genetic Risk of Primary Open-angle Glaucoma-Population-based Familial Aggregation study. *Arch Ophthalmol.* 1998; 116:1640-1645

29 Hulsman CAA, Houwing-Duistermaar JJ, van Duijin et al., Family score as an indicator of greater risk of primary open angle glaucoma. *Arch Ophthalmology.* 2002; 120:1726-1731.

30 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.

31 Varma R, Ying-Lai M, Francis BA et al., Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. *Ophthalmology.* 2004; 111:1439-48.

32 Rotchford AP, Johnson GJ. Glaucoma in Zulus: a population-based cross-sectional survey in a rural district in South Africa. *Arch Ophthalmol.* 2002; 120:471-8.

33 Rotchford AP, Kirwan JF, Muller MA et al., Temba glaucoma study: a population-based cross-sectional survey in urban South Africa. *Ophthalmology* 2003; 110:376-82.

34 Bonovas S, Peponis V, Filioussi K. Diabetes mellitus as a risk factor for primary open-angle glaucoma: a meta-analysis. *Diabet Med.* 2004; 21(6): 609-614.

35 Mitchell P, Smith W, Chey T et al., Open-angle glaucoma and diabetes: the Blue Mountains eye study, Australia. *Ophthalmology*. 1997; 104(4): 712-718

36 Dielemans I, de Jong PTVM, Stolk R, et al., Primary Open-angle glaucoma, Intraocular pressure, and Diabetes Mellitus in the General Elderly Population- The Rotterdam Study. *Ophthalmology*. 1996; 103:1271-1275

37 Mitchell P, Lee AJ, Rotchina E, et al., Open angel glaucoma and systemic hypertension: the blue mountain eye study. *J Glaucoma.* 2004; 13:319-326

38 Tielsch JM, Katz J, Sommer A, et al., Hypertension, Perfusion Pressure, and Primary Open-angle Glaucoma-A population- based assessment. *Arch Ophthalmol.* 1995; 113:216-221

39 Dielemans I, Vingerling JR, AlgraD et al., Primary open angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population. The Rotterdam study. *Ophthalmol.*1995; 102:54-60

40 Bonomi L, Marchini G, Marraffa J et al., Vascular risk factor for primary open angle glaucoma: the Egna-Neumarkt Study. *Ophthalmology*. 2000; 107:1287-1293

41 Leske MC, Connell AMS, Wu S, et al., Risk factors for open-angle glaucoma: The Barbados eye studies. *Arch ophhtalmol.*1995; 13:918-92

42 Drance S, Anderson DR, Schulzer M; Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal tension glaucoma. *Am J Ophthalmol.* 2001; 131:699-708

43 Grodum K, Heijl A, Bengtsson B. Refractive error and glaucoma. *Acta Ophthalmol. Scand.* 2001; 79:560-566

44 Mitchell P, Cumming RG, Mackey DA. Inhaled corticosteroids, family history, and risk of glaucoma. *Ophthalmology*. 1999; 106(12):2301-2306

45 Sihota R, Konkal VL, Dada T et al., Prospective, long-term evaluation of steroid-induced glaucoma. *Eye*. 2008 Jan;22(1):26-30

46 Hatt S, Wormald R, Burr J. Screening for prevention of optic nerve damage due to chronic open angle glaucoma. *Cochrane Database Syst Rev.* 2006 Oct 18; (4):CD006129.

47 Fleming C, Whitlock EP, Beil T, et al., Screening for primary open-angle glaucoma in the primary care setting: an update for the US Preventive Services Task Force. Portland, (OR); *Agency For Health Care Research and Quality* (AHRQ Publication No. 04-0548-B); March 2005. 7 p

48 Canadian Task Force on the Periodic Health Examination. Periodic health examination, 1995 update: 3. Screening for visual problems among elderly patients. Canadian Task Force on the Periodic Health Examination. *CMAJ.* 1995 Apr 15; 152(8):1211-22.

49 South East Asia Glaucoma Interest Group (SEAGIG). Asia Pacific glaucoma guidelines. Singapore: South East Asia Glaucoma Interest Group (SEAGIG); 2004. 92 p.

50 Sung VC, Koppens JM, Vernon SA, et al., Longitudinal glaucoma screening for siblings of patients with primary open angle glaucoma: the Nottingham Family Glaucoma Screening Study. *Br J Ophthalmol.* 2006, Jan; 90(1):59-63.

51 Wilson MR, Eezzuduemhoi DR. Ophthalmologic disorders in minority populations. *Med Clin North Am.* 2005 Jul; 89(4):795-804.

52 Quigley HA, Jampel HD. How are glaucoma patients identified? *J Glaucoma.* 2003 Dec; 12(6):451-5

53 Kohn AN, Moss AP, Podos SM. Relative afferent pupillary defects in glaucoma without characteristic field loss. *Arch Ophthalmol.* 1979; 97:294-6.

54 Brown RH, Zilis JD, Lynch MG, Sanborn GE. The afferent pupillary defect in asymmetric glaucoma. *Arch Ophthalmol.* 1987; 105:1540-3.

55 Wingert TA, Bassi CJ, McAlister WH, et al., Clinical evaluation of five portable tonometers. *J Am Optom Assoc.* 1995 Nov; 66(11):670- 674.

56 Iester M, Mermoud A, Achache F et al., New Tonopen XL: comparison with the Goldmannn tonometer. *Eye.* 2001 Feb; 15(Pt 1):52-8.

57 Horowitz GS, Byles J, Lee J, et al., Comparison of the Tono-Pen and Goldmannn tonometer for measuring intraocular pressure in patients with glaucoma. *Clin Experiment Ophthalmol.* 2004 Dec; 32(6):584-9.

58 David R, Zangwill L, Briscoe D et al., Diurnal intraocular pressure variations: an analysis of 690 diurnal curves. *Br J Ophthalmol.* 1992; 76: 280-283

59 Doughty MJ & Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. *Surv Ophthalmol.* 2001; 44: 367-408.

60 Brandt JD, Beiser JA, Kass MA et al., CCT in the Ocular Hypertension Treatment Study (OHTS). *Ophthalmology.* 2001; 108: 1779-1788.

61 Kass MA, Heuer DK, Higginbotham EJ et al., The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002; 120:701-13; discussion 829-30.

62 Herndon LW, Weizer JS, Stinnett SS. Central corneal thickness as a risk factor for advanced glaucoma damage. *Arch Ophthalmol.* 2004; 122:17-21.

63 Jonas JB, Budde WM, Panda-Jonas S. Ophthalmoscopic evaluation of the optic nerve head. *Surv Ophthalmol.* 1999 Jan-Feb; 43(4):293-320

64 Garway-Heath DF, Hitchings RA. Quantitative evaluation of the optic nerve head in early glaucoma. *Br J Ophthalmol.* (1998 a) Apr; 82(4):352-361.

65 Wollstein G, Schuman JS, Price LL et al., Optical coherence tomography longitudinal evaluation of retinal nerve fiber layer thickness in glaucoma. *Arch Ophthalmol.* 2005 Apr; 123(4):464-470.

66 Zangwill LM, Bowd C, Berry CC et al., Discriminating between normal and glaucomatous eyes using the Heidelberg Retina Tomograph, GDx Nerve Fiber Analyzer, and Optical Coherence Tomograph. *Arch Ophthalmol.* 2001 Jul; 119(7):985-993.

67 Nguyen NX, Horn FK, Hayler J et a., Retinal nerve fiber layer measurements using laser scanning polarimetry in different stages of glaucomatous optic nerve damage. *Graefes Arch Clin Exp Ophthalmol.* 2002 Aug; 240(8):608-614

68 Greaney MJ, Hoffman DC, Garway-Heath DF et al., Comparison of Optic Nerve Imaging Methods to Distinguish Normal Eyes from Those with Glaucoma. *Investigative Ophthalmology & Visual Science.* 2002; Jan; 43(1):140-5

69 Caprioli J, Prum B, Zeyen T. Comparison of methods to evaluate the optic nerve head and nerve fiber layer for glaucomatous change. *Am J Ophthalmol.* 1996 Jun; 121(6):659-67.

70 Medeiros FA, Zangwill LM, Bowd C et al., Influence of Disease Severity and Optic Disc Size on the Diagnostic Performance of Imaging Instruments in Glaucoma. *Invest Ophthalmol Vis Sci.* 2006; 47:1008?1015

71 Shah NN, Bowd C, Medeiros FA, et al., Combining structural and functional testing for detection of glaucoma. *Ophthalmology*. 2006 Sep; 113(9):1593-602.

72 Jonas JB, Bergua A, Schmitz-Valckenberg P, et al., Ranking of optic disc variables for detection of glaucomatous optic nerve damage. *Invest Ophthalmol Vis Sci.* 2000 Jun; 41(7):1764-1773.

73 Garway-Heath DF, Ruben ST, Viswanathan A, et al., Vertical cup/disc ratio in relation to optic disc size: its value in the assessment of the glaucoma suspect. *Br J Ophthalmol.* 1998 Oct; 82(10):1118-1124.

74 Foster JP, Buhrmann R, Quigley HA, et al., The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol.* 2002; 86: 238-242

75 Bourne RR, Sukudom P, Foster PJ et al., Prevalence of glaucoma in Thailand: a population based survey in Rom Klao District, Bangkok. *Br J Ophthalmol.* 2003 Sep; 87(9):1069-1074

76 Tuulonen A, Airaksinen PJ, Erola E et al., The Finnish evidence-based guideline for open-angle glaucoma. *Acta Ophthalmol Scand.* 2003 Feb; 81(1):3-18.

77 Wilson MR. Epidemiological features of glaucoma. *Int Ophthalmol Clin.* 1990 Summer; 30(3):153-60.

78 Jonas JB, Schiro D. Localised wedge shaped defects of the retinal nerve fibre layer in glaucoma. *Br J Ophthalmol.* 1994 Apr; 78(4):285-290

79 Sugiyama K, Uchida H, Tomita G et al., Localized wedge-shaped defects of retinal nerve fiber layer and disc hemorrhage in glaucoma. *Ophthalmology.* 1999 Sep; 106(9):1762-1767.

80 Healey PR, Mitchell P, Smith W, Wang JJ. Optic disc hemorrhages in a population with and without signs of glaucoma. *Ophthalmology.* 1998 Feb;105(2):216-23

81 Gazzard G, Morgan W, Devereux J et al., Optic disc hemorrhage in Asian glaucoma patients. *J Glaucoma.* 2003 Jun; 12(3):226-231.

82 Emdadi A, Kono Y, Sample PA et al., Parapapillary atrophy in patients with focal visual field loss. *Am J Ophthalmol.* 1999 Nov; 128(5):595-600.

83 South East Asia Glaucoma Interest Group (SEAGIG). *Asia Pacific glaucoma guidelines. Singapore: South East Asia Glaucoma Interest Group (SEAGIG);* 2004. 92 p.

84 Katz J, Sommer A, Gaasterland DE, Anderson DR. Comparison of analytic algorithms for detecting glaucomatous visual field loss. *Arch Ophthalmol.* 1991 Dec; 109(12):1684-1689.

85 Casson R, James B, Rubinstein A, Ali H. Clinical comparison of frequency doubling technology perimetry and Humphrey perimetry. *Br J Ophthalmol.* 2001, Mar; 85(3):360-362.

86 Wu LL, Suzuki Y, Kunimatsu S et al., Frequency doubling technology and confocal scanning ophthalmoscopic optic disc analysis in open-angle glaucoma with hemifield defects. *J Glaucoma.* 2001 Aug; 10(4):256-260.

87 Paczka JA, Friedman DS, Quigley HA et al., Diagnostic capabilities of frequency-doubling technology, scanning laser polarimetry, and nerve fiber layer photographs to distinguish glaucomatous damage. *Am J Ophthalmol.* 2001 Feb; 131(2):188-97.

88 Fogagnolo P, Mazzolani F, Rossetti L et al., Detecting glaucoma with frequency ? doubling technology perimetry. A comparison between N-30 and C-20 Screening Programs 2005. *J Glaucoma.* 2005; 14(6):485-91

89 Birt CM, Shin DH, Samudrala V et al., Analysis of reliability indices from Humphrey visual field tests in an urban glaucoma population. *Ophthalmology.* 1997 Jul; 104(7):1126-1130.

90 Teesalu P, Airaksinen PJ, Tuulonen A. Blue-on-yellow visual field and retinal nerve fiber layer in ocular hypertension and glaucoma. *Ophthalmology.* 1998 Nov; 105(11): 2077-2081.

91 No authors listed. The Advanced Glaucoma Intervention Study (AGIS): 1. Study design and methods and baseline characteristics of study patients. *Control Clin Trials.* 1994 Aug; 15(4):299-325.

92 No authors listed. The Advanced Glaucoma Intervention Study (AGIS): 4. Comparison of treatment outcomes within race. Seven-year results. *Ophthalmology.* 1998 Jul; 105(7):1135-1136

93 AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 9. Comparison of glaucoma outcomes in black and white patients within treatment groups. *Am. J Ophthalmol.* 2001 Sep; 132(3):311-320.

94 Gordon MO, Kass MA. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol.* 1999 May; 117(5):573-83.

95 Keltner JL, Johnson CA, Quigg JM et al., Confirmation of visual field abnormalities in the Ocular Hypertension Treatment Study. Ocular Hypertension Treatment Study Group. *Arch Ophthalmol.* 2000 Sep; 118(9):1187-1194

96 Leske MC, Hyman L, Hussein M et al., Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *Am J Ophthalmol.* 1999 May; 127(5):625-6.

97 Schulzer M. Errors in the diagnosis of visual field progression in normal-tension glaucoma. *Ophthalmology.* 1994 Sep; 101(9):1479-1480.

98 Maier PG, Funk J, Schwarzer G et al., Treatment of ocular hypertension and open angle glaucoma : meta-analysis of randomised controlled trials. BMJ. 2005 Jul 16;331(7509):120-1

99 Helji A, Leske MC, Bengtsson B et al., Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from Early Manifest Glaucoma Trial. *Arch Ophthalmol.* 2002; 120:1268-1279

100 No authors listed. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *Am J Ophthalmol.* 1998 Oct; 126(4):498-505.

101 Lichter PR, Musch DC, Gillespie BW et al., CIGTS Study Group. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmol* 2001; 108: 1939-1950

102 No authors listed. The advanced glaucoma intervention study, 6: effect of cataract on visual field and visual acuity. The, AGIS Investigators. *Arch Ophthalmol.* 2000 Dec; 118(12):1639-52.

103 Palmberg P. Evidence-Based Target Pressures: How to Choose and Achieve Them. Int. *Ophthalmol Clin.* 2004; Spring 44 (2): 1-14.

104 European Glaucoma Society. *Treatment principles and options*, 2nd edition, 2003, p. Italy; Dogma

105 No authors listed .Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *Am J Ophthalmol.* 1998 Oct; 126(4):487-97.

106 Van der Valk R, Webers CAB, Schouten JSAG et al., Intraocular Pressure-Lowering Effects of all Commonly Used Glaucoma Drugs. A Meta-anaysis of Randomised Clinical Trials. *Ophthalmol.* 2005; 112:1177-1185.

107 Zhang WY, Wan AL, Dua HS et al., Meta-analysis of randomized controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. *Br J Ophthalmol.* 2001; 85:983-990

108 Becker HI, Walton RC, Diamant JI, Zegans ME. Anterior uveitis and concurrent allergic conjunctivitis associated with long-term use of topical 0.2% brimonidine tartrate. *Arch Ophthalmol.* 2004; 122:1063-1066

109 Manni G, Centofanti M, Sacchetti M et al., Demographic and clinical factors associated with development of brimonidine tartrate 0.2%-induced ocular allergy. *J Glaucoma.* 2004; 13:163-167

110 Higginbotham EJ, Diestelhorst M, Pfeiffer N, et al., The Efficacy and D, Safety of Unfixed and Fixed Combinations of Latanoprost and other Anti-glaucoma Medications. Surv *Ophthalmol.* 2002; 47 (Suppl 1):S133-S140.

111 Stewart WC, Konstas Anastasios CP, Pfeiffer N. Patient and Ophthalmologist Attitudes Concerning Compliance and Dosing in Glaucoma Treatment. *J. Ocular Pharmacol. Ther.* 2004; 20(6):461-469.

112 Nordstrom BL, Friedman DS, Mozaffari E et al., Persistence and Adherence with Topical Glaucoma Therapy. *Am J Ophthalmol.* 2005; 140: 598?606.

113 Sleath B, Robin A L Covert D, Byrd J E et al. Patient-Reported Behavior and Problems in Using Glaucoma Medications. *Ophthalmology* 2006;113:431?436

114 Kaback M, Geanon J, Katz G, Ripkin D, Przydryga J; START Study Group. Ocular Hypotensive efficacy of Travoprost Patients Unsuccessfully Treated with Latanoprost. *Curr Med Res Opin.* 2004; 20(9):1341-1345.

115 Gandolfi SA. Effect of bimatoprost on patients with primary open-angle glaucoma or ocular hypertension who are nonresponders to latanoprost. *Ophthalmol.* 2003;110(3): 609-614

116 Neelakantan A, Vaishnav HD, Iyer SA, Sherwood MB. Is addition of a third or fourth antiglaucoma medication effective? *J Glaucoma.* 2004 Apr; 13(2):130-6.

117 Jay JL, Allan D. The benefit of early trabeculectomy versus conventional management in primary open angle glaucoma relative to severity of disease. *Eye.* 1989; 3(Pt 5):528-535.

118 Araujo SV, Spaeth GL, Roth SM, Starita RJ. A ten-year follow-up on a prospective, randomized trial of postoperative corticosteroids after trabeculectomy. *Ophthalmology.* 1995 Dec;102(12):1753-1759.

119 Wilson P. Trabeculectomy: long-term follow-up. *Br J Ophthalmol.* 1977 Aug; 61(8):535-8.

120 Burr J, Azuara-Blanco A, Avenell A. Medical versus surgical interventions for open angle glaucoma. In: *The Cochrane Database of Systematic Reviews*, 2, 2004.

121 Wilkins M, Indar A, Wormald R. Intraoperative mitomycin for glaucoma surgery *Cochrane Database Syst Rev.* 2005;(4):CD002897

122 Liebmann JM, Kim J. *Glaucoma Surgery: Trabeculectomy, Open Angle Glaucoma, edited by Robert N. Weinreb and Jonathan G. Crowston. Consensus Series 2.* Kugler Publications, The Hague, The Netherlands, 2005

123 Liebmann JM, Ritch R, Marmor M et al., Initial 5-fluorouracil trabeculectomy in uncomplicated glaucoma. *Ophthalmology.* 1991 Jul; 98(7):1036-41.

124 Singh K, Egbert PR, Byrd S et al., Trabeculectomy with intraoperative 5-fluorouracil vs mitomycin C. *Am J Ophthalmol.* 1997 Jan; 123(1):48-53.

125 Tan JC, Hitchings RA. Non-penetrating glaucoma surgery: the state of play. *Br J Ophthalmol.* 2001 Feb; 85(2):234-7.

126 El Sayyad F, Helal M, El-Kholify H, et al., Nonpenetrating deep sclerectomy versus trabeculectomy in bilateral primary open-angle glaucoma. *Ophthalmology.* 2000 Sep; 107(9):1671-4.

127 Netland PA. Nonpenetrating glaucoma surgery. *Ophthalmology.* 2001;108(2):416?21

128 Lim KS, Allan BDS, Muir LA et al., Glaucoma drainage devices; past, present and future. *Br J Opthalmol* 1998; 82:1083-1089

129 Roy S, Ravinet E, Mermoud A. Baerveldt implant in refractory glaucoma: long-term results and factors influencing outcome. *Int Ophthalmol.* 2001; 24(2):93-100.

130 Hong CH, Arosemena A, Zurakowski D, Ayyala RS. Glaucoma Drainage Devices: A Systematic Literature Review And current Controversies. *Survey of Ophthalmology* 2006; 60: 48-59

131 No authors listed. The Glaucoma Laser Trial (GLT). 2. Results of argon laser trabeculoplasty versus topical medicines. The Glaucoma Laser Trial Research Group. *Ophthalmology.* 1990 Nov; 97(11):1403-13.

132 Spaeth GL, Baez KA. Argon laser trabeculoplasty controls one third of cases of progressive, uncontrolled, open angle glaucoma for 5 years. *Arch Ophthalmol.* 1992 Apr; 110(4):491-4.

133 Schwartz AL, Love DC, Schwartz MA. Long-term follow-up of argon laser trabeculoplasty for uncontrolled open-angle glaucoma. *Archives of Ophthalmology.* 1985; 103(10):1482-4.

134 Kosoko O, Gaasterland DE, Pollack IP, Enger CL. Long-term outcome of initial ciliary ablation with contact diode laser transscleral cyclophotocoagulation for severe glaucoma. The Diode Laser Ciliary Ablation Study Group. *Ophthalmology.* 1996; 103:1294-302.

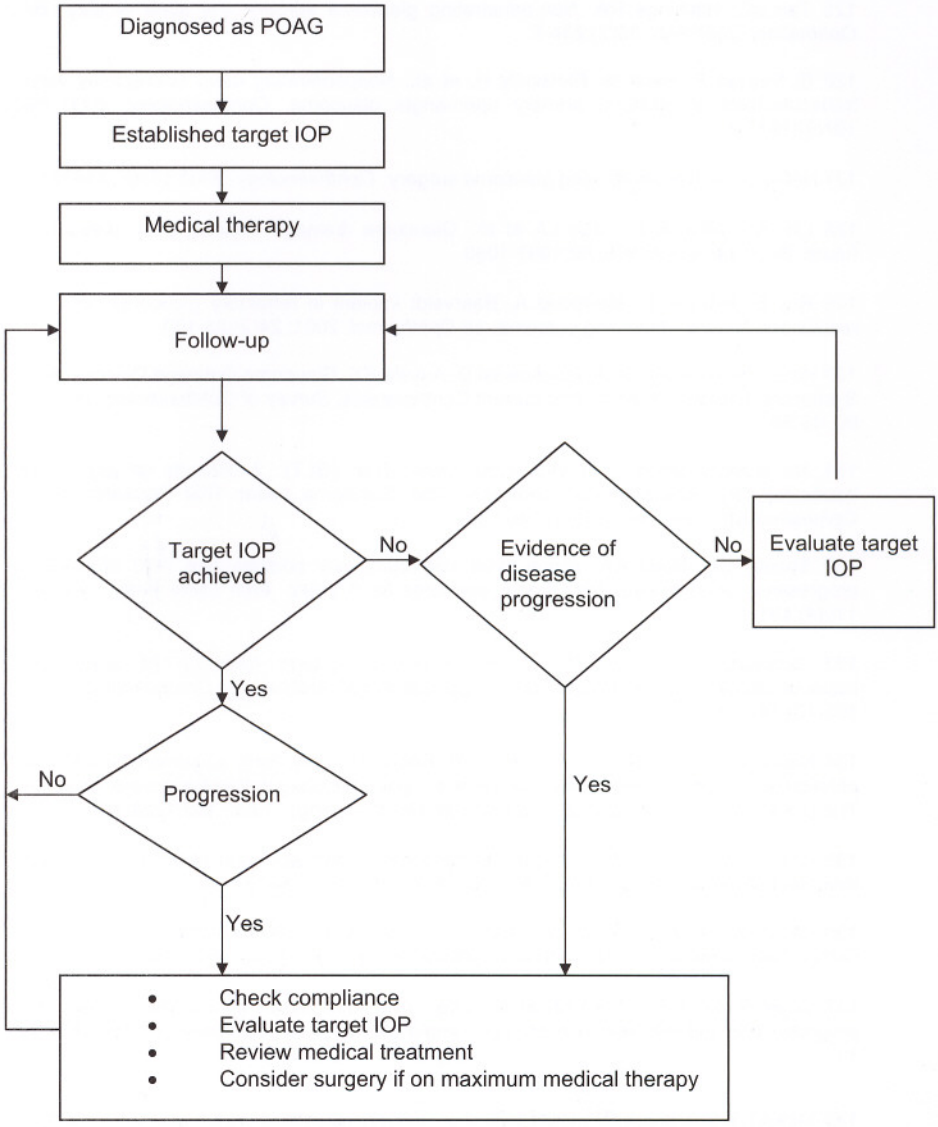
135 Chen J, Cohn RA, Lin SC et al., Endoscopic photocoagulation of the ciliary body for treatment of refractory glaucomas. *Am J Ophthalmol.* 1997; 124:787-96.

136 Anderson DR, Drance SM, Schulzer M. Collaborative Normal-Tension Glaucoma Study Group. Natural history of normal-tension glaucoma. *Ophthalmology.* 2001 Feb;108(2):247-53

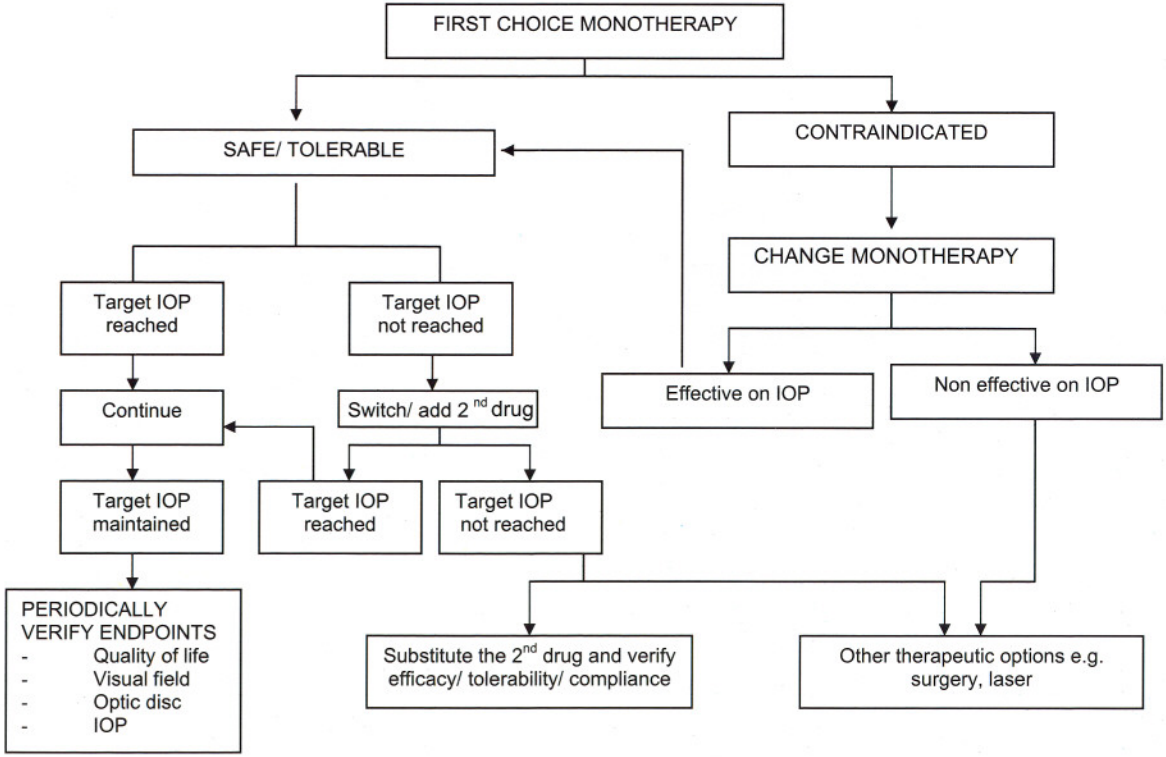
137 Vogel R, Crick RP, Mills KB et al., Effect of timolol versus pilocarpine on visual field progression in patients with primary open-angle glaucoma. *Ophthalmology* 1992; 99:1505-11.

138 Stewart WC, Chorak RP, Hunt HH, et al. Factors associated with visual loss in patients with advanced glaucomatous changes in the optic nerve head. *Am J Ophthalmol* 1993; 116:176-81.

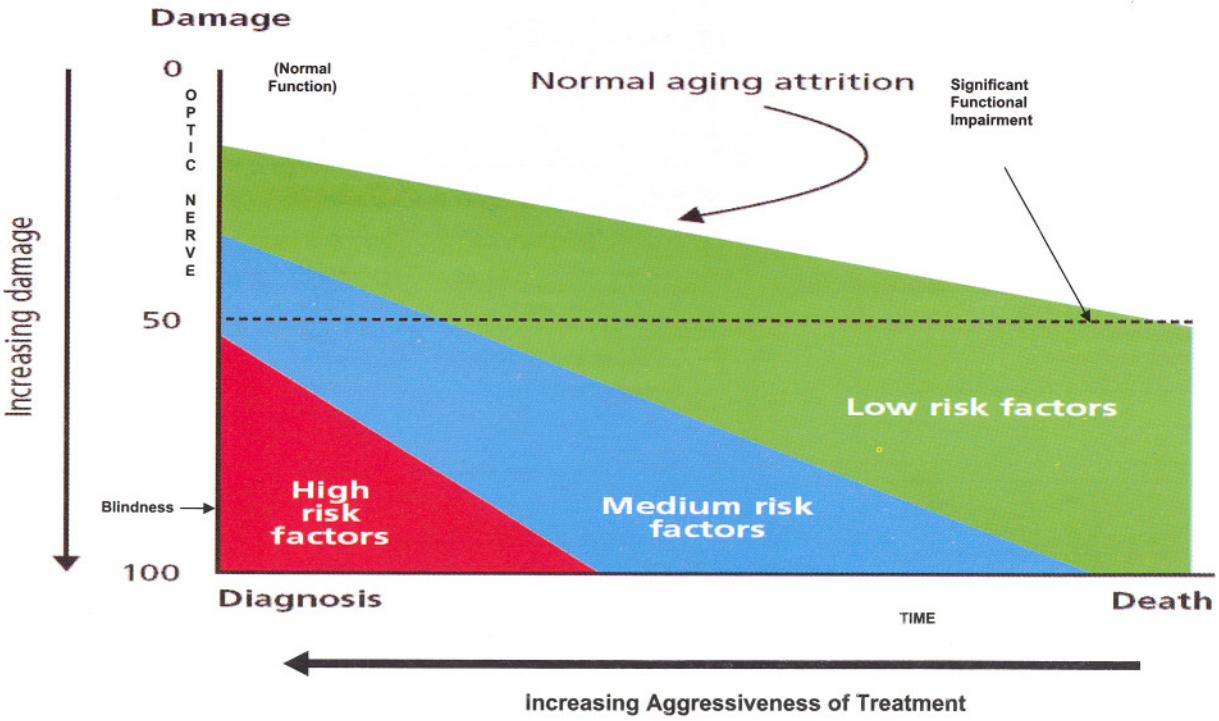
Algorithm on Management of POAG



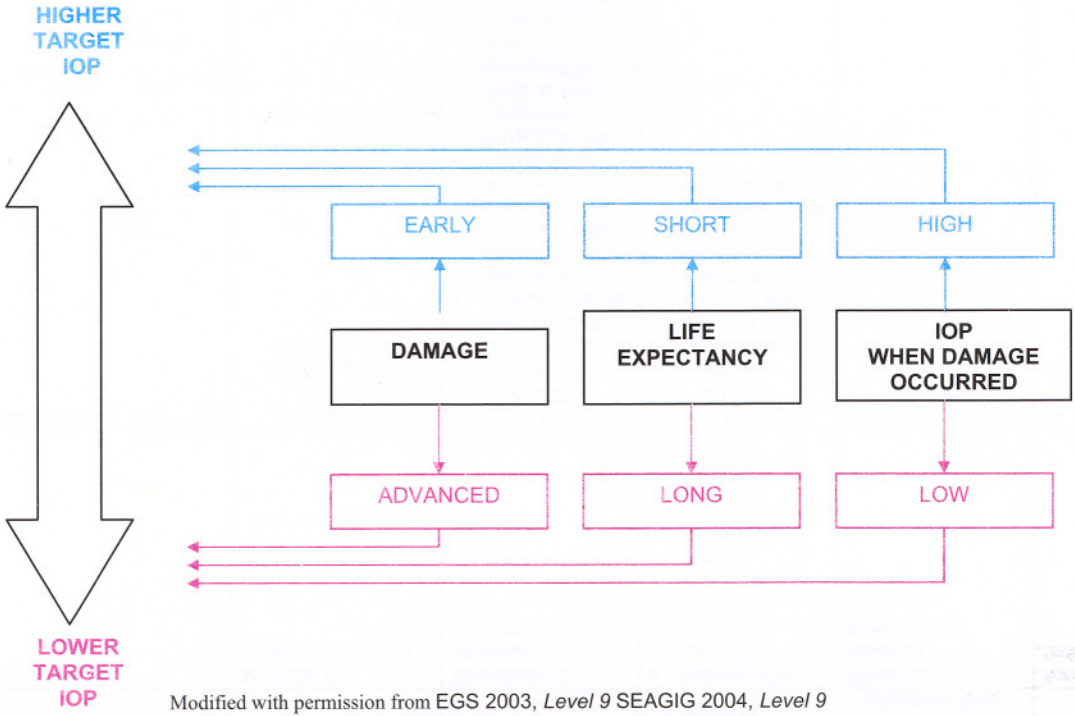
Algorithm on Medical Treatment



The Glaucoma Life Story



Target IOP



Modified with permission from EGS 2003, *Level 9* SEAGIG 2004, *Level 9*

Main Features of Topical Anti-glaucoma Agents

	Prostaglandin analog/ Prostamides	β-blockers	α_2-adrenergic agonists	Topical Carbonic Anhydrase Inhibitors (CAI)	Cholinergic (direct acting)
Mechanism of action	Increase in uveoscleral outflow	Reduction of aqueous production	• Reduction of aqueous production • Increase in uveoscleral outflow (Brimonidine 0.15% also have this mechanism of action)	Reduction of aqueous production	Increase in trabecular outflow
IOP reduction efficacy	++++ 25-30% (Better control of circadian IOP)	+++ 20-25% • Selective β-blockers has lower efficacy • Efficacy maybe reduced by simultaneous treatment with systemic β-blockers • In one- eyed therapeutic trial, cross-over effect to fellow eye must be taken in account • Tachyphylaxis may occur	++ to +++ 20-25% • Long term use of apraclonidine may be limited due to allergic reactions & tachyphylaxis (lower incidence with brimonidine)	+ to ++ 15-20%	+ to ++ 20-25%
Duration of effect	24 hours	12 hours	12 hours	8 hours	6-7 hours

Appendix 3

Neuroprotective effect	-	± (Selective β-blockers may have this effect)	± (Brimonidine may have this effect)	±	-
Treatment option	1st or 2nd choice (Switching within this class maybe of benefit as patients may respond differently)	1st or 2nd choice	*1st or 2nd choice (α_1- selective agents maybe used as short term primary therapy following anterior segment procedures for preventing acute spike in IOP)	2nd choice	3rd choice
Instillation frequency	Once daily (except unoprostone bid) • Paradoxical effect (↑ IOP) may occur if more than once daily dosing • More effective if administered in the evening	1-2 times daily	2-3 times daily	2-3 times daily (Monotherapy – tds dosing, adjunctive therapy – bid dosing)	3-4 times daily
Wash out period	4-6 weeks	2-5 weeks	1-3 weeks	1 week	3 days
Drug combinations – additive effect					
Prostaglandin analog/ Prostamides		+	+	+	+/-
β-blockers	+		+	+	+
α_2 agonists	+	+		+	+
Topical CAIs	+	+	+		+
Cholinergics	+/-	+	+	+	
Non-preservatives or with different preservative preparations	No	†Yes (both preparations available)	†Yes (preparation with different preservative available)	† No	†Yes (non preservative preparation available)

Appendix 3

Fixed combination preparations					
Prostaglandin analog/ Prostamides		†Yes	No	No	No
β-blockers	†Yes		No	†Yes	†Yes
α_2-agonists	No	†No		No	No
Topical CAIs	No	†Yes	No		No
Commercially available preparation	• †Latanoprost 0.005% • †Travoprost 0.004% • †Bimatoprost 0.03% • Unoprostone 0.12%, 0.15%	Non selective • †Timolol 0.25%, 0.5% • †Levo bunolol 0.25%, 0.5% • Befunolol 0.5% • Metipranolol 0.1% , 0.3% • Cartelolol 0.5%, 2% • Pindolol 0.5% β_1– selective †Betaxolol 0.25%, 0.5%	α_1- selective • †Brimonidine 0.15% • †Apraclonidine 0.5%, 1% • Clonidine 0.125%, 0.5% Non-selective • Dipivefrin 0.1%; • Epinephrine 0.25% , 0.5	Topical • †Brinzolamide 1% • †Dorzolamide 2%	**Direct-acting** • †Pilocarpine 0.5% - 4% • Aceclidine 2 % • Carbachol 0.75-3% • Acetylcholine 1% **Indirect-acting** • Demecarium bromide 0.125%, 0.25% • Ecothiophate iodide 0.03%-0.25%\ • Physostigmine
Cost	+++	+	++	++	+

†Drugs available in Malaysia

* Reference – EGS 2003, *Level 9* SEAGIG 2004, *Level 9*, Guidelines and individual product information sheet

*The information on various anti-glaucoma drugs on this section only serves as a general guide and is not all-inclusive

Safety Profiles of Topical Anti-glaucoma Agents

	Prostaglandin analog/ Prostamides	Beta blockers (β-blockers)	Alpha blockers (α_2-agonists)	Topical CAIs	Cholinergics
Contraindications	Relative contraindication • Uveitis • HVS keratitis • Cystoid macular oedema Caution • Complicated intraocular surgery (e.g. posterior capsule rupture)	• Bronchial asthma, chronic obstructive pulmonary disease • Bradycardia, heart block, cardiac failure (relative contraindication for β1- selective)	• On monoamine oxidase inhibitor (MAO) therapy • Children less than 2 years old due to the possibility of central nervous system suppression	• Compromised corneal endothelium • Sulfonamide allergy • Severe renal impairment • Hepatic impairment (caution)	• Uveitic, neovascular and lens induced glaucomas • Aqueous misdirection syndrome
Pregnancy and nursing mothers	Human studies are lacking. Use only if potential benefit justifies the potential risk to foetus/ infant	Human studies are lacking. Use only if potential benefit justifies the potential risk to fetus/infant	Human studies are lacking. Use only if potential benefit justifies the potential risk to fetus/infant	Human studies are lacking. Use only if potential benefit justifies the potential risk to fetus/infant (Teratogenic effect seen with high dose of systemic CAIs [in animal studies])	Human studies are lacking . Use only if potential benefit justifies the potential risk to fetus/infant
Common drug interactions	Chronic pilocarpine use may reduce efficacy of these agents	Systemic β-blockers Calcium antagonists Digitalis Catecholamine-depleting drugs	CNS depressants (alcohol, barbiturates,opiates, sedatives, anesthetics) tricyclic antidepressants	Caution in patients on steroid (potential for hypokalemia)	Competitive interaction on outflow with prostalglandin
Topical allergies	+/-	+/-	++	+/-	+/-
Ocular adverse-effects	+ to ++	+	++	++ (Brinzolamide 1% cause less ocular discomfort)	+++

	Ocular discomfort (stinging, burning, foreign body sensation sensation) Pruritis Photophobia Tearing Dry eye Blurred vision Asthenopia Allergy (conjunctivitis, eyelid erythema) Conjunctival hyperemia (usually transient & not infectious) Subconjunctival haemorrhage Hypertrichosis Blephritis Eyelid skin darkening Corneal oedema Punctate epithelial keratopathy Reactivation of Herpes Simplex Virus, keratitis Iris darkening Cataract Anterior uveitis Cystoid macular oedema	Ocular discomfort (stinging, burning, foreign body sensation) Pruritis Photophobia Tearing Conjunctival hyperemia Decreased corneal sensitivity Punctate epithelial keratopathy Allergy (conjunctivitis, eyelid erythema)	Ocular discomfort (stinging, burning, foreign body sensation) Pruritis Allergy (conjunctivitis, eyelid erythema) Conjunctival hyperemia Subconjunctival haemorrhage Lid retraction Pupil dilatation (apraclonidine)	Ocular discomfort (stinging, burning, foreign body sensation) Pruritis Tearing Allergy (conjunctivitis, eyelid erythema) Blurred vision Transient myopia Punctate epithelial keratopathy	Brow ache Lacrimation Miosis Dimness of vision, blurring, myopic shift Ciliary spasm Aggravate pupillary block Retinal detachment
Systemic adverse-effects:	0	+ to +++ (Selective β - blockers has a wider safety margin (less systemic side-effects especially cardiopulmonary side-effect).	+ to ++	0 to ++	0 to ++
Cardiovascular		Bradyarrhythmias			Arrhythmia

		Hypotension Cardiac failure Nocturnal hypotension			Flushing
Respiratory		Bronchospasm			Bronchoconstriction
Neurology		Syncope Drowsiness Anergy Fatigue Depression Aggravation of myasthenia gravis Memory impairment	Apnoea in infants Syncope Drowsiness Headache Asthenia Fatigue Depression	Dizziness Headache Asthenia Depression Paresthesia	Headache
GIT		GIT discomfort Oral dryness	GIT discomfort Oral dryness	Throat irritation Altered taste	Salivation Abdominal cramps Diarrhea Vomiting
Others		Masked hypoglycemia Hypercholesterolemia Sexual dysfunction (loss of libido,impotence) Reduced effort tolerance Increased falls in the elderly		Urolithiasis	Urinary frequency

* Reference – EGS 2003, *Level 9* SEAGIG 2004, *Level 9*, Guidelines and individual product information sheet

*The information on various anti-glaucoma drugs on this section only serves as a general guide and is not all-inclusive

Appendix 5

Application of Mitomycin C (MMC) or 5 Flourouracil (5-FU) in Trabeculectomy

Antimetabolite	Timing of application	Dose and duration	Mode of application
Mitomycin C (MMC)** (comes in a vial as purple colour powder in 10 mg potency. It is freshly reconstituted with distilled water or normal saline in concentration of 0.2 – 0.4 mg/ml)	During surgery/intra-operatively.	0.2 to 0.4 mg/ml applied for 1- 5 minutes For primary surgery, a concentration of 0.4mg/ml is applied for 1 minute, whereas for poor prognosis filters/ cases the same concentration can be applied for 3 minutes.	Applied subconjunctivally using multiple pieces of cut Merocel sponges soaked in MMC. The sponges are placed under the conjunctiva before or after the dissection of scleral flap. The aims are to treat a large sub-conjunctival area and to avoid contact with the cut edges of the conjunctiva. After the requisite time limit, the sponges are removed and the area washed with copious irrigation of balanced salt solution, normal saline or ringer lactate solution. One should keep count on the number of sponges placed to ensure complete removal of all sponges. This is to avoid unwanted pos-top complications.
	Post-operatively / prior to needling	0.01 ml of MMC (0.4mg/ml) and 0.02 ml of bupivacaine with epinephrine	Subconjunctival injection. A mixture of 0.01 ml of MMC (0.4mg/ml) and 0.02 ml of bupivacaine with epinephrine can be injected subconjunctivally superior to the bled. A needle is than used to perforate the area of subconjunctival fibrosis and re-establish flow.
5 Flourouracil (5-FU)** (comes in 50mg/ml solution in 5 ml vial and is used without dilution)	During surgery/intra-operatively	50 mg /ml for 1 – 3 minutes	Applied subconjunctivally using multiple pieces of cut Merocel sponges soaked in 5-FU. The sponges are placed under the conjunctiva before or after the dissection of scleral flap. The aims are to treat a large sub-conjunctival area and to avoid contact with the cut edges of the conjunctiva. After the requisite time limit, the sponges are removed and the area washed with copious irrigation of balanced salt solution, normal saline or ringer lactate solution. One should keep count on the number of sponges placed to ensure complete removal of all sponges. This is to avoid unwanted pos-top complications.
	Post-operatively/ prior to needling	5 mg/0.1 ml for up to 4 post-operative weeks	Subconjunctival injection- The injection are given posterior to the bleb, using preferably a 30 gauge needle. The number and frequency of injection is titrated according to the appearance of the bleb.

**** Antimetabolites usage should be individualized to each patient depending on the complexity of cases.**

Care in the preparation and disposal of antimetabolites:

- It is recommended to prepare antimetabolites on a separate trolley using aseptic technique.
- The instruments used in MMC or 5-FU application are not used again in the surgery to avoid contamination of the surgical field.
- The soaked sponges must be disposed in an incinerator or safely in concordance with bio-waste rules.
- Disposal of leftover / unused antimetabolites should be taken with the same care as any other chemotherapies. It should be sent back to local pharmacy department for proper disposal.

Adapted from SEAGIG 2003

LIST OF ABBREVIATIONS

POAG	Primary Open Angle Glaucoma
IOP	Intraocular Pressure
CDR	Cup Disc Ratio
CCT	Central Corneal Thickness
TM	Trabecular Meshwork
RNFL	Retinal Nerve Fibre Layer
CAI	Carbonic Anhydrase Inhibitor
MMC	Mitomycin C
5-FU	5 Fluorouracil
SWAP	Short -Wave Length Automated Perimetry
FDT	Frequency Doubling Technology
TOP	Tendency-Oriented Perimetry
OCT	Optical Coherent Topography
OHT	Ocular Hypertension
HRT	Heidelberg Retinal Topography
NRR	Neuroretinal Rim
ISNT	Inferior Superior Nasal Temporal

ACKNOWLEDGEMENT

The committee of this guideline would like to express their gratitude and appreciation to the following for their contributions:

- Panel of external reviewers who reviewed the draft.
- Technical Advisory Committee for Clinical Practice Guidelines for their valuable input and feedback.
- Datin Dr Rugayah Bakri, Head of Health Technology Assessment Unit, Medical Development Division, Ministry of Health, Malaysia.

DISCLOSURE STATEMENT

The panel members have completed disclosure forms. None holds shares in pharmaceutical firms or acts as consultants to such firms. (Details are available upon request from the CPG Secretariat)

SOURCES OF FUNDING

The development of the CPG on Management of Primary Open Angle Glaucoma was supported financially in its entirety by the Ministry of Health Malaysia and was developed without any involvement of the pharmaceutical industry.

LEVELS OF EVIDENCE SCALE

Level	Strength of evidence	Study design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM THE CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT & RESEARCH, (CAHTAR) SPAIN

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)