Appendix U: Glaucoma:

diagnosis and management of chronic open angle glaucoma and ocular hypertension

DRAFT VERSION- 2nd version

METHODS, EVIDENCE & GUIDANCE

Produced by the National Collaborating Centre for Acute Care

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Foreword

"O loss of sight, of thee I most complain!"

John Milton (1608–1674)

The World Health Organisation has estimated that globally there are 12.5 million people blind from glaucoma with the total number affected by this condition around 66 million. Approximately 10% of UK blindness registrations are ascribed to glaucoma and around 2% of people older than 40 years have chronic open angle glaucoma, a figure which rises to almost 10% in people older than 75 years. With changes in population demographics the number of individuals affected by glaucoma is expected to rise. Based on these estimates there are around 480,000 people affected by chronic open angle glaucoma in England, who receive over a million glaucoma related outpatient visits in the hospital eye service annually. Once diagnosed, affected individuals require lifelong monitoring for disease control and to detection of possible progression of visual damage. Once lost, vision cannot be restored, disease control with prevention, or at least minimisation of ongoing damage is therefore paramount to maintenance of a sighted lifetime.

Chronic open angle glaucoma, and its frequent precursor, ocular hypertension are the subject of this NICE guideline. Individuals with early to moderate chronic glaucoma are mostly asymptomatic and unaware of any damage to their field of vision. Once vision loss becomes apparent up to 90% of optic nerve fibres may have been irrecoverably damaged. Early detection and effective treatment by healthcare professionals are thus key elements in avoiding permanent blindness. Screening and case finding have been the subject of a published HTA assessment and lie outside the scope of this guidance, which focuses on prevention of vision loss through treatment.

Reports on treatments for chronic open angle glaucoma (COAG) have been systematically searched out and evaluated. The clinical effectiveness, cost effectiveness and patients' views of a variety of treatments have been professionally assessed by the scientists and methodologists in the National Collaborating Centre for Acute Care (NCC-AC), with interpretation and setting in context by the clinicians and patient representatives comprising the Guideline Development Group (GDG). Long term lowering of intraocular pressure (IOP) remains the only strategy known to be effective against sight loss. As a long term progressive condition, COAG presents challenges to the researcher in terms of the extended time frames necessary to assess comparative outcomes of direct relevance to vision. Many shorter duration randomised treatment trials focus on IOP reduction and for this reason a link was sought between pressure reduction and protection against vision loss. Methodologically crucial, this link formalises the use of IOP reduction as a valid proxy or surrogate outcome and quantifies IOP reduction in terms of protection of vision. A further methodological achievement lay in establishing a quantitative relationship between visual loss and reduced quality of life, without which economic evaluation of the evidence would have been problematic.

Ocular hypertension (OHT) is elevated eye pressure in the absence of visual field loss or glaucomatous optic nerve damage. It is estimated that 3% to 5% of those over 40 years have OHT, around one million people in England. OHT represents a major risk for future development of COAG with visual damage. Lowering IOP has been shown to protect against conversion to COAG. A key question for the guideline therefore related to whether or not treatment for OHT would be cost effective in preventing vision loss in the long term. Once again, establishment of a quantitative link between IOP reduction and protection against development of COAG and the threat to a sighted lifetime was an essential step in the assessment of the cost effectiveness of treating OHT. Without a detailed knowledge of the cost effectiveness of treatment for various risk strata of OHT, recommendations for preventative treatment would not have been possible.

The main treatments covered in the guideline are pharmacological agents for topical use as eye drops, laser procedures and drainage surgery with or without pharmacological augmentation. Where multiple randomised controlled trials (RCT) of sufficient quality were found these were merged using meta-analytical techniques in order to obtain a single result from all available evidence. Reporting of adverse events and patients' views from trials and other sources was considered and factored into the interpretation of evidence by the GDG. Evaluation of the cost effectiveness of the various treatment options for both COAG and OHT required the development of original cost effectiveness analyses carried out by the NCC-AC staff. For the clinicians and patient representatives of the GDG this important aspect of the guideline was relatively unfamiliar territory at the outset. The professional staff of the centre however provided general and specific guidance which allowed the GDG to not only understand these complex analyses, but also to influence them with clinically relevant information. Thus drainage surgery may appear to be the most cost effective treatment when analysed, but this result needs to be interpreted in the context of relatively rare though serious complications, as well as patient preference, fear of surgery and personal risk aversiveness.

Despite meticulous methodology and attention to detail there will always remain areas of uncertainty. Trial evidence may be absent, and where this exists it cannot refer to those patients whose clinical features lie outside the inclusion criteria and extrapolations are required when stepping beyond the fringes. Even within the boundaries of the evidence there are uncertainties, hence the clinically familiar use of confidence intervals around effect sizes. Dealing with uncertainty in the economic evaluation requires a different approach, a sensitivity analysis varies the model's input parameters and examines the impact this has on the model outputs. Science and medicine aside, the circumstances and views of individual patients must be taken into account and 'one size' will never 'fit all'. Thus there will always be clinical exceptions and the intention of the guideline is to provide recommendations which will apply to 80% of clinical situations on 80% of occasions.

Management of a largely asymptomatic though potentially irreversibly blinding long term condition such as COAG requires ongoing monitoring by healthcare professionals. Measurement of intra ocular pressure is a convenient device for assessing level of disease control but the ultimate outcome is preservation of vision. Rates of progression vary widely between patients and timely detection of progression requires accurate and consistent measurement of visual fields with assessment of optic nerve head features over years. Conscientious and regular monitoring according to the perceived threat to a patient's sighted lifetime is crucial to success and the quality of any service has much to do with this aspect of patient care. Unusually in this NICE guideline we were asked to include recommendations on the most appropriate service models. To this end we considered options for management of different patient groups in terms of relevant healthcare professionals, their roles, their

training requirements, and the standards of performance which might be expected of them. We also considered requirements for equipment and issues of continuity of care for patients.

There have been many challenges and methodological obstacles encountered in the development of this clinical guideline. Overcoming these stands is a testament to the effort, commitment and quality of the professionals in the collaborating centre, and the dedication and expert knowledge of the clinician members and patient representatives of the guideline development group. Our efforts will be amply rewarded if this guideline helps to preserve vision for those whose sighted lifetime is threatened by that 'silent thief of sight', chronic open angle glaucoma.

John Sparrow

Chair, Guideline Development Group

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Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring concordance to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives.

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Addenbrooke's NHS Trust
Alcon Laboratories (UK) Ltd
Allergan UK
Alliance Pharmaceuticals Ltd
Association of British Dispensing Opticians
Association of Ophthalmologists
Association of Optometrists
Barnsley Acute Trust
Barnsley Hospital NHS Foundation Trust
Barnsley PCT
Bedfordshire & Hertfordshire Strategic Health Authority
Bedfordshire PCT
Bournemouth & Poole PCT
British and Irish Orthoptic Society
British Association for Counselling and Psychotherapy
British Dietetic Association
British Geriatrics Society
British Institute of Organ Studies
British National Formulary (BNF)
Buckinghamshire PCT
BUPA
Caldedale PCT
Cambridge University Hospitals NHS Foundation Trust
Care Quality Commission
CASPE
Central Liverpool PCT
Chesterfield PCT
Cochrane Eyes & Vision Group
College of Optometrists
Commission for Social Care Inspection
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Dudley Group of Hospitals NHS Trust, The
East & North Herts PCT & West Herts PCT
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General Optical Council
Harrogate and District NHS Foundation Trust
Health and Safety Executive
Heart of England NHS Foundation Trust
International Glaucoma Association
King's College Hospital NHS Trust
Kirklees PCT
Leeds PCT
Liverpool PCT
Luton & Dunstable Hospital NHS Foundation Trust
Maternity Health Links
Medicines and Healthcare Products Regulatory Agency
Mental Health Act Commission
Merck Sharp & Dohme Ltd
Mid Essex Hospitals NHS Trust
Milton Keynes PCT
Moorfields Eye Hospital NHS Foundation Trust
National Patient Safety Agency
National Public Health Service – Wales
National Treatment Agency for Substance Misuse
NCCHTA
NHS Clinical Knowledge Summaries Service
NHS Health and Social Care Information Centre
NHS Kirklees
NHS Pathways
NHS Plus
NHS Purchasing & Supply Agency
NHS Quality Improvement Scotland
NHS Sheffield
Norfolk & Norwich University Hospital NHS Trust
North Yorkshire & York PCT
Northwest London Hospitals NHS Trust
Ophthalmic Pharmacy Group
Paediatric Glaucoma Forum
PERIGON (formerly The NHS Modernisation Agency)
Peterborough & Stamford NHS Hospitals Trust
Pfizer Limited
Primary Care Pharmacists' Association
Princess Alexandra Hospitals NHS Trust
Prodigy

Regional Public Health Group - London
Royal College of General Practitioners
Royal College of Midwives
Royal College of Nursing
Royal College of Ophthalmologists
Royal College of Paediatrics and Child Health
Royal College of Radiologists
Royal National Institute of Blind People (RNIB)
Royal Pharmaceutical Society of Great Britain
Royal Society of Medicine
SACAR
Sandwell PCT
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield South West PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Social Care Institute for Excellence (SCIE)
South East Sheffield PCT
South Warwickshire General Hospitals NHS Trust
Staffordshire Moorlands PCT
Stockport PCT
Sussex Eye Hospital
The David Lewis Centre
The Practice
University Hospital Birmingham NHS Foundation Trust
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
West Suffolk Hospital
Western Cheshire Primary Care Trust
Western Health and Social Care Trust
York NHS Foundation Trust
York NHS Trust

Abbreviations

ANCOVA	Analysis of covariance
ALT	Argon laser trabeculoplasty
BB	Beta-blockers
BNF	British National Formulary
CACG	Chronic angle closure glaucoma
CAI	Carbonic anhydrase inhibitors
CCA	Cost-consequences analysis
CCT	Central corneal thickness
CEA	Cost-effectiveness analysis
CI	Confidence interval
COAG	Chronic open angle glaucoma
CUA	Cost-utility analysis
DH	Department of Health
5-FU	5-Fluorouracil
GAT	Goldmann applanation tonometry
GDG	Guideline Development Group
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRP	Guideline Review Panel
HES	Hospital Eye Services
HRQL	Health-related quality of life
HTA	Health technology assessment
HRT	Heidelberg retina tomography
ICC	Intraclass correlation coefficient
ICER	Incremental cost-effectiveness ratio
ISNT	Inferior, Superior, Nasal, Temporal
INB	Incremental net benefit
IOP	Intraocular pressure
IQR	Inter-quartile range
ITT	Intention to treat

LOS	Length of Stay
LY	Life-year
MHRA	Medicines and Healthcare Products Regulatory Agency
MMC	Mitomycin-C
MTC	Mixed-treatment comparisons
NCC-AC	National Collaborating Centre for Acute Care
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
NRR	Neuroretinal rim
NTG	Normal tension glaucoma
OCT	Optical Coherence Tomography
OHT	Ocular hypertension
OR	Odds ratio
PACG	Primary angle closure glaucoma
PAS	Peripheral anterior synechiae
PASA	NHS Purchasing and Supply Agency
PDS	Pigment dispersion syndrome
PXF	Pseudoexfoliation
PG	Pigmentary glaucoma
PGA	Prostaglandin analogues
PICO	Framework incorporating patients, interventions, comparison and outcome
POAG	Primary open-angle glaucoma
PPA	Peri-papillary atrophy
PPIP	Patient and Public Involvement Programme
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SAP	Standard automated perimetry
SD	Standard deviation
SLT	Selective laser trabeculoplasty
SR	Systematic review
VAS	Visual analogue scale
VCD	Vertical cup-to-disc ratio
VF	Visual field

Glossary of Terms

Absolute risk reduction (Risk difference)	The difference in the risk of an event between two groups (one subtracted from the other) in a comparative study.
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Adherence	The extent to which the patient's behaviour matches the prescriber's recommendations. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the doctor's recommendation.[105]
Adjustment	A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.
Acceptable IOP	Intraocular pressure at the target level considered by the healthcare professional treating the patient to be sufficiently low to minimise or arrest disease progression. See **Target IOP**
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Appraisal of Guidelines Research and Evaluation, (AGREE)	An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines.
Aqueous humour	"Clear, colourless fluid that fills the anterior and posterior chambers of the eye. It is a carrier of nutrients for the lens and for part of the cornea. It contributes to the maintenance of the intraocular pressure. It is formed in the ciliary processes, flows into the posterior chamber, then through the pupil into the anterior chamber and leaves the eye through the trabecular meshwork passing to the canal of Schlemm

	and then to veins in the deep scleral pleral plexus." [100]
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Audit	See 'Clinical audit'.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding (masking)	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Blindness	1. Inability to see. 2. Absence or loss of sight severe enough for someone to be unable to perform any work for which eyesight is essential. [100] The World Health Organisation definition of blindness is less than 3/60 in the better seeing eye. This means that the better seeing eye cannot read the top letter on the Snellen visual acuity chart at three metres. (Cochrane Eyes and Vision Group, http://www.cochraneeyes.org/glossary.htm) For the purposes of the economic analysis in this guideline the definition of severe visual impairment was considered by the GDG to be Mean Defect <-20 dB. It was further assumed that both eyes were similar.
Capital costs	Costs of purchasing major capital assets (usually land, buildings or equipment). Capital costs represent investments at one point in time.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Chronic open angle glaucoma (COAG)	See glaucoma, chronic open-angle
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.

Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinical impact	The effect that a guideline recommendation is likely to have on the treatment or treatment outcomes, of the target population.
Clinical question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cluster	A closely grouped series of events or cases of a disease or other related health phenomena with well-defined distribution patterns, in relation to time or place or both. Alternatively, a grouped unit for randomisation.
Cochrane Library	A regularly updated electronic collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews.
Cochrane Review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Co-morbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Compliance	The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence' or 'concordance'.[105]
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.[105]
Conference proceedings	Compilation of papers presented at a conference.

Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial(CCT)	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.
Conversion	Worsening of suspected COAG or OHT with the development of visual field loss in keeping with optic nerve head appearance. To make this judgement the healthcare professional must know the eye's earlier clinical state.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.

Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible interval	The Bayesian equivalent of a confidence interval.
Cup to disc ratio	The ratio of the diameter of the optic nerve head central excavation or cup to that of the diameter of the optic disc itself. Clinically the vertical diameters are normally used to estimate this ratio. High cup to disc ratios imply loss of neural tissue with thinning of the neuro-retinal rim of the optic nerve head.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Decibels (dB)	This refers to the brightness of the test stimulus used during a visual field test
Decision problem	A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Dosage	The prescribed amount of a drug to be taken, including the size and timing of the doses.
Double blind/masked study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment nor intervention the subject is receiving. The purpose of blinding/masking is to protect against bias.
Drop-out	A participant who withdraws from a clinical trial before the end.

Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
Equity	Fair distribution of resources or benefits.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Expert consensus	See 'Consensus methods'.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Follow up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another

	should acknowledge that these costs might vary across the country.
Glaucoma	A disease of the optic nerve with characteristic changes in the optic nerve head (optic disc) and typical defects in the visual field with or without raised intraocular pressure. (*see also types of glaucoma listed below*)
Glaucoma, angle closure	Glaucoma in which the angle of the anterior chamber is blocked by the root of the iris which is in apposition to the trabecular meshwork[100].
Glaucoma, chronic open-angle	Glaucoma without evident secondary cause which follows a chronic time course and occurs in the presence of an open anterior chamber angle (the trabecular meshwork is visible on gonioscopy). In this guideline the term COAG is used regardless of the level of intraocular pressure and has been extended to include COAG associated with pseudoexfoliation and pigment dispersion (unless specifically stated otherwise).
Glaucoma, normal tension /glaucoma, low tension	A type of chronic open-angle glaucoma where intraocular pressure has rarely been recorded above 21 mm of Hg (a figure frequently taken as the 'statistical' upper limit of the normal range).
Glaucoma, open-angle	When the anterior chamber angle (defined by gonioscopy) is open:
Glaucoma, pigmentary	Glaucoma caused by the deposition of pigment in the trabecular meshwork as a result of pigment dispersion syndrome.
Glaucoma, primary open-angle (POAG)	Chronic open angle glaucoma in the absence of any other ocular, systemic or pharmacological cause and accompanied by elevated intraocular pressure.
Glaucoma, pseudoexfoliative	Glaucoma in the presence of pseudoexfoliative material.
Glaucoma, secondary	Glaucoma associated with raised intraocular pressure due to a recognised or systemic disease or pharmacological treatment.
Glaucoma, suspected	When, regardless of the level of the IOP, the optic nerve head (optic disc) and/or visual field show changes that suggest possible glaucomatous damage.
Glaucomatous optic neuropathy	Characteristic morphological changes within the optic nerve head associated with specific patterns of visual field loss.
Gold standard	See 'Reference standard'.
Gonioscope	Mirrored contact lens (goniolens), used with slit lamp biomicroscopy, or a contact prism lens (gonioprism) to enable observation of the anterior chamber angle.
Gonioscopy	Examination of the anterior chamber angle using a gonioscope to observe angle structures and estimate depth of angle.
Goodness-of-fit	How well a statistical model or distribution compares with the observed data.

Grey literature	Reports that are unpublished or have limited distribution, and are not included in the common bibliographic retrieval systems.
Harms	Adverse effects of an intervention.
Healthcare professional	For the purposes of this guideline the term 'healthcare professional' refers to a trained individual involved in glaucoma related care including: ophthalmologists, optometrists, orthoptists, pharmacists, nurses and general practitioners.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heidelberg retina tomography	A confocal laser scanning system providing 3-D images of the posterior segment of the eye to enable quantitative topographical assessment of ocular structures and changes over time.
Heterogeneity	Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Homogeneity	This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
Hypothesis	A supposition made as a starting point for further investigation.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another. $ICER=(Cost_A – Cost_B) / (Effectiveness_A – Effectiveness_B)$.

Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Index	In epidemiology and related sciences, this word usually means a rating scale, for example, a set of numbers derived from a series of observations of specified variables. Examples include the various health status indices, and scoring systems for severity or stage of cancer.
Indication (specific)	The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).
Intention-to-treat analysis (ITT analysis)	An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.
Intermediate outcomes	Outcomes that are related to the outcome of interest but may be more easily assessed within the context of a clinical study: for example, intraocular pressure reduction is related to the risk of conversion to COAG or COAG progression.
Internal validity	The degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study's findings. See 'External validity'.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraocular pressure	The internal pressure the fluid contained within the eye.
Intraoperative	The period of time during a surgical procedure.
ISNT	The pattern by quadrant of the optic nerve head neural retinal rim thinning, i.e. Inferior, Superior, Nasal, Temporal
Kappa statistic	An index which compares the agreement against that which might be expected by chance
Laser trabeculoplasty	A surgical procedure to deliver a series of laser burns to the trabecular meshwork to improve the outflow of aqueous humour in open-angle glaucoma.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Literature review	An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their

	findings. It may or may not be systematically researched and developed.
Markov model	A method for estimating long term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Medical devices	All products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or handicap.
Medicines and Healthcare Products Regulatory Agency (MHRA)	The Executive Agency of the Department of Health protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Narrative summary	Summary of findings given as a written description.
Nerve fibre layer (NFL)	"The layer of the retina composed of the unmyelinated axons of the ganglion cells which converge towards the optic disc where they exit the eye and form the optic nerve."[100]
Normal tension glaucoma (NTG) (low tension glaucoma)	See Glaucoma, normal tension
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Ocular hypertension	Consistently or recurrently elevated intraocular pressure (greater than 21 mm Hg) in the absence of clinical evidence of optic nerve damage or visual field defect.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Off-label	A drug or device used treat a condition or disease for which it is not specifically licensed.

Older people	People over the age of 65 years.
Open angle glaucoma	*See Glaucoma, open angle*
Operating costs	Ongoing costs of carrying out an intervention, excluding capital costs.
Ophthalmic nurse	A nursing professional with specialist training and expertise in the care of conditions of the eye.
Ophthalmologist	A medically qualified specialist with expert knowledge of conditions affecting the eye and orbit, including diagnosis, management and surgery.
Opportunity cost	The opportunity cost of investing in a healthcare intervention is the loss of other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Orthoptist	A healthcare professional with specialist training and expertise in the care of conditions of the eye, especially measurement of vision in children and binocular function in children and adults
Optometrist	A healthcare professional with specialist training and expertise in conditions of the eye, especially measurement of vision and refractive error, prescription and dispensing of spectacles and contact lenses. Extended role optometrists or optometrists with a specialist interest increasingly participate in delivery of healthcare services for eye disease.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
P value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Peer review	A process where research is scrutinised by experts that have not been involved in the design or execution of the studies.
Perimetry	The systematic measurement of visual field function using different types and intensities of stimuli.
Perioperative	The period from admission through surgery until discharge, encompassing preoperative and post-operative periods.
Pigment dispersion syndrome (PDS)	"A degenerative process in the iris and ciliary body epithelium in which pigment granules are disseminated and deposited on the back surface of the cornea, the lens, the zonules and within the trabecular meshwork." "Deposition of pigment in the trabecular meshwork may give rise to glaucoma (called pigmentary glaucoma)"[100].

Pigmentary glaucoma	See Glaucoma, pigmentary
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Placebo effect	A beneficial (or adverse) effect produced by a *placebo* and not due to any property of the *placebo* itself.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Preoperative	Pertaining to the period before surgery commences.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.
Primary open angle glaucoma (POAG)	See Glaucoma, primary open angle
Primary research	Study generating original data rather than analysing data from existing studies (which is called secondary research).
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Progression	The worsening of COAG as clinically judged by the healthcare professional caring for the patient on the basis of the assessment of visual field loss and optic nerve head appearance. To make this judgement the healthcare professional must know the eye's earlier clinical state.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are *retrospective*.
Pseudoexfoliation	"Deposition of grayish-white, flake-like basement membrane material on the anterior lens capsule, the iris and the ciliary processes with free-floating particles in the anterior chamber"[100].
Pseudoexfoliative glaucoma	See Glaucoma, pseudoexfoliative
Qualitative research	Research concerned with subjective outcomes relating to social, emotional and experiential phenomena in health and social care.
Quality of life	See 'Health-related quality of life'.

Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Remit	The brief given by the Department of Health and Welsh Assembly Government at the beginning of the guideline development process. This defines core areas of care that the guideline needs to address.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are *prospective*.
Secondary benefits	Benefits resulting from a treatment in addition to the primary, intended outcome.
Secondary glaucoma	See Glaucoma, secondary

Selection bias (also allocation bias) A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.

Selection criteria Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.

Sensitivity Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects.

See the related term 'Specificity'

Sensitivity analysis A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.

One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.

Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated.

Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.

Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).

Specificity The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases.

See related term 'Sensitivity'.

In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.

Stakeholder Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.

Statistical power The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.

Synthesis of A generic term to describe methods used for summarising (comparing

evidence	and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Target IOP	A dynamic, clinical judgement about what level of intraocular pressure is considered by the healthcare professional treating the patient to be sufficiently low to minimise or arrest disease progression or onset and avoid disability from sight loss within a person's expected lifetime.
Time horizon	The time span used in the NICE appraisal which reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.
Tonometry	A test to measure intraocular pressure using an instrument called a tonometer.
Trabecular meshwork	"Meshwork of connective tissue located at the angle of the anterior chamber of the eye and containing endothelium-lined spaces through which passes the aqueous humor to Schlemm's canal."[100]
Trabeculectomy	A surgical procedure that lowers IOP by creating a fistula, which allows aqueous outflow from the anterior chamber to the sub-tenon space.[71]
Treatment allocation	Assigning a participant to a particular arm of the trial.
Treatment options	The choices of intervention available.
Unacceptable IOP	Intraocular not at target. See **Target IOP**
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Van Herick Test	The Van Herick's peripheral anterior chamber depth assessment test is a slit lamp estimation of the depth of the peripheral anterior chamber of the eye and is used as a proxy measure for judging whether the anterior chamber angle is open.
Visual field	The area which can be seen when the eye is directed forward, including both central and peripheral vision.

1 Introduction

1.1 What is a guideline?

Our clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific clinical questions.

Clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Collaborating Centre for Acute Care (NCC-AC)
- The National Collaborating Centre for Acute Care establish a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations

- There is a consultation on the draft guideline.
- The final guideline is produced.

The National Collaborating Centre for Acute Care and NICE produce a number of versions of this guideline:

- the **full guideline** contains all the recommendations, plus details of the methods used and the underpinning evidence
- the **NICE guideline** presents the recommendations from the full version in a format suited to implementation by health professionals and NHS bodies
- the **quick reference guide** presents recommendations in a suitable format for health professionals
- information for the public (‘**understanding NICE guidance’**) is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from the NCC-AC website at www.rcseng.ac.uk/surgical_research_units/nccac/ or are available from NICE www.NICE.org.uk.

1.2 The need for this guideline

Chronic open-angle glaucoma tends to be asymptomatic and therefore many people will not notice any symptoms until severe visual damage has occurred. Once diagnosed, affected individuals require lifelong monitoring for disease control and detection of prossible progression of visual damage. It is estimated that in the UK about 2% of people older than 40 years have chronic open angle glaucoma, and this rises to almost 10% in people older than 75 years. There are around 480,000 people affected by chronic open angle glaucoma in England, who receive over a million glaucoma related outpatient visits in the hospital eye service annually. With changes in population demographics the number of people affected by glaucoma is expected to rise. Approximately 10% of UK blindness registrations are ascribed to glaucoma, and since with appropriate treatment blindness is largely avoidable, this figure suggests that there may be room for improvements both in case ascertainment and ongoing care following diagnosis.

A plethora of topical medications and combinations of medications are available for treatment of COAG. In addition there exist a number of laser and surgical procedures which may be used to reduce IOP and arrest or slow progression of vision loss. There are wide variations across the NHS in terms of management of COAG, a reflection of the uncertainties and sometimes conflicting reports in the scattered literature. Recent evidence indicates that treating elevated IOP prior to the onset of glaucoma reduces by half the risk of conversion from OHT to COAG. Whether such preventative treatment is cost effective in terms of long term avoidance of blindness has been unclear.

Service pressures and centrally imposed imperatives to bring down waiting times in the NHS by prioritisation of new referrals has in many areas displaced capacity away from chronic disease monitoring with consequent cancellations and long delays in follow up

appointments. Such distortions of clinical practice, where a new referral for someone who may or may not have a significant eye problem gains priority over a patient with a diagnosed and potentially blinding eye disease has resulted in service failures for individuals and cannot be accepted. Guidance on chronic disease monitoring, including monitoring intervals and service models, is therefore timely. Lord Darzi's quality initiative provides an opportune backdrop for a rebalancing of service priorities towards overall clinical need, inclusive of long term conditions such as chronic open angle glaucoma.

1.3 The National Collaborating Centre for Acute Care

This guideline was commissioned by NICE and developed by the National Collaborating Centre for Acute Care. The centre is one of seven national collaborating centres funded by NICE and comprises a partnership between a variety of academic, professional and patient-based organisations. As a multidisciplinary centre we draw upon the expertise of the healthcare professions and academics and ensure the involvement of patients in our work. Further information on the centre and our partner organisations can be found at our website (www.rcseng.ac.uk/surgical_research_units/nccac/).

1.4 Remit

The following remit was received by the NCC-AC from the Department of Health in January 2006 as part of NICE's 12th wave programme of work.

The Department of Health asked the Institute:

"To prepare a clinical guideline on the diagnosis and management of chronic open angle glaucoma and ocular hypertension (raised intraocular pressure). The guideline should include recommendations on the most appropriate service models where evidence of effectiveness is available."

1.5 What the guideline covers

This guideline covers adults (18 and older) with a diagnosis of chronic open angle glaucoma or ocular hypertension and those with chronic open angle glaucoma or ocular hypertension associated with pseudoexfoliation or pigment dispersion. In addition, the guideline will cover populations who have a higher prevalence of glaucoma and may have worse clinical outcomes including people with a family history of glaucoma, younger people (<50 years) and people who are of black African or black Caribbean descent. Options for pharmacological, surgical, laser and complimentary or alternative treatments are considered in terms of clinical effectiveness and cost effectiveness. Further details of the scope of the guideline can be found in Appendix A.

1.6 What the guideline does not cover

This guideline does not cover patients under the age of 18 years. In addition, the guideline does not cover patients with secondary glaucoma (for example neovascular or uveitic) except for those described above, those with, or at risk of, primary or secondary angle closure glaucoma and adults with primary congenital, infantile or childhood glaucoma.

1.7 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this

guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Collaborating Centre for Acute Care (NCC-AC) and thus supported the development of this guideline. The GDG was convened by the NCC-AC and chaired by Mr. John Sparrow in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every 6-8 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B).

Members are either required to withdraw completely or for part of the discussion if their declared interest makes it appropriate, however this was not deemed necessary for any group members on this guideline.

Staff from the NCC-AC provided methodological support and guidance for the development process. They undertook systematic searches, retrieval and appraisal of the evidence and drafted the guideline. The glossary to the guideline contains definitions of terms used by staff and the GDG.

1.8 Assumptions made

1.8.1 Ocular Hypertension (OHT)

The GDG agreed the following assumptions regarding the definition of ocular hypertension:

- open drainage angles on gonioscopy
- an untreated IOP above 21mmHg, confirmed on a separate occasion
- absence of typical optic disc damage (e.g. glaucomatous cupping and loss of neuroretinal rim)
- absence of detectable nerve fibre layer defect
- absence of visual field defect
- included variants:
    - OHT with pigment dispersion
    - OHT with pseudo-exfoliation
- absence of other secondary cause for IOP elevation (e.g. trauma, uveitis)

1.8.2 Chronic open-angle glaucoma suspect (COAG Suspect)

The GDG agreed the following assumptions regarding the definition of suspected COAG:

- open drainage angles on gonioscopy
- 1 or more of:
    - possible optic disc damage with suspicion of glaucomatous cupping
    - possible optic disc damage with suspicion of loss of neuroretinal rim
    - possible nerve fibre damage with suspicion of nerve fibre layer defect

    - normal or equivocal visual field
- included variants
    - COAG Suspect with pigment dispersion
    - COAG Suspect with pseudo-exfoliation
    - COAG Suspect with repeatedly elevated untreated IOP (above 21mmHg) identified as Primary Open Angle (POAG) Suspect
    - COAG Suspect with repeatedly normal untreated IOP (21mmHg or less) identified as Normal Tension Glaucoma (NTG) Suspect
- absence of other secondary cause for IOP elevation if present (e.g. trauma, uveitis)

1.8.3 Chronic open-angle glaucoma (COAG)

The GDG agreed that the following assumptions would normally apply regarding the definition of COAG:

- open drainage angles on gonioscopy
- visual field damage compatible with nerve fibre loss
- 1 or more of
    - optic disc damage with glaucomatous cupping
    - optic disc damage with loss of neuroretinal rim
    - nerve fibre damage with nerve fibre layer defect
- included variants
    - COAG with repeatedly elevated untreated or treated IOP (above 21mmHg) identified as Primary Open Angle (POAG)
    - COAG with repeatedly normal untreated IOP (21mmHg or less) identified as Normal Tension Glaucoma (NTG)
    - COAG with pigment dispersion
    - COAG with pseudo-exfoliation
- absence of other secondary cause for IOP elevation (e.g. trauma, uveitis)

1.8.4 Glaucomatous changes to the optic nerve

Glaucomatous changes to the optic nerve may include:

- **Features strongly suggestive of optic nerve damage:**
    - Localised or generalised thinning of the neuro-retinal rim
    - Notches in the neuro-retinal rim
    - Optic nerve head haemorrhages without apparent secondary cause (e.g. diabetes)
    - Evidence of nerve fibre layer tissue loss (not always visible)
    - Vertical cup to disc ratio >0.85 (less in the presence of a small sized optic disc)

- **Features suggestive of possible optic nerve damage:**
    - Cup-to-disc ratio Asymmetry >0.2
    - Cup-to-disc > 0.6
    - Nasal cupping
    - Peri-papillary atrophy
    - Neuro-retinal rim thinning with possible disturbance of the 'Inferior-Superior – Nasal – Temporal' pattern (ISNT rule)
    - Deep cup with prominent lamina cribrosa (soft sign)
    - Bayoneting of the optic nerve head vessels (soft sign)

1.8.5 Glaucomatous changes of the visual field

Glaucomatous changes of the visual field which reflect nerve fibre bundle loss include one or more of the following in the absence of other ocular or neurological disease affecting the visual field:

- **Unequivocal:**
  - Arcuate Scotomas in the 30 degree central field
  - Nasal Steps
  - Altitudinal Scotomas
  - Focal Defects e.g. paracentral scotomas
  - Absolute defects

- **Suspicious:**
  - Generalised defect
  - Relative defect
  - Enlarged blind spot

1.8.6 Stages of glaucomatous visual field loss

Glaucomatous visual field loss is defined by Hodapp Classification[63] as below:

- **Early:**
  - Mean Defect > -6dB
  - 5% Probability level defect for < 18 of tested points (tested field locations)
  - 1% Probability level defect for < 10 of tested points
- **Moderate:**
  - Mean Defect -6dB > -12dB
  - 5% Probability level defect for < 37 of tested points
  - 1% Probability level defect for < 20 of tested points
  - Sensitivity <15dB in central 5 degrees on only one hemifield
- **Advanced:**
  - Mean Defect -12dB > -20
  - 5% Probability level defect for > 37 of tested points
  - 1% Probability level defect for > 20 of tested points
  - Sensitivity <15dB in central degrees on both hemifield

1.8.7 Target IOP

The setting of a target IOP is a clinical decision and it may be necessary to change the target through the course of the disease. General principles will include the notion of a reduction of 25%-30% from the untreated pressure for cases of COAG and an IOP below 21mmHg for cases of ocular hypertension. Consideration should be given to the perceived threat to sighted lifetime, status of fellow eye, adherence to treatment, the likelihood of surgical success and patient preferences regarding treatment options.

1.8.8 Progression

Progression may be considered to have occurred when there is reliable evidence that visual field damage and / or glaucomatous optic neuropathy has worsened significantly. Since COAG is defined as a 'progressive optic neuropathy' a key concept in its management is the rate of progression. In spite of treatment most glaucoma will continue to progress. The aim of lowering IOP is to slow the rate of progression and the main treatment challenge is to avoid loss of sight and disability within a patient's expected lifetime.

1.8.9 Pseudoexfoliation and pigment dispersion

Patients with the variants pseudoexfoliation and pigment dispersion would be expected to follow a slightly different natural history and in accordance with such variations informed clinical judgment should be used to maintain optimal care.

1.8.10 Severe Visual Impairment

There is no legal definition of sight impairment. The guidelines are that a person can be certified as sight impaired if they are 'substantially and permanently handicapped by defective vision caused by congenital defect or illness or injury'. The National Assistance Act 1948 states that a person can be certified as severely sight impaired if they are "so blind as to be as to be unable to perform any work for which eye sight is essential" (National Assistance Act Section 64(1)).[128]

For the purposes of the economic analysis the definition of severe visual impairment was considered by the GDG to be:

- Mean Defect <-20 dB

It was further assumed that both eyes were similar.

1.8.11 Risk factors for patients with COAG

Evidence of benefit from differentially treating patients with particular risk factors was not found. The rate of progression to vision loss may however vary between certain patient groups using standard treatment regimes and those perceived clinically to be at higher risk may need a lower target IOP.

2 Methodology

2.1 Guideline methodology

This guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in 'The guidelines manual' updated in April 2007[106]. The scope was developed according to the version of the manual published in April 2006.

2.2 Developing the clinical questions

Clinical questions were developed to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). They were drafted by the review team and refined and validated by the guideline development group (GDG). The questions were based on the scope (Appendix A). Further information on the outcome measures examined follows this section.

2.2.1 Questions on diagnosis

Questions on diagnosis related to tools that can be used to measure particular outcomes in patients with ocular hypertension or chronic open angle glaucoma. In summary:

- Is non-contact tonometry suitable as an alternative to Goldmann Applanation Tonometry for measuring intraocular pressure?
- Are disposable prisms suitable as an alternative to Goldmann prisms when using Goldmann Applanation Tonometry?
- Are any other imaging tests suitable as alternatives to biomicroscopic slit lamp examination with stereophotography?
- Are any other visual field tests suitable as alternatives to 24-2 SITA Humphrey perimetry for diagnosis of glaucomatous visual field damage?
- Are other methods of assessing anterior chamber angles suitable as alternatives to gonioscopy?

2.2.2 Questions on monitoring

The questions on monitoring related to two areas:

- Which diagnostic tools could be used at monitoring visits? (The same data was used for these questions as the data used for diagnosis).

- At what intervals should patients be offered monitoring?

2.2.3 Questions on effectiveness of IOP-lowering interventions

These questions aimed to determine which are the most effective pharmacological, laser and surgical treatments for patients with ocular hypertension or chronic open angle glaucoma. They included:

- Which are the most clinically and cost effective and least harmful pharmacological treatments from the following classes of drugs?
    - topical beta-blockers
    - topical prostaglandin analogues
    - topical sympathomimetics
    - topical and systemic carbonic anhydrase inhibitors
    - topical miotics
- Which is the most effective and least harmful concentration of timolol between 0.5% and 0.25%?
- Are combinations of topical medications (pre-prepared in one bottle or as separate bottles) more effective and less harmful than single medications?
- Which is the most effective and least harmful laser treatment between argon laser trabeculoplasty and selective laser trabeculoplasty?
- Which is the most effective and least harmful surgical treatment between trabeculectomy, deep sclerectomy and viscocanalostomy?
- Does pharmacological augmentation to surgery with fluorouracil (5-FU) or mitomycin C (MMC) improve outcomes?
- Which is the most clinically and cost effective and least harmful treatment between medications, laser and surgery?

2.2.4 Questions on complementary and alternative medicines

- Is there evidence that complementary or alternative treatments can be used for treating patients with ocular hypertension or chronic open angle glaucoma?
- Is there evidence that neuroprotective agents are effective alone or in addition to IOP lowering treatments?

2.2.5 Question on risk factors in patients with ocular hypertension

- What evidence is there that risk factors affect the number of patients converting from ocular hypertension to COAG?

2.2.6 Questions on service provision

- Can professionals other than consultant ophthalmologists diagnose, monitor and/or treat ocular hypertension and/or COAG?

2.2.7 Questions on provision of information for patients

- What are the most effective ways of providing information to patients?

2.3 Outcomes

We looked for the following primary outcomes:

- COAG progression defined as visual field defect progression and/or increased optic nerve damage.

- Conversion to COAG in ocular hypertensive patients.

Since all treatments aim to reduce the risk of progression by lowering IOP we looked for a link between IOP reduction and protection against progression. Two scenarios were considered: firstly a link between IOP reduction and reduced progression of established COAG, and secondly a link between IOP reduction and reduced conversion from OHT to COAG. We included only studies reporting the relative risk of each mmHg reduction in IOP for progression or conversion, as judged by deterioration in visual field or optic nerve appearance or both.

Two studies reported the relative risk of progression in patients with COAG for each unit reduction of IOP[86,87]. Using the more recent data with longer follow up[87] the percentage reduction in the probability of progressing was 8% per mmHg reduction of IOP in COAG.

A single study reported the relative risk of developing COAG from OHT for each unit reduction of IOP[50]. The percentage reduction in the probability of converting from OHT to COAG was 10% per mmHg reduction of IOP.

Having established credible links between IOP reduction and disease progression the GDG accepted a reduction in IOP as a valid surrogate outcome measure.

- We extracted data for a change in IOP from baseline, expressed as an absolute value with standard deviation, and the number of patients reaching an unacceptable or acceptable target IOP. Studies of pharmacological treatments tended to report the number of patients reaching an acceptable target IOP.

- Outcome data for laser and surgical treatments was extracted from systematic reviews and primary studies. These focused on the number of patients with an unacceptable IOP as a measure of treatment failure. The cut-off points used in the studies where significantly variable.

We looked for the following secondary outcomes:

- Number of patients experiencing adverse events of pharmacological treatments and longer term postoperative complications for surgical and laser treatments.
- Quality of life and patient outcome data where reported.

The GDG decided that to assess effectiveness of treatments a minimum of 6 months follow up would be required since in practice they would not consider a treatment a success unless it had been shown to be effective over at least this period.

2.4 Literature search

2.4.1 Clinical literature search

The aim of the literature search was to find 'evidence within the published literature,' to answer the clinical questions identified. We searched clinical databases using filters (or hedges), using relevant medical subject headings and free-text terms. Non-English language studies and abstracts were not reviewed.

Each database was searched up to 04 August 2008 (Week 32). We performed one initial search and then two update searches nearer the end of guideline development period. No papers after this date were considered.

The search strategies can be found in Appendix C.

The following databases were searched:

- The Cochrane Library up to Issue 3 2008
- Medline 1950-2008 (OVID)
- Embase 1980-2008 (OVID)
- Cinahl 1982-2008 (Dialog Datastar and later NLH Search 2.0)
- PsycINFO 1800s-2008 (NLH Search 2.0)
- AMED 1985-2008 (NLH Search 2.0)
- Health economic and evaluations database (HEED) up to August 2008

There was no systematic attempt to search for grey literature or unpublished literature although all stakeholder references were followed up. We searched for guidelines and reports via relevant websites including those listed below.

- American Academy of Ophthalmology (http://www.aao.org/)
- Constituent websites of the Guidelines International Network (http://www.g-i-n.net)

- International Council of Ophthalmology Guidelines (http://www.icoph.org/guide/guideintro.html)
- International Glaucoma Association (http://www.glaucoma-association.com)
- National Guideline Clearing House (http://www.guideline.gov/)
- National Institute for Health and Clinical Excellence (NICE) (http://www.nice.org.uk)
- National Institutes of Health Consensus Development Program (http://consensus.nih.gov/)
- National Library for Health (http://www.library.nhs.uk/)
- National Library for Health Eyes and Vision Specialist Library (http://www.library.nhs.uk/eyes/)
- NHS Connecting for Health Do Once and Share Glaucoma project (http://www.doasglaucoma.org/)
- Royal College of Ophthalmologists (http://www.rcophth.ac.uk/)

2.4.2 Economic literature search

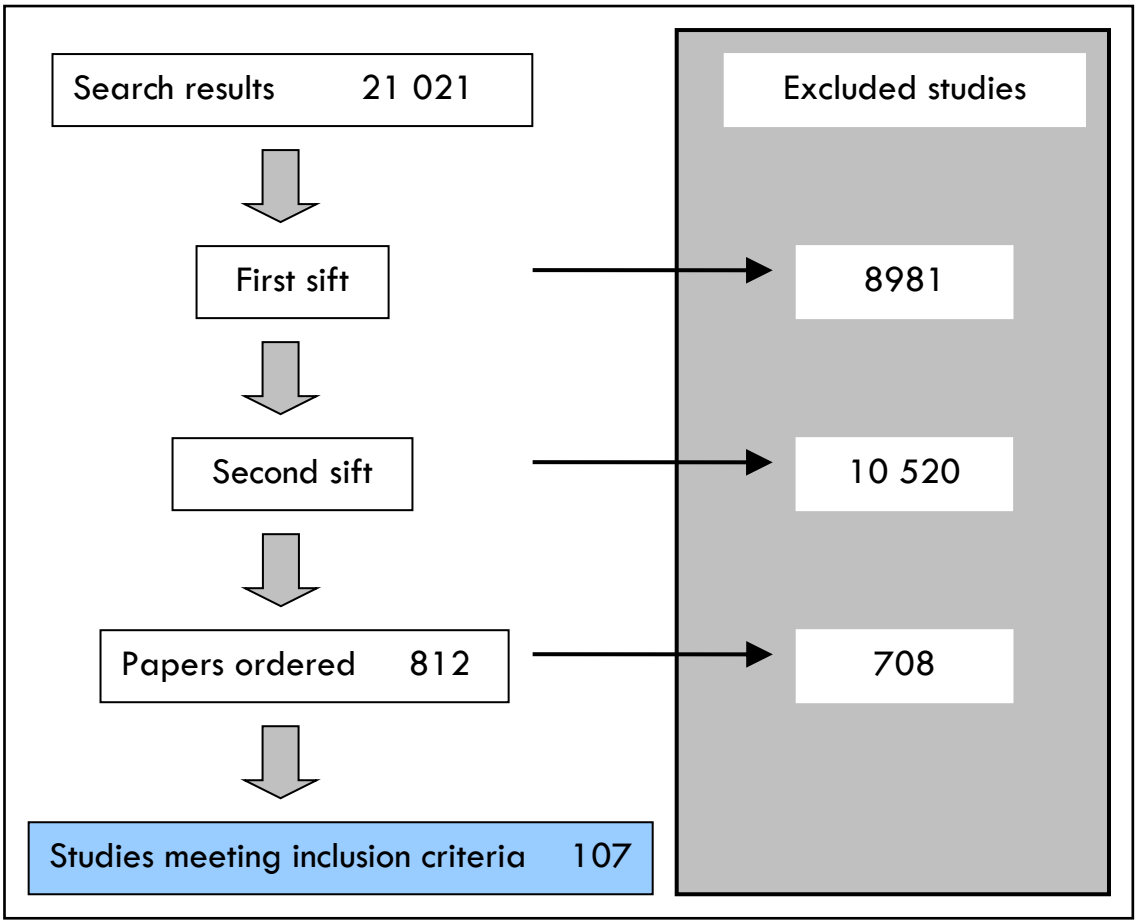
We obtained published economic evidence from a systematic search of the following databases:

- The Cochrane Library up to Issue 3 2008
- Medline 1950-2008 (OVID)
- Embase 1980-2008 (OVID)
- Health economic and evaluations database (HEED) up to August 2008

The information specialists used the same search strategy as for the clinical questions, using an economics filter in the place of a systematic review or randomised controlled trial filter. Each database was searched from its start date up to August 2008. Papers identified after this date were not considered. Search strategies can be found in Appendix C.

Each search strategy was designed to find any applied study estimating the cost or cost-effectiveness of an included intervention. A health economist reviewed the abstracts. Relevant references in the bibliographies of reviewed papers were also identified and reviewed.

The results of the searches with the final number of studies meeting the inclusion criteria for the clinical questions are shown below.



2.5 Hierarchy of clinical evidence

2.5.1 Diagnosis and Monitoring

To grade individual studies according to diagnostic accuracy we used the hierarchy of evidence recommended in the Guidelines Manual April 2007 which was developed by NICE using 'The Oxford Centre for Evidence-based Medicine Levels of Evidence' (2001) and the Centre for reviews and Dissemination 'Report Number 4 (2001). See Table 2-1 below.

We considered only one study design. We included studies applying both tests to a consecutive group of patients to answer clinical questions on diagnostic accuracy.

Table 2-1: - Levels of evidence for studies of accuracy of diagnostic tests (reproduced by kind permission from the NICE guidelines manual (April 2007))

Level of evidence	*Type of evidence*
1a	Systematic review with homogeneity (a) of level-1 studies (b)
1b	Level-1 studies (b)
II	Level-2 studies (c) Systematic reviews of level-2 studies

Level of evidence	Type of evidence
III	Level-3 studies (d) Systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

(a) Homogeneity indicates there are none or minor variations in the directions and degrees of results between individual studies included in the systematic review
(b) Level-1 studies:
- Use a blind comparison of the test with a reference standard (gold standard)
- Are conducted in a sample of patients that reflects the population to whom the test would apply

(c) Level-2 studies have only **one** of the following:
- Narrow population (sample does not reflect the population to whom the test would apply)
- A poor reference standard (where tests are not independent)
- The comparison between the test and reference standard is not masked
- A case-control study design

(d) Level-3 studies have **two** or **three** of the above features

2.5.2 Treatment

To grade individual treatment studies we used the system developed by the Scottish Intercollegiate Guidelines Network (SIGN) recommended in the Guidelines Manual April 2007, shown in Table 2-2 below.

For each clinical question the highest level of evidence was sought. Where an appropriate systematic review, meta-analysis or randomised controlled trial was identified, we did not search for studies of a weaker design.

Table 2-2: Levels of evidence for intervention studies
(reproduced with permission of the Scottish Intercollegiate Guidelines Network)

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies (For example, case reports, case series)
4	Expert opinion, formal consensus

2.5.3 Service provision

We selected the kappa weighted statistic or intraclass correlation coefficient as the outcome measure of agreement between healthcare professionals for diagnosis, monitoring and treatment decisions. Most studies (RCTs or observational) used an agreement scale developed by Landis and Koch, 1977[81] (see Table 2-3 below) to compare the reported statistics. The GDG felt that only agreement levels of moderate or greater should be considered as adequate evidence of clinical agreement because lower levels of agreement would not provide sufficient consistency of quality or continuity of care for a service delivered by different healthcare provider groups.

Table 2-3: Kappa agreement scale developed by Landis and Koch, 1977[81]

Kappa value	*Agreement*
-1.00 – 0	poor
0.01 – 0.20	slight
0.21 - 0.40	fair
0.41 - 0.60	moderate
0.61 - 0.80	substantial
0.81 – 0.99	almost perfect
+ 1.00	perfect

2.5.4 GRADE

Outcome evidence was written up using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software developed by the working group, GRADEpro, was used to assess pooled outcome data using individual study quality assessments and results from meta-analysis.

Each outcome was examined for the following quality elements listed in Table 2-4 and each graded using the quality levels listed in Table 2-5. Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems and then an overall quality of evidence for each outcome was applied by selecting from the options listed in Table 2-6.

Results were presented as two separate tables. The clinical study characteristics table includes details of the quality assessment and the clinical summary outcome table includes pooled outcome data and an absolute measure of intervention effect calculated in the GRADEpro software using the control event rate and the risk ratio values from the meta-analysis.

The GRADE toolbox is currently designed only for randomized controlled trials and observational studies but we adapted the quality assessment elements and outcome presentation for diagnostic accuracy studies and service provision.

Table 2-4: Descriptions of quality elements in GRADE

Quality element	*Description*
Limitations	For each study reporting the outcome of interest the limitations are considered in terms of bias introduced by randomisation method, allocation concealment, masking of outcome assessment and loss to follow-up. The outcome evidence may be downgraded if the studies are

	of sufficiently poor quality.
Inconsistency	The significance of statistical heterogeneity is considered between the pooled studies using the forest plots. If subgroup analysis does not explain significant heterogeneity then the outcome evidence may be downgraded.
Indirectness	There may be serious indirectness if the study population does not completely represent the guideline population.
Imprecision	The magnitude of the confidence intervals around the point estimate is considered as well as the number of patients and events. Even if the sample size is sufficiently powered, wide confidence intervals falling within a clinically insignificant range may cause the estimate of effect to become uncertain and the outcome data downgraded.

Table 2-5: Levels for quality elements in GRADE

Level	*Description*
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 2-6: Overall quality of outcome evidence in GRADE

Level	*Description*
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

2.5.5 NICE Economic Profile

Since GRADE was not originally designed for economic evidence, the NICE economic profile has been used to present cost and cost-effectiveness estimates from published studies or analyses conducted for the guideline. As for the clinical evidence, the economic evidence has separate tables for the quality assessment and for the summary of results. The quality assessment is based on two criteria – limitations and applicability (Table 2-7) and each criterion is graded using the levels in Table 2-8 and Table 2-9.

Table 2-7: Description of quality elements for economic evidence in NICE economic profile

Quality element	*Description*
Limitations	This criterion relates to the methodological quality of cost, cost-effectiveness or net benefit estimates.
Applicability	This criterion relates to the relevance of the study to the specific guideline question and NICE Reference Case.

Table 2-8: Levels for limitations for economic evidence in NICE economic profile

Level	*Description*
Minor limitations	The study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost-effectiveness.
Serious limitations	The study fails to meet one or more quality criteria, and this could change the conclusion about cost-effectiveness
Very serious limitations	The study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost-effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.

Table 2-9: Levels for applicability for economic evidence in NICE economic profile

Level	*Description*
Directly applicable	The applicability criteria are met, or one or more criteria are not met but this is not likely to change the cost-effectiveness conclusions.
Partially applicable	One or more of the applicability criteria are not met, and this might possibly change the cost-effectiveness conclusions.
Not applicable	One or more of the applicability criteria are not met, and this is likely to change the cost-effectiveness conclusions.

An overall score of the evidence is not given as it is not clear how the quality elements could be summarised into a single quality rating.

A summary of results is presented for each study including:

- incremental cost,
- incremental effectiveness,
- incremental cost-effectiveness ratio
- uncertainty.

2.6 Literature reviewing process

2.6.1 Clinical literature reviewing process

References identified by the systematic literature search were screened for appropriateness by title and abstract by an information scientist and systematic reviewer. Studies were selected that reported one or more of the outcomes listed in section 2.3. Selected studies were ordered and assessed in full by the NCC-AC team using agreed inclusion/exclusion criteria specific to the guideline topic, and using NICE

methodology quality assessment checklists appropriate to the study design[106]. Further references suggested by the guideline development group were assessed in the same way. Not enough data was available from RCTs for serious adverse events related to pharmacological interventions. Consequently, an additional literature review of observational data was performed to supplement the RCT evidence.

2.6.2 Economic literature reviewing process

Economic studies identified in the systematic search were excluded from the review if:

- The study did not contain any original data on cost or cost-effectiveness (that is, it was a review or a clinical paper)
- The study population did not comply with the inclusion criteria as established in the clinical effectiveness review methods
- The analysis was not incremental and was not described adequately to allow incremental analysis (so studies reporting only average cost-effectiveness ratios were excluded unless they provided data to allow the calculation of incremental cost-effectiveness ratios)
- The study was a non-UK cost-analysis
- The study was a letter or written in a foreign language
- The estimates of treatment effectiveness in the economic study were obtained from a follow-up less than six months (see section 2.3).

Included papers were reviewed by a health economist. In the evidence tables, costs are reported as in the paper. However, where costs were in a currency other than pounds sterling, the results were converted into pounds sterling using the appropriate purchasing power parity for the study year.

We have included studies from all over the world in our review, however, we use overseas studies with caution since resource use and especially unit costs vary considerably. Particular caution is applied to studies with predominantly private health insurance (For example, USA or Switzerland) where unit costs may be much higher than in the UK and to developing countries where costs may be much lower.

Each study was categorised as one of the following: cost analysis, cost-effectiveness analysis, cost–utility analysis (that is, cost–effectiveness analysis with effectiveness measured in terms of QALYs), or cost consequences analysis. We did not find any 'cost benefit analyses' (studies that put a monetary value on health gain).

Models are analogous to systematic reviews because they pool evidence from a number of different studies and therefore if well-conducted they should out-rank studies based on a single RCT. Statistical significance is not usually applicable to models and uncertainty is explored using sensitivity analysis instead. Hence the results reported in economic GRADE tables, evidence tables and write-up may not necessarily imply statistical significance.

2.6.3 Cost-effectiveness modelling

The details of the economic model are described in Appendix F.

2.7 Methods of combining studies

Where possible, meta-analyses were conducted to combine the results of studies for each clinical question using Cochrane Review Manager software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: number of patients with visual field progression, number of patients with an acceptable or unacceptable IOP or numbers of adverse events, and the continuous outcome for change in IOP from baseline was analysed using an inverse variance method for pooling weighted mean differences. When combining data for number of patients with visual field progression we acknowledge that there may be limitations as it is difficult to standardise this outcome when each study has defined and measured visual field progression differently. Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.05$ and an I-squared of $\geq 25\%$ to indicate significant heterogeneity.

Where significant heterogeneity was present we explored a number of possible predefined differences including COAG population and study design (open label or masked) by doing subgroup analyses. Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

For the outcome change in IOP from baseline some studies did not report standard deviations or provided only baseline and end point data. The methods outlined in section 7.7.3 of the Cochrane Handbook (February 2008) 'Data extraction for continuous outcomes' were applied if p values and confidence intervals had been reported. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (February 2008) 'Missing standard deviations' were applied. Detailed data provided for IOP at baseline, end point and change from another study in the comparison were used as inputs for the calculations.

2.8 Development of the recommendations

Over the course of the guideline development process, the GDG was presented with the following:

- Evidence tables of the clinical and economic evidence reviewed. All evidence tables are in appendix D
- Forest plots of meta-analyses. (appendix E)
- A description of the methods and results of the cost-effectiveness analysis (appendix F)

Recommendations were drafted on the basis of this evidence wherever it was available.

When clinical and economic evidence was poor or absent, the GDG proposed recommendations based on their expert opinion.

The GDG added supporting recommendations whenever it was necessary in order to improve clinical practice. The supporting recommendations were not derived from clinical questions and they were based on GDG expert opinion.

The development of the recommendations required several steps:

- A first draft of all recommendations was circulated to the GDG using an internet based system. NCC-AC staff facilitated a structured discussion considering each recommendation so that GDG members could evaluate their own feedback in relation to other GDG members.
- NCC-AC staff modified the recommendations as a result of the discussion and in the light of NICE guidance on writing recommendations.
- The GDG was asked to independently feed back their comments on these modified recommendations to the NCC. This procedure allowed the NCC to verify the level of agreement between the GDG members.
- All GDG feedback was collated and circulated again to the GDG. The recommendations were then finalised.
- During the writing up phase of the guideline, the GDG could further refine each recommendation working in subgroups on each chapter.
- NCC-AC staff verified the consistency of all recommendations across the guideline.

The GDG then developed a care pathway algorithm according to the recommendations.

2.9 Research Recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities,
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility

2.10 Prioritisation of recommendations for implementation

To assist users of the guideline in deciding the order in which to implement the recommendations, the GDG identified ten key priorities for implementation. The decision was made after discussion and voting by the GDG. They selected recommendations that would:

- have a high impact on outcomes that are important to patients
- have a high impact on reducing variation in care and outcomes
- lead to a more efficient use of NHS resources
- promote patient choice
- promote equalities.

In doing this the GDG also considered which recommendations were particularly likely to benefit from implementation support. They considered whether a recommendation:

- Requires changes in service delivery
- Requires retraining of professionals or the development of new skills and competencies
- Affects and needs to be implemented across various agencies or settings (complex interactions)
- May be viewed as potentially contentious, or difficult to implement for other reasons

2.11 Validation of the guideline

The first draft of this guideline was posted on the NICE website for consultation between 29th September – 24th November 2008 and registered stakeholders were invited to comment. The GDG responded to comments and an amended version of the guideline was produced.

2.12 Related NICE guidance

NICE is developing the following guidance (details available from www.nice.org.uk):

- Canaloplasty for primary open-angle glaucoma[107]

2.13 Updating the guideline

This guideline will be updated when appropriate. The decision to update will balance the need to reflect changes in the evidence against the need for stability, as frequent changes to the recommendations would make implementation difficult. We check for new evidence 2 and 4 years after publication, to decide whether all or part of the guideline should be updated. In exceptional circumstances, if important new evidence is published at other times, we may conduct a more rapid update of some recommendations. Any update will follow the methodology outlined in the NICE guidelines manual[106].

3 Summary of Recommendations

Below are the recommendations that the GDG selected as the key priorities for implementation followed by the complete list of recommendations and research recommendations.

3.1 Key priorities for implementations

The GDG identified ten key priorities for implementation. The decision was made after discussion and voting by the GDG. They selected recommendations that would:

- Have a high impact on outcomes that are important to patients (**A**)
- Have a high impact on reducing variation in care and outcomes (**B**)
- Lead to a more efficient use of NHS resources (**C**)
- Promote patient choice (**D**)
- Promote equalities.(**E**)

In doing this the GDG also considered which recommendations were particularly likely to benefit from implementation support. They considered whether a recommendation:

- Requires changes in service delivery (**W**)
- Requires retraining of professionals or the development of new skills and competencies (**X**)
- Affects and needs to be implemented across various agencies or settings (complex interactions) (**Y**)
- May be viewed as potentially contentious, or difficult to implement for other reasons (**Z**)

For each key recommendation listed below, the selection criteria and implementation support points are indicated by the use of the letters shown in brackets above.

➢ At diagnosis offer all people who have COAG, who are suspected of having COAG or who have OHT all of the following tests:

- intraocular pressure measurement using Goldmann applanation tonometry (slit lamp mounted)
- central corneal thickness (CCT) measurement
- peripheral anterior chamber configuration and depth assessments using gonioscopy
- visual field measurement using standard automated perimetry (central thresholding test)
- optic nerve assessment, with dilatation, using stereoscopic slit lamp biomicroscopy with fundus examination.

(Selection criteria: A, B, E, F. Implementation support: W, X,Y,Z)

➢ Ensure that all of the following are made available at each clinical episode to all healthcare professionals involved in a person's care:

- records of all previous tests and images relevant to COAG and OHT assessment
- records of past medical history which could affect drug choice
- current systemic and topical medication
- glaucoma medication record
- drug allergies and intolerances..

(Selection criteria: A, B, E, F. Implementation support: W, X, Y ,Z)

➢ Monitor at regular intervals people with OHT or suspected COAG recommended to receive medication, according to their risk of conversion to COAG as illustrated by the following table:

Table: Monitoring intervals for people with OHT or suspected COAG who are recommended to receive medication

Clinical assessment			**Monitoring intervals (months)**	
IOP at target [a]	**Risk of conversion to COAG [b]**	**Outcome [c]**	**IOP alone [d]**	**IOP, optic nerve head and VF**
Yes	Low	No change in treatment plan	Not applicable	12 to 24
Yes	High	No change in treatment plan	Not applicable	6 to 12
No	Low	Review target IOP OR Change treatment plan	1 to 4	6 to 12
No	High	Review target IOP OR Change treatment plan	1 to 4	4 to 6

[a] *Person is treated and IOP is at or below target. If IOP cannot be adequately controlled medically, refer to consultant ophthalmologist.*
[b] *To be clinically judged in terms of relevant risk indicators: age, IOP, CCT, appearance and size of optic nerve head.*
[c] *For change of treatment plan refer to treatment recommendations.*
[d] *For people started on treatment for the first time check IOP 1 to 4 months after start of medication.*

(Selection criteria: A, B, E, F. Implementation support: W, X, Y, Z)

➢ Monitor at regular intervals people with COAG according to their risk of progression to sight loss as illustrated in the following table:

Table: Monitoring intervals for people with COAG

Clinical assessment			Monitoring intervals (months)	
IOP at target [a]	**Progression [b]**	**Outcome [c]**	**IOP alone [d]**	**IOP, optic nerve head and visual field**
Yes	No [e]	No change in treatment plan	Not applicable	6 to 12
Yes	Yes	Review target IOP AND Change treatment plan	1 to 4	2 to 6
Yes	Uncertain	No change in treatment plan	Not applicable	2 to 6
No	No [e]	Review target IOP OR Change treatment plan	1 to 4	6 to 12
No	Yes / uncertain	Change treatment plan	1 to 2	2 to 6

[a] *IOP at or below target.*
For people started on treatment for the first time check IOP in 1 to 4 months after start of medication.
[b] *Progression = increased optic nerve damage and/or visual field change confirmed by repeated test where clinically appropriate.*
[c] *For change of treatment plan refer to treatment recommendations.*
[d] *For people started on treatment for the first time check IOP 1 to 4 months after start of medication.*
[e] *No = not detected or not assessed*

(Selection criteria: A, B, E, F. Implementation support: W, X, Y, Z)

➢ Offer people with OHT or suspected COAG with high IOP treatment based on estimated risk of conversion to COAG using IOP, CCT and age as illustrated in the following table:

Table: Treatment of people with OHT or suspected COAG

CCT	More than 590 micrometres	555 to 590 micrometres	Less than 555 micrometres	Any

Untreated IOP	>21-25 mmHg	>25-32 mmHg	>21-25 mmHg	>25-32 mmHg	>21-25 mmHg	>25-32 mmHg	>32 mmHg
Age threshold [a]	**None**	**None**	**None**	**up to 60 years**	**up to 65 years**	**up to 80 years**	**None**
Treatment	No Treatment	No Treatment	No Treatment	BB [b]	PGA [c]	PGA [c]	PGA [c]

[a] *Treatment should not be routinely offered to people over the age threshold unless there are likely to be benefits from the treatment over an appropriate time scale. Once a person being treated for OHT reaches the age threshold for stopping treatment but has not developed COAG, healthcare professionals should discuss the option of stopping treatment.*

[b] *If beta-blockers (BB) are contraindicated offer a prostaglandin analogue (PGA)*

[c] *PGA, prostaglandin analogue*(Selection criteria: A, B, C, E, F. Implementation support: W, X, Y, Z)

➢ Offer people newly diagnosed with early or moderate COAG, and at risk of significant visual loss in their lifetime, treatment with a prostaglandin analogue.

(Selection criteria: A, B, C, E, Implementation support: NONE)

➢ Offer surgery with pharmacological augmentation (MMC or 5FU)* as indicated to people with COAG who are at risk of progressing to sight loss despite treatment. Information should be provided on the risks and benefits associated with surgery.

**MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*

(Selection criteria: A, B, C, E, F Implementation support: W, Z)

➢ Refer people with suspected optic nerve damage or suspected visual field defect to a consultant ophthalmologist for consideration of a definitive diagnosis of COAG and formulation of a management plan.

(Selection criteria: A, B, E, F. Implementation support: Z)

➢ People with diagnoses of OHT, suspected COAG and COAG should be monitored and treated by a trained healthcare professional who has all of the following:

- a specialist qualification (when not working under the supervision of a consultant ophthalmologist)
- relevant experience
- ability to detect a change in clinical status.

(Selection criteria: A, B, D, E, F. Implementation support: W, X, Y, Z)

➢ Offer people the opportunity to discuss their diagnosis, prognosis and treatment; and provide them with relevant information in an accessible format at initial and subsequent visits. This may include information on the following:

- their specific condition (OHT, suspected COAG and COAG), its life-long implications and their prognosis for retention of sight
- that once lost, sight cannot be recovered
- that glaucoma can run in families and that family members may wish to be tested for the disease
- that COAG in the early stages and OHT and suspected COAG are symptomless
- that most people treated for COAG will not lose their sight
- the importance of the person's role in their own treatment – for example, the ongoing regular application of eye drops to preserve sight
- the different types of treatment options, including mode of action, frequency and severity of side effects, and risks and benefits of treatment, so that people are able to be active in the decision making process
- how to apply eye drops, including technique (punctal occulsion and devices) and hygiene (storage)
- the need for regular monitoring as specified by the healthcare professional
- methods of investigations during assessment
- the length of time and the possible need for assistance to attend each appointment
- support groups
- compliance aids (such as dispensers) available from their GP or community pharmacist
- Letter of Vision Impairment (LVI), Referral of Vision Impaired Patient (RVI) and Certificate of Visual Impairment (CVI) registration
- Driver and Vehicle Licensing Agency (DVLA) regulations.

(Selection criteria: B, D, E,. Implementation support: W, X, Z)

3.2 Complete list of recommendations

3.2.1 Recommendations on diagnosis of patients with OHT, COAG or suspected COAG

➢ At diagnosis offer all people who have COAG, who are suspected of having COAG or who have OHT all of the following tests:

- intraocular pressure measurement using Goldmann applanation tonometry (slit lamp mounted)
- central corneal thickness (CCT) measurement
- peripheral anterior chamber configuration and depth assessments using gonioscopy
- visual field measurement using standard automated perimetry (central thresholding test)
- optic nerve assessment, with dilatation, using stereoscopic slit lamp biomicroscopy with fundus examination.

➢ Adopt professional /Department of Health guidance to reduce the risk of transmitting infective agents via contact tonometry or gonioscopy.[34,97,127,129].

➢ Use Van Herick's peripheral anterior chamber depth assessment test as an alternative to gonioscopy if clinical circumstances rule out gonioscopy (for example, when people with physical or learning disabilities are unable to participate in the examination).

➢ Obtain an optic nerve head image at diagnosis for baseline documentation.

➢ Ensure that all of the following are made available at each clinical episode to all healthcare professionals involved in a person's care:

- records of all previous tests and images relevant to COAG and OHT assessment
- records of past medical history which could affect drug choice
- current systemic and topical medication
- glaucoma medication record
- drug allergies and intolerances.

➢ Use alternative methods of assessment if clinical circumstances rule out the use of standard methods of assessment (for example, when people with physical or learning disabilities are unable to participate in the examination..

➢ Ensure that all machines and measurement instruments are calibrated regularly according to the manufacturer's instructions.

3.2.2 Recommendations on monitoring of patients with OHT, COAG or suspected COAG

➢ Offer Goldmann applanation tonometry (slit lamp mounted) to all people with COAG, who are suspected of having COAG or who have OHT at each monitoring assessment.

➢ Repeat CCT measurement as necessary (for example, following laser refractive surgery or at onset or progression of corneal pathology).

➢ Offer Van Herick's peripheral anterior chamber depth assessment test to all people with COAG, who are suspected of having COAG or who have OHT at each monitoring assessment.

➢ Repeat gonioscopy when clinically indicated (for example, where a previous examination has been inconclusive or where there is suspicion of a change in clinical status of the anterior chamber angle).

➢ Offer standard automated perimetry (central thresholding test) to all people who have established COAG and those suspected of having visual field defects who are being investigated for possible COAG. People with diagnosed OHT and those suspected of having COAG whose visual fields have previously been documented by standard automated perimetry as being normal may be monitored using supra-threshold perimetry. (see tables for recommended for monitoring intervals).

➢ Where a defect has previously been detected use the same visual field measurement strategy for each visual field test.

➢ Offer stereoscopic slit lamp biomicroscopic examination of the optic nerve head to all people with COAG, who are suspected of having COAG or who have OHT at monitoring assessments (see tables for recommended for monitoring intervals).

➢ When a change in optic nerve head status is detected by stereoscopic slit lamp biomicroscopic examination, obtain a new optic nerve head image for the person's records in order to provide a fresh benchmark for future assessments.

➢ When an adequate view of the optic nerve head and surrounding area is unavailable at a monitoring visit, people undergoing stereoscopic slit lamp biomicroscopy should have their pupils dilated before the assessment.

➢ Monitor at regular intervals people with OHT or suspected COAG recommended to receive medication, according to their risk of conversion to COAG as illustrated by the following table:

Table: Monitoring intervals for people with OHT or suspected COAG who are recommended to receive medication

Clinical assessment			**Monitoring intervals (months)**	
IOP at target [a]	**Risk of conversion to COAG [b]**	**Outcome [c]**	**IOP alone [d]**	**IOP, optic nerve head and VF**
Yes	Low	No change in treatment plan	Not applicable	12 to 24
Yes	High	No change in treatment plan	Not applicable	6 to 12
No	Low	Review target IOP OR Change treatment plan	1 to 4	6 to 12
No	High	Review target IOP OR Change treatment plan	1 to 4	4 to 6

[a] Person is treated and IOP is at or below target. If IOP cannot be adequately controlled medically, refer to consultant ophthalmologist.

[b] *To be clinically judged in terms of relevant risk indicators: age, IOP, CCT, appearance and size of optic nerve head.*
[c] *For change of treatment plan refer to treatment recommendations.*
[d] *For people started on treatment for the first time check IOP 1 to 4 months after start of medication.*

➢ Discuss the benefits and risks of stopping treatment with people with OHT or suspected COAG who have both:

- a low risk of ever developing visual impairment within their lifetime
- an acceptable IOP.

If a person decides to stop treatment following discussion of the perceived risks of future conversion to COAG and sight loss, offer to assess their IOP in 1 to 4 months' time with further monitoring if considered clinically necessary.

➢ In people with OHT or suspected COAG who are not recommended to receive medication, assess IOP, optic nerve head and visual field at the following intervals:

- between 12 and 24 months if there is a low risk of conversion to COAG
- between 6 and 12 months if there is a high risk of conversion to COAG.

If no change in the parameters has been detected after 3–5 years (depending on perceived risk of conversion) the person should be discharged from active glaucoma care to community optometric care.

➢ At discharge advise people who are not recommended for treatment and whose condition is considered stable to visit their primary care optometrist annually so that any future changes in their condition can be detected.

➢ Monitor at regular intervals people with COAG according to their risk of progression to sight loss as illustrated in the following table:

Table: Monitoring intervals for people with COAG

Clinical assessment			**Monitoring intervals (months)**	
IOP at target [a]	**Progression [b]**	**Outcome [c]**	**IOP alone [d]**	**IOP, optic nerve head and visual field**
Yes	No [e]	No change in treatment plan	Not applicable	6 to 12
Yes	Yes	Review target IOP AND Change treatment plan	1 to 4	2 to 6
Yes	Uncertain	No change in treatment plan	Not applicable	2 to 6
No	No [e]	Review target IOP OR Change treatment plan	1 to 4	6 to 12
No	Yes / uncertain	Change treatment plan	1 to 2	2 to 6

[a] *IOP at or below target.*
For people started on treatment for the first time check IOP in 1 to 4 months after start of medication.
[b] *Progression = increased optic nerve damage and/or visual field change confirmed by repeated test where clinically appropriate.*
[c] *For change of treatment plan refer to treatment recommendations.*
[d] *For people started on treatment for the first time check IOP 1 to 4 months after start of medication.*
[e] *No = not detected or not assessed*

➢ Following full recovery from surgery or laser trabeculoplasty, restart monitoring according to IOP, optic nerve head appearance and visual field.

3.2.3 Recommendations on treatment for patients with OHT and suspected COAG

➢ Offer people with OHT or suspected COAG with high IOP treatment based on estimated risk of conversion to COAG using IOP, CCT and age as illustrated in the following table:

Table: Treatment of people with OHT or suspected COAG

CCT	More than 590 micrometres		555 to 590 micrometres		Less than 555 micrometres		Any
Untreated IOP	**>21-25 mmHg**	**>25-32 mmHg**	**>21-25 mmHg**	**>25-32 mmHg**	**>21-25 mmHg**	**>25-32 mmHg**	**>32 mmHg**
Age threshold [a]	**None**	**None**	**None**	**up to 60 years**	**up to 65 years**	**up to 80 years**	**None**
Treatment	No Treatment	No Treatment	No Treatment	BB [b]	PGA [c]	PGA [c]	PGA [c]

[a] *Treatment should not be routinely offered to people over the age threshold unless there are likely to be benefits from the treatment over an appropriate time scale. Once a person being treated for OHT reaches the age threshold for stopping treatment but has not developed COAG, healthcare professionals should discuss the option of stopping treatment.*

[b] *If beta-blockers (BB) are contraindicated offer a prostaglandin analogue (PGA)*

[c] *PGA, prostaglandin analogue*

➢ Check that there are no relevant comorbidities or potential drug interactions before offering medication.

➢ Do not treat people with suspected COAG and normal IOP.

➢ Offer alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to people with OHT or suspected COAG and high IOP who are intolerant of the current medication.

➢ Offer alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to treated patients with OHT or suspected COAG whose IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss. More than one agent may be needed concurrently to achieve target IOP.

➢ Offer a preservative-free preparation to people with OHT or suspected COAG who are at high risk of conversion to COAG (IOP more than 25–32 mmHg and CCT less than 555 micrometres; or IOP more than 32 mmHg) and an allergy to preservatives.

➢ Refer treated people with OHT or suspected COAG whose IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss to a consultant ophthalmologist to discuss other options.

3.2.4 Recommendations on treatment for patients with COAG

➢ Offer people newly diagnosed with early or moderate COAG, and at risk of significant visual loss in their lifetime, treatment with a prostaglandin analogue.

➢ Check that there are no relevant comorbidities or potential drug interactions before offering medication.

➢ Offer people with severe COAG surgery with pharmacological augmentation (MMC or 5FU)* as indicated. Information should be provided on the risks and benefits associated with surgery.

**MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is*

recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.

➢ Offer people who present with severe COAG and who are listed for surgery interim treatment with a prostaglandin analogue.

➢ Encourage people using the prescribed pharmacological treatment to continue with the same treatment unless:

- their IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss
- there is progression of optic nerve head damage
- there is progression of visual field defect
- they are intolerant to the drug.

➢ Check the person's adherence to their treatment and eye drop instillation technique in people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss despite pharmacological treatment. If adherence and eye drop instillation technique are satisfactory offer one of the following:

- alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP
- laser trabeculoplasty
- surgery with pharmacological augmentation (MMC or 5FU)*as indicated

If the pharmacological treatment option is chosen, after trying two alternative pharmacological treatments consider offering surgery with pharmacological augmentation (MMC or 5FU)* as indicated or laser trabeculoplasty.

**MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*

➢ Offer surgery with pharmacological augmentation (MMC or 5FU)* as indicated to people with COAG who are at risk of progressing to sight loss despite treatment. Information should be provided on the risks and benefits associated with surgery.

**MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*

➢ Consider offering people with COAG who are intolerant to a prescribed medication:

- alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) or
- a preservative-free preparation if there is evidence that the person is allergic to the preservative.

After trying two alternative pharmacological treatments consider offering surgery with pharmacological augmentation (MMC or 5FU)* as indicated or laser trabeculoplasty.

**MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*

➢ After offer people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss one of the following:

- pharmacological treatment (a prostaglandin analogues, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP
- further surgery
- Laser trabeculoplasty or cyclo-diode laser treatment.

➢ Offer people with COAG who prefer not to have surgery or who are not suitable for surgery:

- alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP,
- laser trabeculoplasty or cyclo-diode laser treatment.

3.2.5 Recommendations on service provision

➢ Diagnosis of OHT and suspected COAG and formulation of a management plan should be made by a suitably trained healthcare professional with:

- a specialist qualification (when not working under the supervision of a consultant ophthalmologist) and
- relevant experience.

➢ Refer people with suspected optic nerve damage or suspected visual field defect to a consultant ophthalmologist for consideration of a definitive diagnosis of COAG and formulation of a management plan.

➢ Healthcare professionals involved in the diagnosis of OHT, COAG suspect status and preliminary identification of COAG should be trained in case detection and referral refinement and be able to identify abnormalities based on relevant clinical tests and

assessments. They should understand the principles of diagnosis of OHT and COAG and be able to perform and interpret all of the following:

- medical and ocular history
- differential diagnosis
- Goldmann applanation tonometry (slit lamp mounted)
- standard automated perimetry (central thresholding test)
- central supra-threshold perimetry
- stereoscopic slit lamp biomicroscopic examination of anterior segment
- examination of the posterior segment using a slit lamp binocular indirect ophthalmoscopy
- gonioscopy
- Van Herick's peripheral anterior chamber depth assessment test
- CCT measurement.

➢ People with diagnoses of OHT, suspected COAG and COAG should be monitored and treated by a trained healthcare professional who has all of the following:

- a specialist qualification (when not working under the supervision of a consultant ophthalmologist)
- relevant experience
- ability to detect a change in clinical status.

➢ Healthcare professionals involved in the monitoring and treatment of people with OHT, suspected COAG and established COAG should be trained to make management decisions on all of the following:

- risk factors for conversion to COAG
- coexisting pathology
- risk of vision loss
- monitoring and clinical status change detection (for example, visual field changes, stereoscopic slit lamp biomicroscopic examination of anterior segment and posterior segment)
- pharmacology of IOP-lowering medications
- treatment changes for COAG, COAG suspect status and OHT (with consideration given to relevant contraindications and interactions).

➢ People with a confirmed diagnosis of OHT or suspected COAG and who have an established management plan may be monitored (but not treated) by a suitably trained healthcare professional with knowledge of OHT and COAG, relevant experience, and ability

to detect a change in clinical status. The healthcare professional should be able to perform and interpret all of the following:

- Goldmann applanation tonometry (slit lamp mounted)
- standard automated perimetry (central thresholding test)
- central supra-threshold perimetry (this visual field strategy may be used to monitor people with OHT or COAG suspect status when they have normal visual field)
- stereoscopic slit lamp biomicroscopic examination of anterior segment
- Van Herick's peripheral anterior chamber depth assessment test
- examination of the posterior segment using slit lamp binocular indirect ophthalmoscopy.

➢ Healthcare professionals who diagnose, treat or monitor people independently of consultant ophthalmologist supervision should take full responsibility for the care they provide.

3.2.6 Recommendation on provision of information for patients

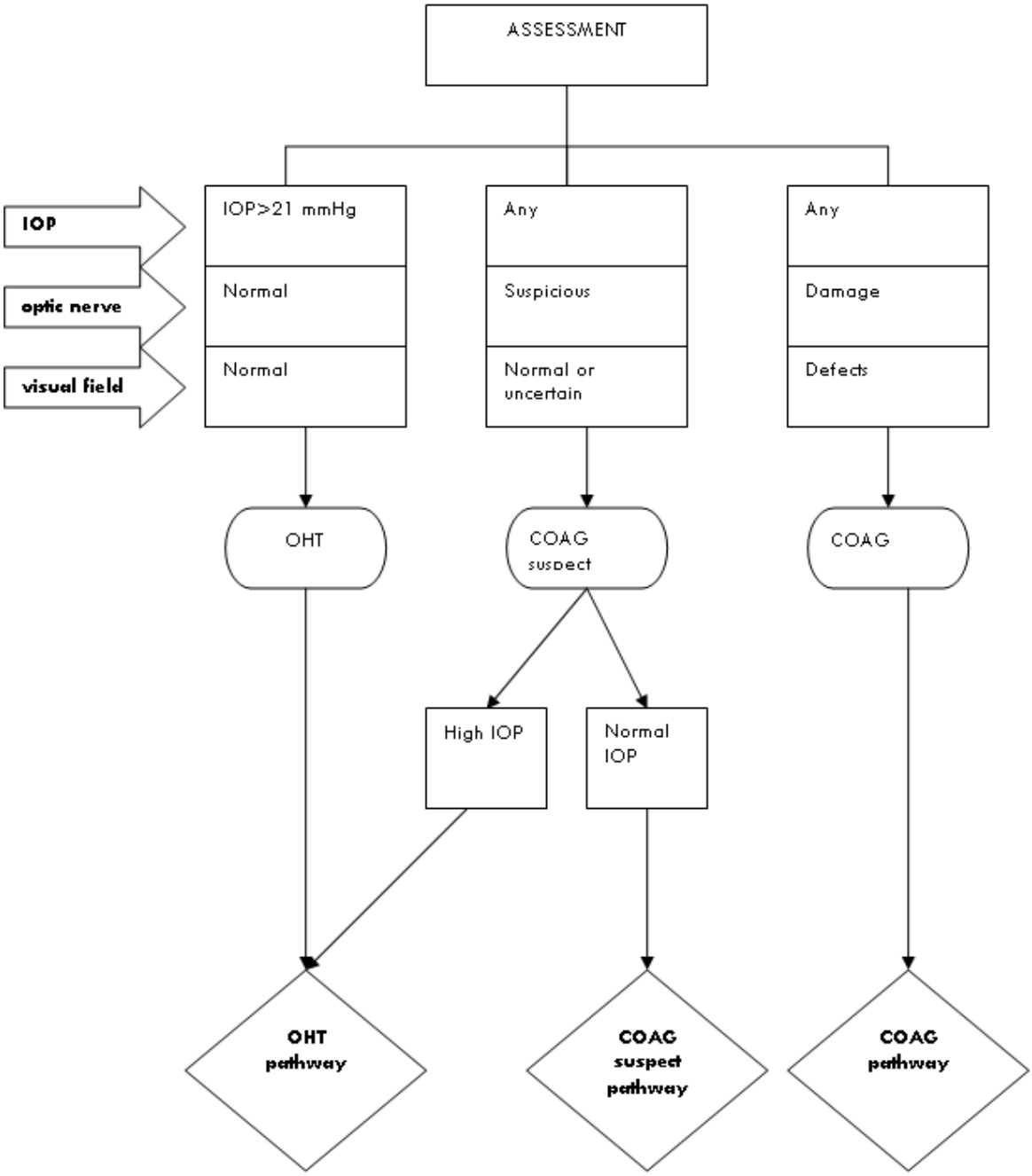
➢ Offer people the opportunity to discuss their diagnosis, prognosis and treatment; and provide them with relevant information in an accessible format at initial and subsequent visits. This may include information on the following:

- their specific condition (OHT, suspected COAG and COAG), its life-long implications and their prognosis for retention of sight
- that once lost, sight cannot be recovered
- that glaucoma can run in families and that family members may wish to be tested for the disease
- that COAG in the early stages and OHT and suspected COAG are symptomless
- that most people treated for COAG will not lose their sight
- the importance of the person's role in their own treatment – for example, the ongoing regular application of eye drops to preserve sight
- the different types of treatment options, including mode of action, frequency and severity of side effects, and risks and benefits of treatment, so that people are able to be active in the decision making process
- how to apply eye drops, including technique (punctal occulsion and devices) and hygiene (storage)
- the need for regular monitoring as specified by the healthcare professional
- methods of investigations during assessment
- the length of time and the possible need for assistance to attend each appointment
- support groups
- compliance aids (such as dispensers) available from their GP or community pharmacist
- Letter of Vision Impairment (LVI), Referral of Vision Impaired Patient (RVI) and Certificate of Visual Impairment (CVI) registration
- Driver and Vehicle Licensing Agency (DVLA) regulations.

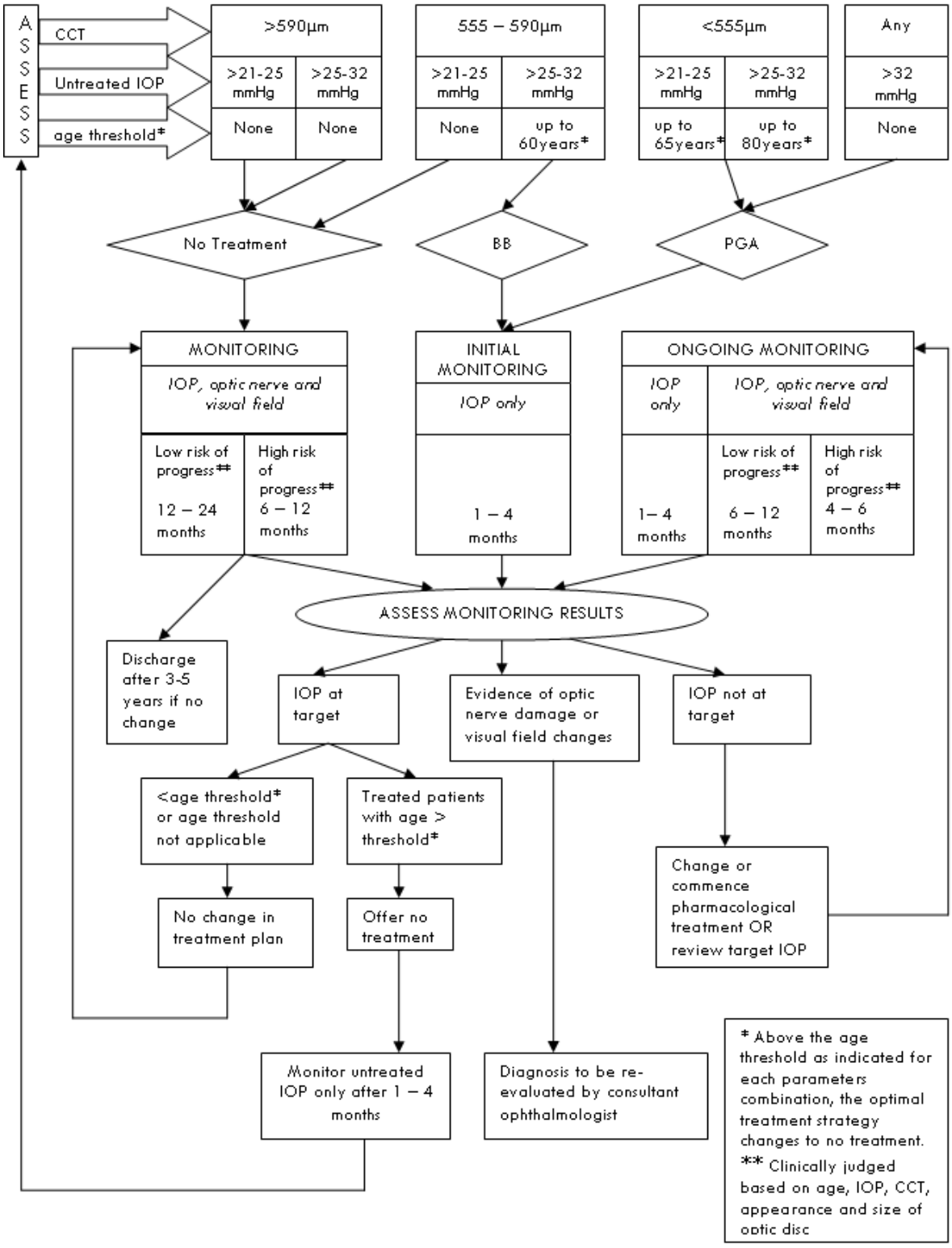
3.3 Algorithms

The GDG developed a care pathway algorithm according to the recommendations, where decision points are represented with boxes linked with arrows

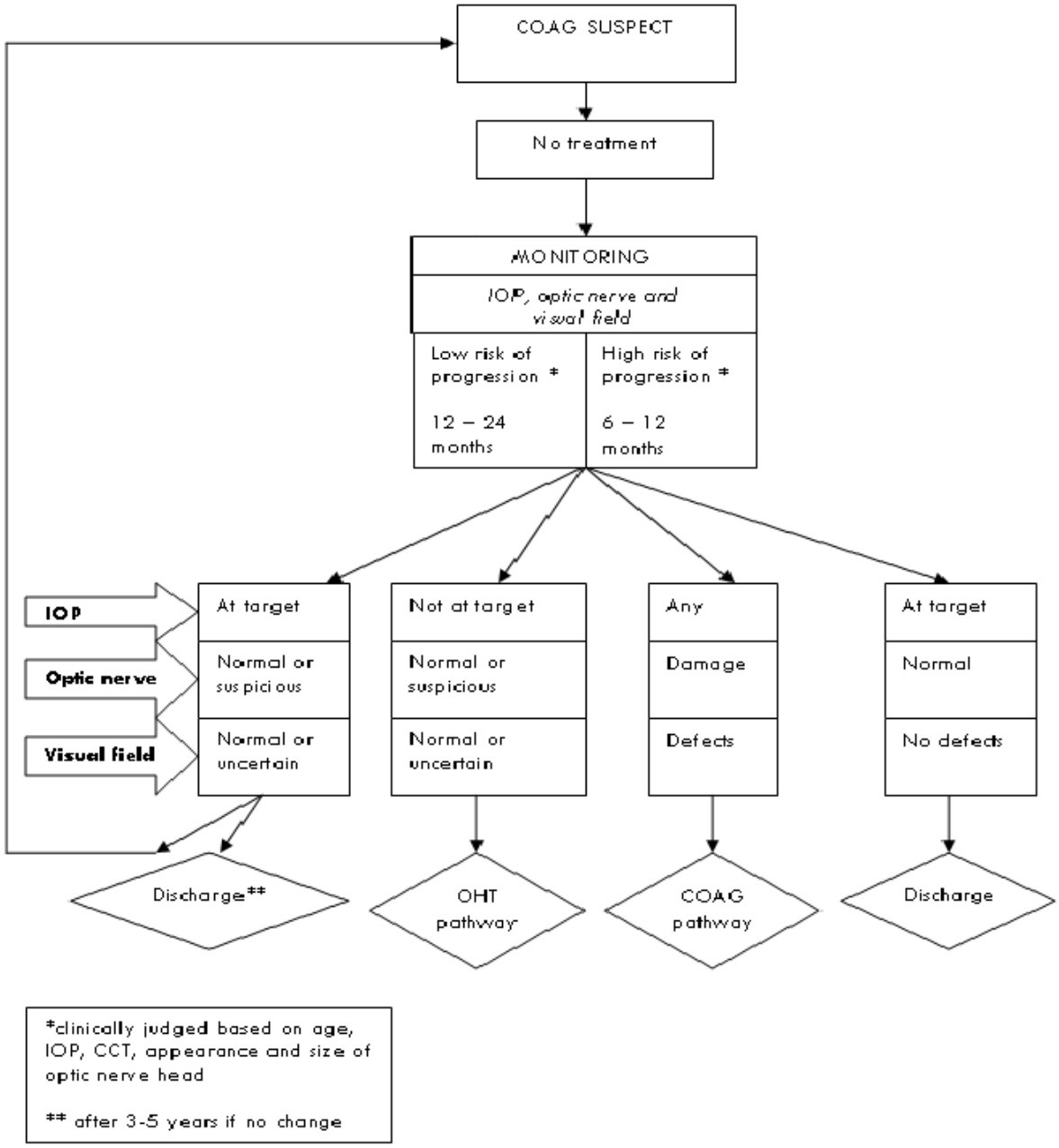
ALGORITHM 1 – DIAGNOSIS



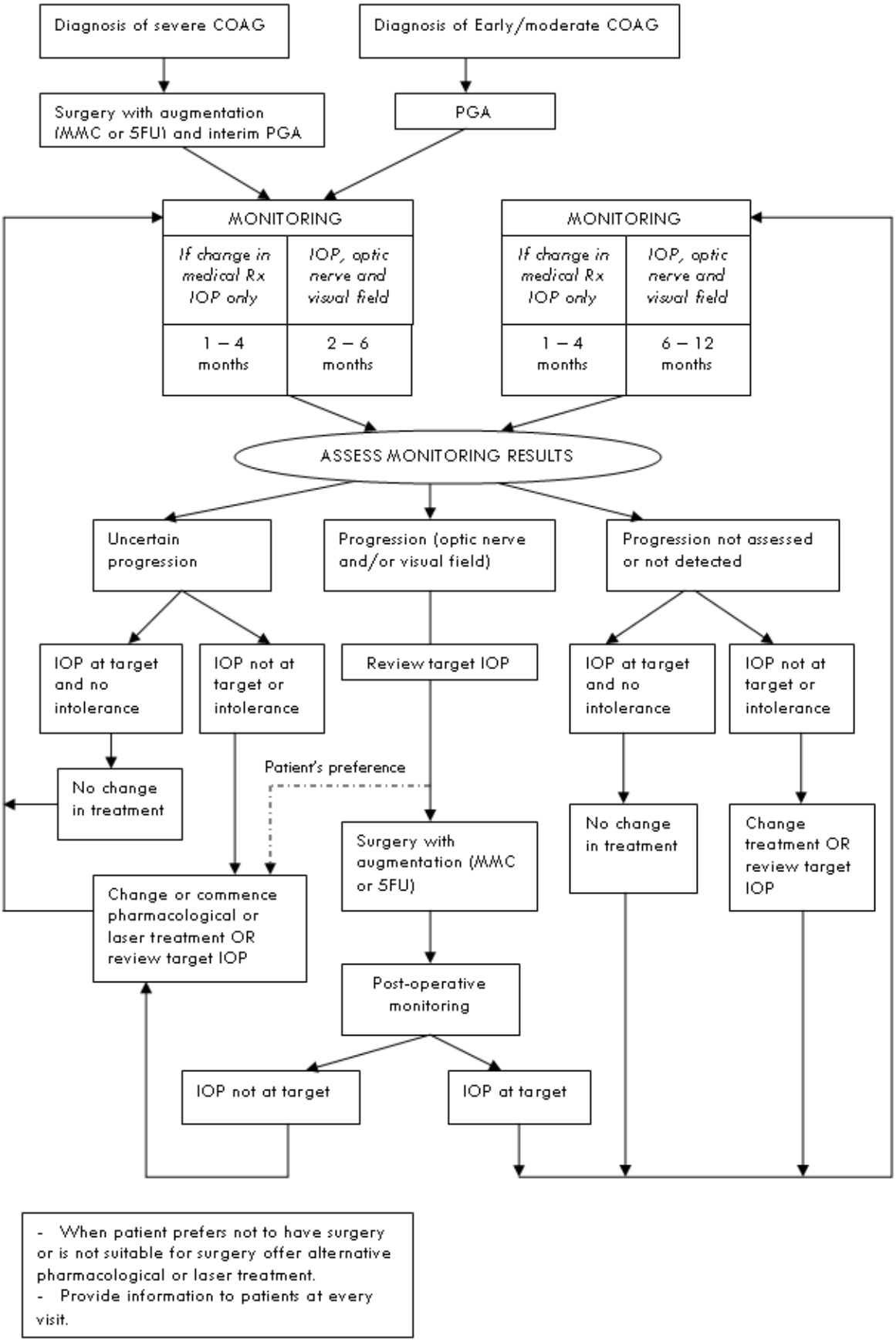
ALGORITHM 2 – OHT PATHWAY (OHT and COAG suspects with high IOP)



ALGORITHM 3 – COAG SUSPECT PATHWAY (COAG suspects with normal IOP)



ALGORITHM 4 – COAG PATHWAY



3.4 Research recommendations

The GDG identified the following priority areas for research:

- Monitoring patients with OHT, COAG and suspected COAG
- Treatment for patients with COAG
- Service provision
- Provision of information for patients

3.4.1 Research recommendation on monitoring patients with OHT, COAG and suspected COAG

The GDG recommended the following research question:

➢ What is the clinical effectiveness and cost effectiveness of using different monitoring intervals to detect disease progression in people with COAG who are at risk of progression?

Why this is important

The answer to this question is key to the recommendations on chronic disease monitoring intervals in this guideline. There is currently no identifiable evidence from randomised controlled trials (RCTs) in this area. Once diagnosed, people with COAG face lifelong treatment and monitoring. Monitoring based on risk-guided intervals would allow people who have a high risk of progression to sight loss to have more intensive monitoring and would stop people with slowly progressing disease having to attend unnecessary appointments. It would also focus resources on the people at greatest risk, making early detection of progression more likely and allowing damage to vision over time to be minimised. A randomised comparative trial of three perceived risk strata (rapid, medium, slow) for progression randomised to two, three and two alternative monitoring intervals, respectively, is suggested. The outcome would be the progression events detected..

3.4.2 Research recommendations on treatment for patients with COAG

3.4.2.1 Update of National Survey of Trabeculectomy

The GDG recommended the following research question:

➢ What are the current NHS national benchmarks for surgical success and complications in people with COAG undergoing trabeculectomy drainage surgery with and without pharmacological augmentation?

Why this is important

The answer to this question would provide more accurate and up-to-date evidence for surgical treatment in COAG. Surgical success and complication rates could then be used to update benchmarks for clinical audit and assist in planning service provision. It would also then be

possible to inform people having surgery of the chances of success and complications. The current evidence base is the National Survey of Trabeculectomy. However, this is now 10 years old and techniques have changed. The benchmarks created from the new survey would set a standard against which newer techniques could be evaluated. The study design would be similar to the audit of 10 years ago, to allow comparison of outcomes now in the light of changes in technique and the recommendations made by that audit..

3.4.2.2 Laser treatment

The GDG recommended the following research question:

➢ What is the clinical effectiveness and cost effectiveness of initial argon, diode or selective laser trabeculoplasty compared with prostaglandin analogues alone or laser trabeculoplasty plus prostaglandin analogues in combination in people with COAG?

Why this is important

The answer to this question would provide data on the comparative clinical effectiveness and cost effectiveness of laser treatment versus modern ocular hypotensive agents, particularly prostaglandin analogues. Laser treatment may control IOP in some people for a time without the need for topical medications, and in others, it may offer additional benefit to topical medications. In either case there may be cost savings and improved prevention of progression. Existing trials of laser trabeculoplasty compared with pharmacological treatment use outdated pharmacological agents. Because of the lack of evidence, the role of laser trabeculoplasty in COAG management cannot be clearly defined. An RCT should be used to answer this research question, and sham laser treatment would be needed to enable double masking or at least single masking..

3.4.3 Research recommendation on service provision

The GDG recommended the following research question:

➢ In people identified on primary examination as exhibiting possible COAG, OHT or suspected COAG, what is the comparative effectiveness of diagnosis by different healthcare professions?

Why this is important

The answer to this question has the potential to improve access to care by increasing the number of available healthcare professionals and locations. The current available evidence is weak. There is one RCT, but it is of limited general use because of its design. There has not been any large-scale research on service provision in this area in the past 10 years. However, the Department of Health did pilot alternative COAG care pathways, which shows that central government is interested in this area. Primary research and several RCTs would be needed to answer the questions in this research recommendation...

3.4.4 Research recommendation on provision of information for patients

The GDG recommended the following research question:

➢ What is the clinical effectiveness and cost effectiveness of providing people with COAG with a 'glaucoma card' or individual record of care compared with standard treatment?

Why this is important

The answer to this question would provide evidence of better care in terms of treatment outcome and the experience that people with COAG have. Involving them and helping them understand how to manage their COAG could reduce stress and uncertainty and potentially improve adherence to medical treatment, allowing them to remain sighted for longer. No RCTs or systematic reviews on the subject were identified. The study design for the proposed research should be an RCT. A qualitative research component would be needed to develop an appropriate intervention and patient-focused outcome measure to assess the experience of people with COAG. A standard visual function (field of vision) test would be appropriate for evaluating visual outcome. A large sample size and long study period – probably at least 5 years – would be needed to determine visual outcome, with the associated cost implications..

4 Diagnosis of patients with ocular hypertension, chronic open angle glaucoma and suspected chronic open angle glaucoma

4.1 Introduction

The correct diagnosis of COAG, OHT and suspected COAG is extremely important for patients since the consequences of both false positive and negative decisions may be severe. Because optic nerve damage from the disease is irreversible, failure to make the diagnosis when the disease is present may be catastrophic and apart from the avoidable suffering endured, the medico-legal consequences are likely to be significant. False positive diagnosis also has serious consequences leading to lifelong inappropriate anxiety, unnecessary exposure to potentially harmful medicines and wastage of resources.

Because COAG is a "primary" diagnosis, it means that it has to be made by the exclusion of other "secondary" causes. It must be differentiated from angle closure disease where there is a mechanical obstruction to the outflow of aqueous humour from the eye and also from all other possible neurological causes of optic nerve damage, including brain tumours, strokes and inflammatory diseases of the eye and brain. Once a patient is given the diagnosis, a lifetime's sentence of an ever present threat to sight is delivered, since the disease cannot be cured; only controlled.

The definition of COAG includes the concept of a progressive condition and implies that if intervention is not provided, progression will take place. Although the rate of progression is variable it is important that with the diagnosis, an appropriate and as far as possible accurate visual prognosis is given, since this varies widely from a negligible threat to an individual's sighted lifetime to almost certain and severe loss of sight. Fortunately only a minority of patients with glaucoma will become significantly vision impaired.

In the great majority of cases, a definite diagnosis of COAG should only be made when there is an irrefutable and consistently demonstrable abnormality of visual function in at least one eye. Usually this will be defined by a relative or absolute scotoma in the field of vision demonstrated by standard automated perimetry (SAP). When a person is unable to cooperate with SAP, alternative methods of defining a functional abnormality of the optic nerve should be used. This functional abnormality should be confidently attributed to glaucomatous optic neuropathy to the exclusion of any other cause and

corroborated by demonstrable abnormality of the optic nerve in the affected eye(s). On occasions there will be genuine uncertainty, for example not all patients are able to perform visual function tests reliably. Depending on the level and source of uncertainty, other signs of COAG such as 'obvious' glaucomatous optic neuropathy may need to be given additional weight in arriving at a considered and accurate diagnosis. A period of observation with repeated clinical measurements may be required to confirm or refute an uncertain diagnosis.

A person may be classified as a COAG suspect when the optic nerve head appearance is suggestive of COAG but the visual fields appear normal, or conversely, where a visual field defect exists yet the optic nerve appears healthy (other causes of visual field defects having been excluded). If the intraocular pressure is raised in the presence of suspicious optic nerve changes the person may be classified as a COAG suspect with ocular hypertension. Where both the visual field and the optic nerve appear normal in the presence of elevated pressure the person is classified as having 'simple' ocular hypertension.

In this chapter we examine the accuracy of various diagnostic tests used to assess intraocular pressure, anterior chamber angle, visual field and the optic nerve.

4.2 Intraocular pressure measurement (IOP)

The GDG considered Goldmann applanation tonometry (slit lamp mounted) to be the reference standard in IOP measurement. In order to find out if alternative methods might be equally suitable we searched for evidence comparing non-contact tonometry to Goldmann contact tonometry.

Using Goldmann prisms introduces the potential for cross infection via contaminated prisms. A disposable prism would not have this risk. Consequently, we also compared the accuracy of disposable versus Goldmann prisms to see if disposable prisms are a suitable alternative.

4.2.1 Diagnostic accuracy of non-contact tonometry versus Goldman contact tonometry

See Evidence Table 1, Appendix D and Cost Analysis in Appendix F -1.4

4.2.1.1 Clinical evidence

Table 4-10: Non-contact vs. contact tonometry - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Detection of IOP ≥21mmHg[5]	3 (a)	Diagnostic study	Serious limitations (b)	Serious inconsistency (c)	No serious indirectness	None

(a) *One study includes three groups using different machines.*
(b) *States patients were selected randomly but no other details are provided. It is also unclear whether the machines were recalibrated before each use.*
(c) *The results show different sensitivities and specificities for the different groups.*

Table 4-11: Non-contact vs. contact tonometry - Clinical summary of findings

Outcome	Sensitivity %	Specificity %	NPV %	PPV %	Prevalence %	Likelihood Ratio (+ve)	Likelihood Ratio (-ve)	Quality
Detection of IOP ≥21mmHg	Range 40 to 81	Range 93 to 95	Range 63 to 85	Range 71 to 93	Range 18 to 31	Range 7.54 to 12.47	Range 0.16 to 0.63	Low

4.2.1.2 Economic evidence

No studies were identified. We conducted a cost analysis on this question. See Appendix F – 1.4 for methods.

Table 4-12: Non-contact vs. contact tonometry - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NCC-AC cost analysis (Appendix F – 1.4)	Serious limitations (a)	Directly applicable	

(a) Not a full economic evaluation. Summary of effectiveness was based on expert opinion.

Table 4-13: Non-contact vs. contact tonometry - Economic summary of findings

Study	Incremental cost	Incremental effects	ICER	Uncertainty
NCC-AC cost analysis (Appendix F – 1.4)	Non-contact tonometry costs £0.39 less per patient.	Contact tonometry more accurate (a)	Not calculated	

(a) Expert opinion

4.2.1.3 Patient views evidence

No studies were identified.

4.2.1.4 Evidence statements - Non-contact vs. contact tonometry

Clinical Studies examining sensitivity and specificity of NCT to detect OHT (IOP>21mmHg) demonstrated a wide range of sensitivities with consistently quite high specificity. (LOW QUALITY)

Economic Contact tonometry is more costly than non-contact tonometry when the cost of false positives and false negatives are excluded. The evidence has serious limitations and direct applicability.

4.2.2 Diagnostic accuracy of disposable prisms versus Goldman prisms

4.2.2.1 Clinical evidence

No studies were identified.

4.2.2.2 Economic evidence

No studies were identified.

4.2.2.3 Patient views evidence

No studies were identified.

4.2.2.4 Evidence statements - Disposable versus Goldmann prisms

Clinical No studies were identified comparing the diagnostic accuracy of disposable to Goldmann prisms.

Economic No studies were identified comparing the costs of disposable to Goldmann prisms.

4.2.3 Recommendations and link to evidence

Recommendations marked by an asterisk (*) are first presented separately due to the difference in supporting evidence. Later these recommendations have been merged into a single recommendation in section 4.7 (Summary of recommendations on diagnosis of patients with OHT, COAG or suspected COAG) to reflect the importance of considering them together when assessing the presence or absence of OHT or COAG.

Recommendation	*** At diagnosis offer all people who have COAG, who are suspected of having COAG or who have OHT intraocular pressure measurement using Goldmann applanation tonometry (slit lamp mounted)**
Relative values of different outcomes	The GDG considered Goldmann applanation tonometry to be the reference standard for measurement of IOP. Since important treatment decisions are based on IOP measurements it is imperative to obtain a reliable IOP reading and for the test to have a high sensitivity and specificity. The available evidence suggests that non-contact tonometry could not accurately measure the higher IOP.
Trade off between clinical benefits and harms	Although there is no written evidence, the GDG noted that the potential for corneal burn is present if sterilising fluid remains or is allowed to dry on the prism with Goldmann applanation tonometry. Using disposable tonometer prisms could adversely affect the accuracy but would be safer for avoidance of transmission of infectious diseases.
Economic considerations	Although contact tonometry is more costly, it also has greater accuracy (expert opinion) than non-contact tonometry and therefore could save costs of inappropriately treating patients for raised IOP. The slit lamp is expensive but it has many other uses including optic nerve stereo biomicroscopy. Using disposable tonometer prisms could increase costs (between £0.70 and £1.40 per patient) but prevent transmission of infective agents.
Quality of evidence	Low quality clinical evidence. The economic evidence has direct applicability but serious limitations as it is not a full economic evaluation and the summary of effectiveness was based on expert opinion.
Other considerations	Hand held methods of tonometry such as Perkins may be useful in a case finding/screening scenario where a person may have difficulty being examined on a slit lamp (for example with curvature of the spine). However there is no evidence to suggest that these methods are equivalent to slit lamp mounted GAT.

4.2.4 Supporting recommendations

Recommendation	**Adopt professional /Department of Health guidance to reduce the risk of transmitting infective agents via contact tonometry or gonioscopy.**
Trade off between clinical benefits and harms	There is a potential trade off between getting an accurate measurement of intraocular pressure and the risk of infection from contact tonometry.
Economic considerations	Not addressed.
Other considerations	The GDG decided not to duplicate work carried out by the Department of Health and other professional bodies therefore we refer to any guidance they provide[34,97,127,129].

4.3 Central corneal thickness measurement

Central corneal thickness was identified as a risk factor of converting from OHT to POAG (Section 7.4). A variety of options exist for measurement of central corneal thickness. There is no universally accepted reference standard. The GDG did not consider it necessary to investigate in detail comparisons between the various machines available. The GDG decided it was important to consider assessing CCT.

4.3.1.1 Clinical evidence

In Section 7.4 we identify central corneal thickness as a risk factor of converting from OHT to POAG.

4.3.1.2 Economic evidence

In Section 7.3 we define the most cost-effective treatment strategy for patients with OHT. This is based on the risk factors for conversion to POAG, which include central corneal thickness. Its measurement is therefore necessary to select the most appropriate and cost-effective treatment option. See Section 7.3 and Appendix F -1.3 for methods and conclusions.

4.3.1.3 Patient views evidence

No studies were identified.

4.3.1.4 Evidence statements - Central corneal thickness measurement vs. no measurement

Clinical No studies were identified which compared the visual outcomes for patients whose clinical management included measurement of CCT compared to those where CCT was not measured.

Economic The most cost-effective strategy for treating OHT patients depends on the results of the central corneal thickness measurement. This evidence has minor limitations and direct applicability.

4.3.2 Recommendations and link to evidence

Recommendations marked by an asterisk (*) are first presented separately due to the difference in supporting evidence. Later these recommendations have been merged into a single recommendation in section 4.7 (Summary of recommendations on diagnosis of patients with OHT, COAG or suspected COAG) to reflect the importance of considering them together when assessing the presence or absence of OHT or COAG.

Recommendation	*** At diagnosis offer all people who have COAG, who are suspected of having COAG or who have OHT central corneal thickness measurement**
Relative values of different outcomes	Central corneal thickness is significantly associated with POAG development. This was shown by a study that included a multivariate model which adjusted for other known risk factors such as positive family history or West African ethnic origin[51]. Its measurement is therefore necessary for estimating an ocular hypertensive patient's risk of developing POAG. Central corneal thickness can act as a confounder of IOP measurement and is therefore of value in interpreting IOP measurements.
Trade off between clinical benefits and harms	Central corneal thickness can be measured by contact or non contact methods. Contact methods may be quicker and more accurate but require corneal anaesthesia and are associated with potential corneal injury or transmission of infection.
Economic considerations	The cost-effectiveness of treatment strategies vary according to the central corneal thickness, therefore this measurement is necessary for prescribing the most cost-effective treatment.
Quality of evidence	No clinical evidence was found. The economic evidence has minor limitations and direct applicability.
Other considerations	Central corneal thickness is affected by laser refractive surgery. See NICE IP guidance 164 (www.nice.org.uk/nicemedia/pdf/IPG164guidance.pdf)

4.4 Anterior chamber angle measurement

The GDG considered gonioscopy as the reference standard for anterior chamber angle measurement. We searched for data comparing gonioscopy and the following non gonioscopic procedures: iris eclipse or shadow test, Van Herick's test, slit lamp assessment, Redmond-Smith slit lamp assessment, Scheimpflug anterior segment photography, ultrasound (A-scan), (Ultra)High resolution B-scan, Ultrasound BioMicroscopy (UBM) and anterior segment optical coherence tomography (OCT).

4.4.1 Diagnostic accuracy of non-gonioscopic methods versus gonioscopic methods of measuring anterior chamber angle

See Evidence Table 2, Appendix D and Cost Analysis in Appendix F -1.4

4.4.1.1 Clinical evidence

Table 4-14: Van Herick's test vs. gonioscopic methods - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Diagnostic accuracy at cut-off ≤ 25% corneal thickness [9,149]	2	Diagnostic study	Serious limitations (a)	No serious inconsistency	Serious indirectness (b)	(c)

(a) *Both studies are in a consecutively selected cohort of patients. In one study[9] it is not clear whether Van Herick's test was performed independently, within a reasonable time frame and in a masked fashion to gonioscopy. Both studies reported full test results for all patients.*

(b) *Both studies are in patients from south-east Asia and the Indian sub-continent where the prevalence of closed-angles tends to be higher.*

(c) *For gonioscopy there are variations between studies in type of gonioscopy lens and grading system used for classification of narrow angles. For Van Herick's test one study[9] uses a modified cut-off grade for of ≤25%of corneal thickness as indicative of narrow angles whereas the other study[149] uses grade 1 <25% corneal thickness as indicative of narrow angles.*

Table 4-15: Van Herick's test vs. gonioscopic methods - Clinical summary of findings

Outcome	Sensitivity %	Specificity %	NPV %	PPV %	Prevalence %	Likelihood Ratio (+ve)	Likelihood Ratio (-ve)	Quality
Diagnostic accuracy at cut-off ≤ 25% corneal thickness	Range: 62 to 85	Range: 89 to 90	Range: 88 to 89	Range: 62 to 87	Range: 22 to 44	Range: 5.80 to 8.13	Range: 0.17 to 0.43	Low

Table 4-16: Flashlight Test vs. gonioscopic methods - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Diagnostic accuracy at cut-off of 1/2 shadow [149]	1	Diagnostic study	No serious limitations	No serious inconsistency	Serious indirectness (a)	
Diagnostic accuracy at cut-off of 1/3 shadow [149]	1	Diagnostic study	No serious limitations	No serious inconsistency	Serious indirectness (a)	

(a) *The study is in patients from the Indian sub-continent where the prevalence of closed-angles tends to be higher.*

Table 4-17: Flashlight Test vs. gonioscopic methods - Clinical summary of findings

Outcome	Sensitivity %	Specificity %	NPV %	PPV %	Prevalence %	Likelihood Ratio (+ve)	Likelihood Ratio (-ve)	Quality
Diagnostic accuracy at cut-off of 1/2 shadow	48	83	85	43	22	2.75	0.63	Moderate
Diagnostic accuracy at cut-off of 1/3 shadow	86	71	95	45	22	2.92	0.20	Moderate

Table 4-18: Scanning Peripheral Anterior Chamber Depth analyser (SPAC) vs. gonioscopic methods - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Diagnostic accuracy at cut-off of suspect angle closure or potential angle closure [9]	1	Diagnostic study	No serious limitations	No serious inconsistency	Serious indirectness (a)	

(a) The study is in patients from south-east Asia where the prevalence of closed-angles tends to be higher.

Table 4-19: Scanning Peripheral Anterior Chamber Depth analyser (SPAC) vs. gonioscopic methods - Clinical summary of findings

Outcome	Sensitivity %	Specificity %	NPV %	PPV %	Prevalence %	Likelihood Ratio (+ve)	Likelihood Ratio (-ve)	Quality
Diagnostic accuracy at cut-off of suspect angle closure or potential angle closure	85	73	86	71	44	3.16	0.21	Moderate

Table 4-20: Non-contact anterior segment optical coherence technology (AS-OCT) vs. gonioscopic methods - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Diagnostic accuracy at cut-off of ≥ 1 quadrants of the angle closed in either eye[112]	1	Diagnostic study	No serious limitations	No serious inconsistency	Serious indirectness (a)	

(a) The study is in patients from south-east Asia where the prevalence of closed-angles tends to be higher.

Table 4-21: Non-contact anterior segment optical coherence technology (AS-OCT) vs. gonioscopic methods - Clinical summary of findings

Outcome	Sensitivity %	Specificity %	NPV %	PPV %	Prevalence %	Likelihood Ratio (+ve)	Likelihood Ratio (-ve)	Quality
Diagnostic accuracy at cut-off ≥ 1 quadrants of the angle closed in either eye	98	55	97	68	50	2.20	0.04	Moderate

4.4.1.2 Economic evidence

No studies were identified. We conducted a cost analysis on this question. See Appendix F – 1.4 for methods.

Table 4-22: Van Herick's test vs. gonioscopic methods - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NCC-AC cost analysis (Appendix F – 1.4)	Serious limitations (a)	Directly applicable	

(a) Not a full economic evaluation. Summary of effectiveness was based on expert opinion.

Table 4-23: Van Herick's test vs. gonioscopic methods - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
NCC-AC cost analysis (Appendix F – 1.4)	Van Herick's test saves £0.40 per patient.	Gonioscopy more accurate (a)	Not calculated	

(a) Expert opinion. See also 4.4.1.1 for clinical evidence.

Table 4-24: Non-gonioscopic vs. gonioscopic methods - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NCC-AC cost analysis (Appendix F – 1.4)	Serious limitations (a)	Directly applicable	

(a) Not a full economic evaluation. Summary of effectiveness was based on expert opinion.

Table 4-25: Non-gonioscopic vs. gonioscopic methods - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
NCC-AC cost analysis (Appendix F – 1.4)	A-scan, B-scan and OCT save respectively £0.28, £0.22, and £0.14 per patient.	Gonioscopy more accurate (a)	Not calculated	

(a) Expert opinion. See also 4.4.1.1 for clinical evidence

4.4.1.3 Patient views evidence

No studies were identified.

4.4.1.4 Evidence statements - Non-gonioscopic vs. gonioscopic methods

Clinical

Van Herick's test at a cut-off of ≤ 25% has a reasonable sensitivity and specificity across the two studies for measuring anterior chamber angle. However the evidence is limited because both studies were in Asian/Indian populations with a higher prevalence of narrow angles and one study was of lower methodological quality. (LOW QUALITY)

The flashlight test has a moderate sensitivity and specificity when a third-shadow is used as the cut-off for measuring anterior chamber angle but has a low sensitivity for a cut-off of a half-shadow. However the evidence is limited because both studies were in Asian/Indian populations with a higher prevalence of narrow angles. (MODERATE QUALITY)

Scanning Peripheral Anterior Chamber Depth analyser (SPAC) at a cut-off of suspect angle closure or potential angle closure has a moderate sensitivity and specificity for measuring anterior chamber angle. However the evidence is limited because both studies were in Asian/Indian populations with a higher prevalence of narrow angles. (MODERATE QUALITY)

Non-contact anterior segment optical coherence technology (AS-OCT) at a cut off ≥1 closed quadrant has a high sensitivity but low specificity for measuring anterior chamber angle. However the evidence is limited because both studies were in Asian/Indian populations with a higher prevalence of narrow angles. (MODERATE QUALITY)

Economic

Van Herick's test, A-scan, B-scan and OCT are less costly than Gonioscopy when the cost of false positives and false negatives are not taken into account. This evidence has serious limitations and direct applicability.

4.4.2 Recommendations and link to evidence

Recommendations marked by an asterisk (*) are first presented separately due to the difference in supporting evidence. Later these recommendations have been merged into a single recommendation in section 4.7 (Summary of recommendations on diagnosis of patients with OHT, COAG or suspected COAG) to reflect the importance of considering them together when assessing the presence or absence of OHT or COAG.

Recommendation	*** At diagnosis offer all people who have COAG, who are suspected of having COAG or who have OHT peripheral anterior chamber configuration and depth assessments using gonioscopy.**
Relative values of different outcomes	The GDG considered gonioscopy to be the accepted reference standard assessment for establishing the configuration and condition of the peripheral anterior chamber and drainage

	angle. Precise knowledge of the state of the chamber angle is essential to avoid missing angle closure if present.
Trade off between clinical benefits and harms	Gonioscopy allows comprehensive visualisation of the interior anterior chamber angle and related structures in a way which is not possible using any of the other tests. However, it is invasive, involves anaesthetic drops and has the potential to damage the surface of the eye if used incorrectly. Other tests are not invasive except high resolution ultrasound. The importance of knowing the angle details outweighs the potential harms and risks. No technique was considered a suitable alternative to gonioscopy in describing the status of the drainage angle. For exclusion of angle closure and accurate diagnosis the reference standard is therefore required.
Economic considerations	Even if gonioscopy costs more than Van Herick's test, A-scan and B-scan, it has higher precision in detecting angle closure.
Quality of evidence	Low quality clinical evidence in an indirect population The economic evidence has direct applicability but serious limitations as it is not a full economic evaluation and the summary of effectiveness was based on expert opinion.
Other considerations	Some patients may not be able to be assessed with gonioscopy. For example, some patients with physical or learning disabilities may be unable to participate in the examination and therefore an alternative test should be offered (see below).
Recommendation	**Use Van Herick's peripheral anterior chamber depth assessment test as an alternative to gonioscopy if clinical circumstances rule out gonioscopy (for example, when people with physical or learning disabilities are unable to participate in the examination).**
Relative values of different outcomes	As indicated above, the GDG considered precision of the test to be the most important issue. Although Van Herick's test is not as accurate as gonioscopy, the GDG considered it to be an adequate alternative for use where gonioscopy was not possible.
Trade off between clinical benefits and harms	The GDG considered it important to get a diagnosis in the interest of providing the correct management plan for all individuals. If the best test is not possible for or desirable to a patient then Van Herick's test is a suitable alternative.
Economic considerations	Other non-gonioscopic methods are more expensive than Van Herick's test without adding any useful information.

Quality of evidence	Low quality clinical evidence in an indirect population. The economic evidence has partial applicability because not direct to a population with physical or learning disabilities. It has serious limitations as it is not a full economic evaluation and the summary of effectiveness was based on expert opinion.
Other considerations	None

4.4.3 Supporting recommendations

Recommendation	**Adopt professional /Department of Health guidance to reduce the risk of transmitting infective agents via contact tonometry or gonioscopy.**
Trade off between clinical benefits and harms	There is a potential trade off between getting an accurate assessment of anterior chamber angle and the small risk of infection from gonioscopy.
Economic considerations	None.
Other considerations	The GDG decided not to duplicate work carried out by the Department of Health and other professional bodies therefore we refer to any guidance they provide[34,97,127,129].

4.5 Visual field measurement

The GDG considered 24-2 SITA Humphrey tests as the reference standard in assessing visual field. We searched for data comparing 24-2 SITA Humphrey tests and the following alternative visual field tests: Henson, Dicon, Octopus, frequency doubling technology (FDT) and Humphrey tests other than 24-2 SITA.

4.5.1 Diagnostic accuracy of Henson, Dicon, Octopus, frequency doubling technology (FDT) or Humphrey tests (other than 24-2 SITA) versus Humphrey tests (24-2 SITA)

No studies were identified.

4.5.1.1 Clinical evidence

No studies were identified.

4.5.1.2 Economic evidence

No studies were identified.

4.5.1.3 Patient views evidence

No studies were identified.

4.5.1.4 Evidence statements - Other perimetry tests vs. Humphrey 24-2 SITA

Clinical No studies reported diagnostic accuracy of other perimetry tests compared to Humphrey 24-2 SITA standard.

Economic No studies reported cost-effectiveness of other perimetry tests compared to Humphrey 24-2 SITA standard.

4.5.2 Recommendations and link to evidence

Recommendations marked by an asterisk (*) are first presented separately due to the difference in supporting evidence. Later these recommendations have been merged into a single recommendation in section 4.7 (Summary of recommendations on diagnosis of patients with OHT, COAG or suspected COAG) to reflect the importance of considering them together when assessing the presence or absence of OHT or COAG.

Recommendation	*** At diagnosis offer all people who have COAG, who are suspected of having COAG or who have OHT visual field measurement using standard automated perimetry (central thresholding test).**
Relative values of different outcomes	The GDG considered accurate identification and quantification of a visual field defect attributable to glaucoma as the most important outcome.
Trade off between clinical benefits and harms	The GDG considered that without evidence that visual field assessment by another method is at an acceptable level of diagnostic accuracy, the benefit outweighs the potential harm of using another method providing a less certain diagnosis.
Economic considerations	Not addressed.
Quality of evidence	Lack of clinical evidence was due to the studies not comparing other perimetric tests against the reference standard Humphrey 24-2 SITA Standard.
Other considerations	Implementation: the GDG recommended testing using a threshold strategy, although this need not be machine specific. Where Humphrey Field Analyzers are used, the GDG consensus is that 24-2 SITA Standard is preferred. Where a patient is unable to perform standard automated perimetry reliably, an alternative test of visual field should be considered. Patient views: patients may find a shorter, easier test from a different machine more comfortable but may prefer the longer Humphrey 24-2 SITA standard test in the knowledge that it is the most accurate.

4.6 Optic nerve assessment

The GDG considered biomicroscopic slit lamp examination by a trained clinician as the reference standard for optic nerve assessment. This is frequently combined with imaging,

stereophotography being the imaging standard. We searched for evidence comparing biomicroscopic slit lamp examination with or without stereophotography to Heidelberg retina tomography, optical coherence tomography, scanning laser polarimetry and monoscopic photography.

4.6.1 Diagnostic accuracy of Heidelberg retina tomography, optical coherence tomography, scanning laser polarimetry or monoscopic photography versus bio-microscopic slit lamp examination with or without stereophotography when assessing initial optic nerve damage.

See Cost Analysis in Appendix F -1.4

4.6.1.1 Clinical evidence

No studies were identified.

4.6.1.2 Economic evidence

No studies were identified. We undertook our own cost analyses including an analysis to estimate the increase in cost when stereophotography is added to the clinical biomicroscopic slit lamp examination. See Appendix F – 1.4 for methods.

Table 4-26: Other optic nerve imaging vs. biomicroscopic slit lamp examination - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
NCC-AC cost analysis (Appendix F – 1.4)	Serious limitations (a)	Directly applicable	

(a) Summary of effectiveness was based on expert opinion.

Table 4-27: Other optic nerve imaging vs. biomicroscopic slit lamp examination - Economic summary of findings

Study	*Incremental cost*	*Incremental effects*	*ICER*	*Uncertainty*
NCC-AC cost analysis (Appendix F – 1.4)	Slit lamp examination is cost saving	Slit lamp examination is more accurate (a)	Slit lamp examination is dominant	

(a) *This test is the accepted clinical standard. Other methods (e.g. experts comparing serial stereo disc photographs) are more accurate but impractical for routine use in the NHS. There was no evidence that alternative disc imaging techniques result in better patient outcomes. It was the opinion of the GDG that this is the most accurate method among the practical ones.*

Table 4-28: Biomicroscopic slit lamp examination with stereophotography vs. Biomicroscopic slit lamp examination - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
NCC-AC cost analysis (Appendix F – 1.4)	Serious limitations (a)	Partially applicable (b)	

(a) Not a full economic evaluation.
(b) Stereophotography is not commonly available in clinical practice.

Table 4-29: Biomicroscopic slit lamp examination with stereophotography vs. Biomicroscopic slit lamp examination - Economic summary of findings

Study	*Incremental cost per patient (£)*	*Incremental effects*	*ICER*	*Uncertainty*
NCC-AC cost analysis (Appendix F – 1.4)	0.11	Not calculated	Not calculated	

4.6.1.3 Patient views evidence

No studies were identified.

4.6.1.4 Evidence statements - Other optic nerve assessment methods vs. stereoscopic slit lamp biomicroscopy

Clinical No studies reported diagnostic accuracy of other optic nerve measurement methods compared to slit lamp biomicroscopy with stereophotography.

Economic Stereoscopic slit lamp examination dominates other optic nerve measurement methods. This evidence has serious limitations and direct applicability. Adding stereophotography to slit lamp examination is more costly. This evidence has serious limitations and partial applicability.

4.6.2 Recommendations and link to evidence

Recommendations marked by an asterisk (*) are first presented separately due to the difference in supporting evidence. Later these recommendations have been merged into a single recommendation in section 4.7 (Summary of recommendations on diagnosis of patients with OHT, COAG or suspected COAG) to reflect the importance of considering them together when assessing the presence or absence of OHT or COAG

Recommendation	*** At diagnosis offer all people who have COAG, who are suspected of having COAG or who have OHT optic nerve assessment using stereoscopic slit lamp biomicroscopy.**
Relative values of different outcomes	The GDG considered that finding optic disc abnormalities due to glaucoma using visualisation of morphological features of glaucomatous optic disc damage was the most important outcome, and any abnormal disc appearance should be interpreted in the light of other clinical findings.
Trade off between clinical benefits and harms	The GDG considered that bio-microscopic slit lamp examination is the most important part of the assessment of optic nerve appearance. The GDG also considered that using stereophotography combined with bio-microscopic slit lamp examination is not always practical in the clinical setting. There is no clear evidence that stereophotography or other imaging methodologies provide added value beyond biomicroscopic examination alone. Therefore, biomicroscopic slit lamp examination is recommended. The requirement for an optic disc image is made in a separate recommendation as it is specifically required at baseline and when there is a suggestion of morphological change.
Economic considerations	Stereoscopic slit lamp biomicroscopy is less costly and it is the accepted clinical standard. Other methods (e.g. experts comparing serial stereo disc

	photographs) are more accurate but impractical for routine use in the NHS. There was no evidence that alternative disc imaging techniques result in better patient outcomes. It was the opinion of the GDG that this is the most accurate method among the practical ones. Furthermore the cost of the slit lamp could have been omitted from the economic analysis as this equipment is already adopted for the IOP measurement (see recommendation 4). Adding stereophotography to slit lamp examinations generates more costs with no evidence that provides any added value.
Quality of evidence	There was a lack of evidence investigating the diagnostic accuracy of other optic disc imaging techniques against the reference standard. The economic evidence has serious limitations and direct applicability.
Other considerations	Patient views: dilatation for optic disc examination may be required which may affect a patient's ability to drive afterwards. The requirement for a stereo photograph as well as slit lamp examination may impact on patient time at the clinic. Alternative tests. Optical coherence tomography requires pupil dilatation. Scanning laser polarimetry and Heidelberg retina tomography usually do not require dilatation though this may be needed for certain patients. There may be a role for these technologies in detection of progressive change through sequential monitoring but evidence is as yet inadequate to support a recommendation in this regard

4.6.3 Supporting recommendations

Recommendation	**Obtain an optic nerve head image at diagnosis for baseline documentation.**
Trade off between clinical benefits and harms	The GDG decided it is important to have an image of the optic disc from which to determine if there has been a change in its appearance. Without this image as a baseline reference a clinician may not make an accurate assessment of progression of optic nerve damage over time.
Economic considerations	Adding stereophotography to biomicroscopy slit lamp examination increases costs. The economic evidence has serious limitations as it is not a full economic evaluation, and partial applicability as stereophotography is not commonly available in clinical practice.
Other considerations	Although stereophotography would be the imaging standard there are other imaging modalities which may also be used, in which case continuity with previous similar images should be available for purposes of comparison.

Recommendation	*** At diagnosis offer all people who have COAG, who are suspected of having COAG or who have OHT dilatation of their pupils before undergoing stereoscopic slit lamp biomicroscopy for fundus examination.**
Trade off between clinical benefits and harms	Assessment of the optic disc with stereoscopic slit lamp biomicroscopy is most accurately performed when the patient's pupils are dilated. Without dilatation important ocular co-pathology may be missed. The potential of harm from inducing an acute angle closure attack should not arise because gonioscopy will have been performed prior to dilatation as recommended above. Contraindications to dilatation should be observed and would include possible angle closure and an iris supported lens implant.
Economic considerations	The cost of dilating drops per patient is about £0.30 per patient which

	could be offset by the cost of the missed pathology.
Other considerations	Patient views: dilatation for optic disc examination may affect a patient's ability to drive afterwards due to blurring of vision. The need for an accurate diagnostic assessment however outweighs this inconvenience.

Recommendation	**Ensure that all of the following are made available at each clinical episode to all healthcare professionals involved in a person's care:** • **records of all previous tests and images relevant to COAG and OHT assessment** • **records of past medical history which could affect drug choice** • **current systemic and topical medication** • **glaucoma medication record** • **drug allergies and intolerances.**
Trade off between clinical benefits and harms	The GDG considered it important to ensure the continuity of care that all information is available to healthcare professionals when assessing a patient, particularly if the patient was previously seen by a different healthcare professional.
Economic considerations	There are costs associated with the delivery of care at multiple sites.
Other considerations	None

Recommendation	**Use alternative methods of assessment if clinical circumstances rule out the use of standard methods of assessment (for example, when people with physical or learning disabilities are unable to participate in the examination.**
Trade off between clinical benefits and harms	The GDG considered it important to get a diagnosis in the interest of providing the correct management plan for all individuals. If the best test is not possible or desirable for a patient then an alternative method of assessment should be offered, even if it is less accurate.
Economic considerations	None.
Other considerations	None

Recommendation	**Ensure that all machines and measurement instruments are calibrated regularly according to the manufacturer's instructions.**
Trade off between clinical benefits and harms	Machines need to be regularly calibrated to ensure the correct measurements are being obtained.
Economic considerations	There are costs associated with the machines calibration but an accurate measurement of clinical parameters could offset these costs.
Other considerations	None

4.7 Summary of recommendations on diagnosis of patients with OHT, COAG or suspected COAG

The recommendation marked with an asterisk (*) is the result of the merging of other recommendations in previous sections in this chapter.

➢ * At diagnosis offer all people who have COAG, who are suspected of having COAG or who have OHT all of the following tests:

- intraocular pressure measurement using Goldmann applanation tonometry (slit lamp mounted)
- central corneal thickness (CCT) measurement
- peripheral anterior chamber configuration and depth assessments using gonioscopy
- visual field measurement using standard automated perimetry (central thresholding test)
- optic nerve assessment, with dilatation, using stereoscopic slit lamp biomicroscopy with fundus examination.

➢ Adopt professional /Department of Health guidance to reduce the risk of transmitting infective agents via contact tonometry or gonioscopy.[34,97,127,129].

➢ Use Van Herick's peripheral anterior chamber depth assessment test as an alternative to gonioscopy if clinical circumstances rule out gonioscopy (for example, when people with physical or learning disabilities are unable to participate in the examination).

➢ Obtain an optic nerve head image at diagnosis for baseline documentation.

➢ Ensure that all of the following are made available at each clinical episode to all healthcare professionals involved in a person's care:

- records of all previous tests and images relevant to COAG and OHT assessment
- records of past medical history which could affect drug choice
- current systemic and topical medication
- glaucoma medication record
- drug allergies and intolerances.

➢ Use alternative methods of assessment if clinical circumstances rule out the use of standard methods of assessment (for example, when people with physical or learning disabilities are unable to participate in the examination.

➢ Ensure that all machines and measurement instruments are calibrated regularly according to the manufacturer's instructions.

5 Monitoring of patients with ocular hypertension, chronic open angle glaucoma and suspected chronic open angle glaucoma

5.1 Introduction

COAG is a lifelong condition with a variable course. Treatment is aimed at achieving stability with no evidence of progression or progression at a rate which is compatible with a sighted lifetime without disability. This is increasingly likely to include fitness to drive. Monitoring is required to establish whether stability or disease control is achieved and what optimally acceptable treatment regime is able to provide this. In some circumstances, no treatment may be required since progression is static or slow, while in others it may be very difficult to achieve control of aggressive and rapidly progressive disease. Fortunately, the former is more common than the latter.

People with ocular hypertension or who are suspected of having COAG may develop COAG for other reasons and monitoring is required in case frank COAG develops and a different intervention strategy becomes necessary. Interventions may be provided to reduce this risk of conversion and monitoring is then needed to gauge their effect. As a rule a 'one stop' approach is easier for patients and whenever possible the tests necessary for monitoring should be undertaken at a single visit.

Monitoring requires the maintenance and availability of reliable and complete documentation of the patient's clinical record so that clinical findings over time can be traced and coherent continuity of care provided. A patient may not see the same practitioner at each visit but clear communication between each carer and the patient should ensure that the duration until the next assessment is agreed and what will be done and why also clearly understood by all concerned. This should be stipulated by an agreed management plan owned by the patient and shared with the carers, appropriate to the severity of disease and prognosis and regularly reviewed by the management team authorised by the consultant responsible for the care of the individual patient. It would be expected that clinicians use judgement in interpreting results, with tests being repeated as deemed clinically necessary when the accuracy, reliability or validity of a particular test result is in doubt. Software exists for the sequential analysis of both images of the optic disc and the results of standard automated perimetry which may prove useful in aiding the clinician in making judgments about whether progression has occurred. It has not yet been demonstrated that these technologies will increase the

cost effectiveness and efficiency of managing patients with COAG and it is too soon to recommend routine use in clinical care.

In this chapter we examine two aspects of monitoring: the evidence for the accuracy of various diagnostic tests used to assess intraocular pressure, anterior chamber angle, visual field and the optic nerve; and secondly how often patients should be monitored. For the accuracy of various diagnostic tests used for monitoring we considered the same evidence reviewed in chapter 4 on diagnosis.

5.2 Intraocular pressure measurement (IOP)

The GDG considered Goldmann applanation tonometry (slit lamp mounted) to be the reference standard in IOP measurement. In order to find out if alternative methods might be equally suitable we searched for evidence comparing non-contact tonometry to Goldmann contact tonometry.

Using Goldmann prisms introduces the potential for cross infection via contaminated prisms. A disposable prism would not have this risk. Consequently, we also compared the accuracy of disposable versus Goldmann prisms to see if disposable prisms are a suitable alternative.

5.2.1 Diagnostic accuracy of non-contact tonometry versus Goldmann contact tonometry for monitoring patients

Data relating to the evidence for tonometry are presented in section 4.2.1in the chapter on diagnosis

5.2.1.1 Evidence statements - Non-contact vs. contact tonometry

Clinical Studies examining sensitivity and specificity of NCT to detect OHT (IOP>21mmHg) demonstrated a wide range of sensitivities with consistently quite high specificity. (LOW QUALITY)

Economic Non-contact tonometry is less costly than contact tonometry when the cost of false positives and false negatives are not taken into account. The evidence has serious limitations and direct applicability.

5.2.2 Recommendations and link to evidence

Recommendation	**Offer Goldmann applanation tonometry (slit lamp mounted) to all people with COAG, who are suspected of having COAG or who have OHT at each monitoring assessment.**
Relative values of different outcomes	The GDG considered Goldmann applanation tonometry to be the reference standard for measurement of IOP. Since important treatment decisions are based on IOP measurements it is imperative to obtain a reliable IOP reading. The available evidence suggests that non-contact tonometry could not accurately measure the higher IOP.
Trade off between clinical benefits and harms	Although there is no written evidence the GDG noted that the potential for corneal burn is present if sterilising fluid remains or is allowed to dry on the prism with GAT. Using disposable tonometer prisms could adversely affect the accuracy but would be safer for avoidance of transmission of infectious diseases.
Economic considerations	Although contact tonometry is more costly, it also has greater accuracy (expert opinion) than non-contact tonometry and therefore could save costs of inappropriately treating patients for raised IOP. The slit lamp is expensive but it has many other uses including optic nerve stereo biomicroscopy. Using disposable tonometer prisms could increase costs (between £0.70 and £1.40 per patient) but prevent transmission of infective agents.
Quality of evidence	Low quality clinical evidence. The economic evidence has direct applicability but serious limitations as it is not a full economic evaluation and the summary of effectiveness was based on expert opinion.
Other considerations	None

5.2.3 Supporting recommendations

Recommendation	**Repeat CCT measurement as necessary (for example, following laser refractive surgery or at onset or progression of corneal pathology).**
Trade off between clinical benefits and harms	Central corneal thickness can act as a confounder of IOP measurement and is therefore of value in interpreting IOP measurements. Central corneal thickness should be undertaken at initial assessment and repeated as clinically indicated e.g. following corneal (refractive) surgery. See NICE IP guidance 164 (www.nice.org.uk/nicemedia/pdf/IPG164guidance.pdf).
Economic considerations	None
Other considerations	None

5.3 Anterior chamber angle measurement

The GDG considered gonioscopy as the reference standard in its measurement. We searched for data comparing gonioscopy and the following non gonioscopic procedures: iris eclipse or shadow test, Van Herick's test, slit lamp assessment, Redmond-Smith slit lamp assessment, Scheimpflug anterior segment photography, ultrasound (A-scan), (Ultra)High resolution B-scan, Ultrasound BioMicroscopy (UBM) and anterior segment optical coherence tomography (OCT).

5.3.1 Diagnostic accuracy of non-gonioscopic versus gonioscopic methods of measuring anterior chamber angle

Data relating to the evidence for measuring the anterior chamber angle are presented in section 4.4.1in the chapter on diagnosis

5.3.1.1 Evidence statements - Non-gonioscopic vs. gonioscopic methods

Clinical

Van Herick's test at a cut-off of ≤ 25% has a reasonable sensitivity and specificity across the two studies for measuring anterior chamber angle. However the evidence is limited because both studies were in Asian/Indian populations with a higher prevalence of narrow angles and one study was of lower methodological quality. (LOW QUALITY)

The flashlight test has a moderate sensitivity and specificity when a third-shadow is used as the cut-off for measuring anterior chamber angle but has a low sensitivity for a cut-off of a half-shadow. However the evidence is limited because both studies were in Asian/Indian populations with a higher prevalence of narrow angles. (MODERATE QUALITY)

Scanning Peripheral Anterior Chamber Depth analyser (SPAC) at a cut-off of suspect angle closure or potential angle closure has a moderate sensitivity and specificity for measuring anterior chamber angle. However the evidence is limited because both studies were in Asian/Indian populations with a higher prevalence of narrow angles. (MODERATE QUALITY)

Non-contact anterior segment optical coherence technology (AS-OCT) at a cut of ≥1 closed quadrant has a high sensitivity but low specificity for measuring anterior chamber angle. However the evidence is limited because both studies were in Asian/Indian populations with a higher prevalence of narrow angles. (MODERATE QUALITY)

Economic

Van Herick's test, A-scan, B-scan and OCT are less costly than gonioscopy when the cost of false positives and false negatives are not taken into account. This evidence has serious limitations and direct applicability.

5.3.2 Recommendations and link to evidence

Recommendation	**Offer Van Herick's peripheral anterior chamber depth assessment test to all people with COAG, who are suspected of having COAG or who have OHT at each monitoring assessment.**
Relative values of different outcomes	The GDG considered precision of the test to be the most important issue. Although Van Herick's test is not as accurate as gonioscopy, the GDG considered it to be an adequate alternative for use where gonioscopy has previously been undertaken to establish the configuration and condition of the peripheral anterior chamber. In the absence of uncertainty or suspicion of a change, Van Herick's test is sufficient as a rapid check on peripheral chamber depth in the context of monitoring.
Trade off between clinical benefits and harms	Gonioscopy is more accurate but requires more time, greater specialist skills and it is more invasive.
Economic considerations	Van Herick's assessment is less costly and requires less staff time than gonioscopy. Since the structure examined is unlikely to change much over time, gonioscopy becomes less cost-effective at follow-up visits compared to initial assessment.
Quality of evidence	Low quality clinical evidence in an indirect population. The economic evidence was directly applicable but with serious limitations as it was not a full economic evaluation and the summary of effectiveness was based on expert opinion.
Other considerations	None

Recommendation	**Repeat gonioscopy when clinically indicated (for example, where a previous examination has been inconclusive or where there is suspicion of a change in clinical status of the anterior chamber angle).**
Relative values of different outcomes	The GDG considered gonioscopy to be the accepted reference standard assessment for establishing the configuration and condition of the peripheral anterior chamber and drainage angle. Precise knowledge of the state of the chamber angle is essential to avoid missing angle closure if present. Where there is uncertainty or a suspicion of change gonioscopy provides the clearest information.
Trade off between clinical benefits and harms	Gonioscopy allows comprehensive visualisation of the interior anterior chamber angle and related structures in a way which is not possible using any of the other tests. However, it is invasive, involves anaesthetic drops and has the potential to damage the surface of the eye if used incorrectly. Other tests are not invasive except high resolution ultrasound. The importance of knowing the angle details outweighs the potential harms and risks.
Economic considerations	Gonioscopy costs more than Van Herick's test but has higher precision in detecting angle closure. Other non-gonioscopic methods are more expensive without adding any useful information.
Quality of evidence	Low quality clinical evidence in an indirect population The economic evidence was directly applicable but with serious limitations as it was not a full economic evaluation and the summary of effectiveness was based on expert opinion.
Other considerations	None

5.4 Visual field measurement

Data relating to the evidence for visual field measurement are presented in section 4.5.1 in the chapter on diagnosis

5.4.1.1 Evidence statements - Humphrey 24-2 SITA vs. other perimetry tests

Clinical No studies reported diagnostic accuracy of other perimetry tests compared to Humphrey 24-2 SITA standard.

Economic No studies reported the cost-effectiveness of other perimetry tests compared to Humphrey 24-2 SITA standard.

5.4.2 Recommendations and link to evidence

Recommendation	**Offer standard automated perimetry (central thresholding test) to all people who have established COAG and those suspected of having visual field defects who are being investigated for possible COAG. People with diagnosed OHT and those suspected of having COAG whose visual fields have previously been documented by standard automated perimetry as being normal may be monitored using supra-threshold perimetry (see tables for recommended for monitoring intervals).**
Relative values of different outcomes	The GDG considered accurate location and quantification of any visual field defects in monitoring for conversion to glaucoma and progression of established glaucoma as the most important outcomes. Field results should be repeatable.
Trade off between clinical benefits and harms	To be able to compare test results in order to detect a change in visual field, it is necessary to use the same field testing strategy at monitoring visits as at diagnosis.
Economic considerations	Not addressed.
Quality of evidence	Lack of evidence was due to the studies not comparing other perimetry tests against the reference standard Humphrey 24-2 SITA standard.
Other considerations	Implementation: the GDG recommended testing using a threshold strategy, although this need not be machine specific. Where Humphrey Field Analyzers are used, the GDG consensus is that 24-2 SITA Standard is preferred. Patient views: patients may find a shorter, easier test from a different machine more comfortable but may prefer the longer Humphrey 24-2 SITA standard test in the knowledge that it is the most accurate.

5.4.3 Supporting recommendations

Recommendation	**Where a defect has previously been detected use the same visual field measurement strategy for each visual field test.**
Trade off between clinical benefits and harms	Evidence suggests that it can take several measurements through time to get an accurate assessment of progression. Using the same strategy minimises the inter-test variability which is important to optimise detection of progression when this has occurred.
Economic considerations	None
Other considerations	Where a field test has not been reliably performed this should be repeated following further instruction. Should a patient be consistently unable to perform SAP reliably a supra-threshold test may provide 'best available' information.

5.5 Optic nerve assessment

Data relating to the evidence for optic nerve assessment are presented in section 4.6.1 in the chapter on diagnosis

5.5.1.1 Evidence statements - Biomicroscopic slit lamp examination vs. other optic nerve measurement methods

Clinical No studies reported diagnostic accuracy of other optic nerve measurement methods compared to stereoscopic slit lamp biomicroscopy.

Economic Biomicroscopic slit lamp examination dominates other optic nerve measurement methods. This evidence has serious limitations and direct applicability. Adding stereophotography to slit lamp examination is more costly. This evidence has serious limitations and partial applicability.

5.5.2 Recommendations and link to evidence

Recommendation	**Offer stereoscopic slit lamp biomicroscopic examination of the optic nerve head to all people with COAG, who are suspected of having COAG or who have OHT at monitoring assessments (see tables for recommended for monitoring intervals).**
Relative values of different outcomes	The GDG considered that finding optic disc abnormalities due to glaucoma using visualisation of morphological features of glaucomatous optic disc damage was the most important outcome, though finding an abnormal appearance of the disc is not useful in isolation from other tests.
Trade off between clinical benefits and harms	The GDG considered bio-microscopic slit lamp examination to be the most important part of the assessment of the optic nerve. The GDG also considered that routinely using stereophotography with bio-microscopic slit lamp examination is not always practical in the clinical setting. Therefore, biomicroscopic slit lamp examination is recommended. The requirement for an optic disc image is made in a separate recommendation and is only required at baseline and when there is a suggestion of change. Stereophotography is useful for keeping a visual record of the optic disc at a given point in time but other imaging techniques can be used for this purpose.
Economic considerations	Stereoscopic slit lamp biomicroscopy is less costly and it is the accepted clinical standard. Other methods (e.g. experts comparing serial stereo disc photographs) are more accurate but impractical for routine use in the NHS. There was no evidence that alternative disc imaging techniques result in better patient outcomes. It was the opinion of the GDG that this is the most accurate method among the practical ones. Furthermore the cost of the slit lamp could have been omitted from the economic analysis as this equipment is already adopted for the IOP measurement (see recommendation 4). Adding stereophotography to slit lamp examinations generates more costs with no evidence that provides any added value.
Quality of evidence	There was a lack of evidence investigating the diagnostic accuracy of other optic disc imaging techniques against the reference standard. The economic evidence has serious limitations and direct applicability.
Other considerations	Patient views: Patients should be alerted to possible consequences of having their pupils dilated. Dilatation for optic disc examination may be required which may affect a patient's ability to drive afterwards. Obtaining accurate information outweighs the minor inconvenience caused by pupil dilatation. Requirement of a stereo photograph as well as slit lamp examination may impact on patient time at the clinic. Alternative tests. Optical coherence tomography requires pupil dilatation. Scanning laser polarimetry and Heidelberg retina tomography usually do not require dilatation though this may be needed for certain patients. There may be a role for these technologies in detection of progressive change through sequential monitoring but evidence is as yet inadequate to support a recommendation in this regard.

5.5.3 Supporting recommendations

Recommendation	**When a change in optic nerve head status is detected by stereoscopic slit lamp biomicroscopic examination, obtain a new optic nerve head image for the person's records in order to provide a fresh benchmark for future assessments.**
Trade off between clinical benefits and harms	Having a fresh baseline image following a change in optic disc appearance facilitates future detection of further changes which may arise. Detection of such changes is essential in terms identification of ongoing optic disc damage. Pupil dilatation is needed for stereoscopic disc photography.
Economic considerations	Adding stereophotography to biomicroscopy slit lamp examination increases costs, therefore is should be done only after a detection of change in optic disc status. The economic evidence has serious limitations as it was not a full economic evaluation. It is partially applicable as stereophotography is not commonly available in current practice.
Other considerations	Patient views: Patients should be alerted to possible consequences of having their pupils dilated. Dilatation for optic disc photography is required which may affect a patient's ability to drive afterwards. Obtaining accurate information outweighs the minor inconvenience caused by pupil dilatation.

Recommendation	**When an adequate view of the optic nerve head and surrounding area is unavailable at a monitoring visit, people undergoing stereoscopic slit lamp biomicroscopy should have their pupils dilated before the assessment.**
Trade off between clinical benefits and harms	Small pupil size may exclude a stereoscopic view of the optic disc thereby preventing adequate assessment. Pupil dilatation in the presence of open angles carries low risk provided there are no specific contraindications to dilatation (e.g. iris supported implants).
Economic considerations	Dilatation increases the cost of the assessment in terms of the cost of drops and clinician's time taken.
Other considerations	Patient views: Patients should be alerted to possible consequences of having their pupils dilated. Dilatation for optic disc examination may affect a patient's ability to drive afterwards. Obtaining accurate information outweighs the minor inconvenience caused by pupil dilatation.

5.6 Monitoring intervals for patients with OHT and COAG suspects

5.6.1 What is the optimal frequency of monitoring visits for patients with OHT and COAG suspects?

We searched for evidence comparing different intervals for monitoring of patients with ocular hypertension. We looked for studies comparing either a complete strategy or one part of monitoring, for example, how often should intraocular pressure be measured, how often should visual field changes be checked for, or how frequently should a patient with ocular hypertension be examined?

5.6.1.1 Clinical evidence

No studies identified

5.6.1.2 Economic evidence

There were no economic studies meeting the inclusion criteria. No original economic analysis was conducted on this question.

5.6.1.3 Patient views evidence

No studies were identified.

5.6.1.4 Evidence statements - Frequency of monitoring visits

Clinical No evidence was identified.

Economic No evidence was identified.

5.6.2 Recommendations and link to evidence

Recommendation

Monitor at regular intervals people with OHT or suspected COAG recommended to receive medication, according to their risk of conversion to COAG as illustrated by the following table:

Table: Monitoring intervals for people with OHT or suspected COAG who are recommended to receive medication

Clinical assessment			Monitoring intervals (months)	
IOP at target [a]	**Risk of conversion to COAG [b]**	**Outcome [c]**	**IOP alone [d]**	**IOP, optic nerve head and VF**
Yes	Low	No change in treatment plan	Not applicable	12 to 24
Yes	High	No change in treatment plan	Not applicable	6 to 12
No	Low	Review target IOP OR Change treatment plan	1 to 4	6 to 12
No	High	Review target IOP OR Change treatment plan	1 to 4	4 to 6

[a] Person is treated and IOP is at or below target. If IOP cannot be adequately controlled medically, refer to consultant ophthalmologist.
[b] To be clinically judged in terms of relevant risk indicators: age, IOP, CCT, appearance and size of optic nerve head.
[c] For change of treatment plan refer to treatment recommendations.
[d] For people started on treatment for the first time check IOP 1 to 4 months after start of medication.

Relative values of different outcomes

The most important outcome is conversion to COAG. Risk reduction by control of IOP is the surrogate outcome. If treatment is ineffective at IOP reduction, risk is not controlled and adjustment of medication is necessary. Visual field testing reaffirms the diagnosis if normal, or where a field defect has developed indicates that conversion to COAG has occurred, in which case the patient must be referred to a consultant ophthalmologist for confirmation of COAG diagnosis.

Trade off between clinical benefits and harms

Maintaining IOP control with reduction of risk for conversion to COAG ultimately brings benefits in terms of reducing progression to blindness and maintaining a sighted lifetime. Treatment without monitoring the effectiveness and side effects of the medications used would reduce treatment benefit (if poor control not detected) and expose patients unnecessarily to side effects of drugs. The inconvenience of regular monitoring for the patient is outweighed by the benefits of knowing that risk reduction has been achieved and knowledge regarding possible conversion to COAG.

Economic considerations

If development of COAG is not detected early enough there might be long term costs associated with sight impairment; on the other hand if patients are called in too often there is increased pressure on the NHS resources.

	The range given for each of the monitoring intervals reflects the variability of the clinical picture for individual patients. Similarly the cost-effectiveness for different intervals varies according to the risk of developing COAG.
Quality of evidence	There was no clinical or economic evidence investigating how often patients should be monitored.
Other considerations	Patients receiving medications are reassured by the knowledge that the effectiveness of their treatment is being monitored by a healthcare professional.

Recommendation	**Discuss the benefits and risks of stopping treatment with people with OHT or suspected COAG who have both:** • **a low risk of ever developing visual impairment within their lifetime** • **an acceptable IOP.** **If a person decides to stop treatment following discussion of the perceived risks of future conversion to COAG and sight loss, offer to assess their IOP in 1 to 4 months' time with further monitoring if considered clinically necessary.**
Relative values of different outcomes	The key outcome is knowledge that the IOP has not risen to a dangerous level following cessation of medication. Following a clinical decision made in conjunction with a patient to discontinue treatment it is essential that the correctness of discontinuation is confirmed by an early assessment of IOP off treatment in order to avoid a possible unexpected high IOP going undetected over an extended period.
Trade off between clinical benefits and harms	Where the benefits of treatment for the patient are marginal, stopping treatment may be the best option. Early confirmation that IOP off treatment is acceptable is essential. If a high IOP rise occurs following withdrawal of treatment it may be necessary to re-start treatment and re-institute long term monitoring. During the period of treatment information will have been gathered on the stability of the condition. Patients with progressive disease would not be eligible for stopping treatment. Following withdrawal of treatment a further period of observation may be necessary to confirm stability off treatment prior to formal discharge.
Economic considerations	None
Quality of evidence	None
Other considerations	Following discharge patients should be advised to remain in regular (annual) contact with their primary care optometrist in the interest of COAG / OHT screening for possible future changes in their condition.

Recommendation	**In people with OHT or suspected COAG who are not recommended to receive medication, assess IOP, optic nerve head and visual field at the following intervals:** • **between 12 and 24 months if there is a low risk of conversion to COAG** • **between 6 and 12 months if there is a high risk of conversion to COAG.** **If no change in the parameters has been detected after 3–5 years (depending on perceived risk of conversion) the person should be discharged from active glaucoma care to community optometric care.**
Relative values of different outcomes	The key outcome for OHT patients and COAG suspects who are not eligible for treatment is stability of their clinical condition. A period of observation is needed to establish stability. The length of this period will vary between patients depending on individual clinical circumstances.
Trade off between clinical benefits and harms	A period of observation will provide additional information and strengthen the confidence of both patient and clinician that the decision making is based on good information and therefore appropriate to the needs of the patient.
Economic considerations	The cost-effectiveness of treatment depends on the risk factors and on the likelihood of a patient to develop visual impairment within their lifetime. Once one of these risk indicators changes, the patient management should be reviewed. Additional visits increase cost but provide additional information upon which to base management decisions.
Quality of evidence	There was no clinical or economic evidence investigating how often patients should be monitored.
Other considerations	None

5.6.3 Supporting recommendations

Recommendation	**At discharge advise people who are not recommended for treatment and whose condition is considered stable to visit their primary care optometrist annually so that any future changes in their condition can be detected.**
Trade off between clinical benefits and harms	A person not requiring treatment at a particular time may subsequently experience a deterioration of their clinical status. People who have previously been suspected of having clinical features suggestive of possible COAG might be expected to be at a higher risk of subsequent development of the condition.
Economic considerations	A prompt detection of conversion to COAG or to a status that requires treatment might decrease future treatment costs. Annual primary care eye examinations carry a modest cost and would be of value in reassuring such individuals.
Other considerations	Primary care optometrists are well placed to detect abnormalities suggestive of possible glaucoma and are equipped with suitable visual field screening machines.

5.7 Monitoring intervals for patients with COAG

5.7.1 What is the optimal frequency of monitoring visits for patients with COAG?

5.7.1.1 Clinical evidence

No studies identified

5.7.1.2 Economic evidence

There were no economic studies meeting the inclusion criteria. No original economic analysis was conducted on this question.

5.7.1.3 Patient views evidence

No studies were identified.

5.7.1.4 Evidence statements - Stereoscopic slit lamp biomicroscopy vs. other optic nerve measurement methods

Clinical No evidence was identified

Economic No evidence was identified

5.7.2 Recommendations and link to evidence

Recommendation

Monitor at regular intervals people with COAG according to their risk of progression to sight loss as illustrated in the following table:

Table: Monitoring intervals for people with COAG

Clinical assessment			Monitoring intervals (months)	
IOP at target [a]	**Progression [b]**	**Outcome [c]**	**IOP alone [d]**	**IOP, optic nerve head and visual field**
Yes	No [e]	No change in treatment plan	Not applicable	6 to 12
Yes	Yes	Review target IOP AND Change treatment plan	1 to 4	2 to 6
Yes	Uncertain	No change in treatment plan	Not applicable	2 to 6
No	No [e]	Review target IOP OR Change treatment plan	1 to 4	6 to 12
No	Yes / uncertain	Change treatment plan	1 to 2	2 to 6

[a] IOP at or below target.
For people started on treatment for the first time check IOP in 1 to 4 months after start of medication.
[b] Progression = increased optic nerve damage and/or visual field change confirmed by repeated test where clinically appropriate.
[c] For change of treatment plan refer to treatment recommendations.
[d] For people started on treatment for the first time check IOP 1 to 4 months after start of medication.
[e] No = not detected or not assessed

Relative values of different outcomes

Detection of progression is the most important outcome for COAG. Where the condition appears to be stable on current medication monitoring must continue in order to detect future disease progression should this occur. Detection of progression may be difficult and is facilitated by repeated measurements through time.

Trade off between clinical benefits and harms

Detection of progression through regular monitoring makes it possible to take timely therapeutic action in response to disease progression before further permanent visual damage occurs. Attendance for monitoring causes only minor inconvenience to patients and provides reassurance where the condition is stable.

Economic considerations

If a change in visual field or optic nerve is not detected early enough there might be long term costs associated with the disease progression following inadequate treatment; on the other hand if patients are called in too often there is increased pressure on the NHS resources.

The range given for each of the monitoring intervals reflects the variability

	of the clinical picture for individual patients. Similarly the cost-effectiveness for different intervals varies according to the risk of progression.
Quality of evidence	There was no clinical or economic evidence investigating how often patients should be monitored.
Other considerations	Failures or delays in monitoring will result in permanent visual harm to certain patients whose disease progression may go undetected. Such losses of vision may be severe and lead to significant loss of quality of life.

5.7.3 Supporting recommendations

Recommendation	**Following full recovery from surgery or laser trabeculoplasty, restart monitoring according to IOP, optic nerve head appearance and visual field.**
Trade off between clinical benefits and harms	Trabeculectomy and other glaucoma surgery may result in serious sight threatening complications. Should there be complications of surgery then they need to be identified and attended to in a timely manner to minimise harm. Post operative adjustments may be required to optimise surgical success.
Economic considerations	None
Other considerations	Patients are generally anxious following an eye operation and are reassured by clinical contact. Following full recovery from surgery COAG monitoring should re-commence according clinical circumstances.

5.8 Summary of recommendations on monitoring of patients with OHT, COAG or suspected COAG

➢ Offer Goldmann applanation tonometry (slit lamp mounted) to all people with COAG, who are suspected of having COAG or who have OHT at each monitoring assessment.

➢ Repeat CCT measurement as necessary (for example, following laser refractive surgery or at onset or progression of corneal pathology).

➢ Offer Van Herick's peripheral anterior chamber depth assessment test to all people with COAG, who are suspected of having COAG or who have OHT at each monitoring assessment.

➢ Repeat gonioscopy when clinically indicated (for example, where a previous examination has been inconclusive or where there is suspicion of a change in clinical status of the anterior chamber angle).

➢ Offer standard automated perimetry (central thresholding test) to all people who have established COAG and those suspected of having visual field defects who are being investigated for possible COAG. People with diagnosed OHT and those suspected of having COAG whose visual fields have previously been documented by standard automated perimetry as being normal may be monitored using supra-threshold perimetry. (see tables for recommended for monitoring intervals).

➢ Where a defect has previously been detected use the same visual field measurement strategy for each visual field test.

➢ Offer stereoscopic slit lamp biomicroscopic examination of the optic nerve head to all people with COAG, who are suspected of having COAG or who have OHT at monitoring assessments (see tables for recommended for monitoring intervals).

➢ When a change in optic nerve head status is detected by stereoscopic slit lamp biomicroscopic examination, obtain a new optic nerve head image for the person's records in order to provide a fresh benchmark for future assessments.

➢ When an adequate view of the optic nerve head and surrounding area is unavailable at a monitoring visit, people undergoing stereoscopic slit lamp biomicroscopy should have their pupils dilated before the assessment.

➢ Monitor at regular intervals people with OHT or suspected COAG recommended to receive medication, according to their risk of conversion to COAG as illustrated by the following table:

Table: Monitoring intervals for people with OHT or suspected COAG who are recommended to receive medication

Clinical assessment			Monitoring intervals (months)	
IOP at target [a]	**Risk of conversion to COAG [b]**	**Outcome [c]**	**IOP alone [d]**	**IOP, optic nerve head and VF**
Yes	Low	No change in treatment plan	Not applicable	12 to 24
Yes	High	No change in treatment plan	Not applicable	6 to 12
No	Low	Review target IOP OR Change treatment plan	1 to 4	6 to 12
No	High	Review target IOP OR Change treatment plan	1 to 4	4 to 6

[a] Person is treated and IOP is at or below target. If IOP cannot be adequately controlled medically, refer to consultant ophthalmologist.
[b] To be clinically judged in terms of relevant risk indicators: age, IOP, CCT, appearance and size of optic nerve head.
[c] For change of treatment plan refer to treatment recommendations.
[d] For people started on treatment for the first time check IOP 1 to 4 months after start of medication.

➢ Discuss the benefits and risks of stopping treatment with people with OHT or suspected COAG who have both:

- a low risk of ever developing visual impairment within their lifetime
- an acceptable IOP.

If a person decides to stop treatment following discussion of the perceived risks of future conversion to COAG and sight loss, offer to assess their IOP in 1 to 4 months' time with further monitoring if considered clinically necessary.

➢ In people with OHT or suspected COAG who are not recommended to receive medication, assess IOP, optic nerve head and visual field at the following intervals:

- between 12 and 24 months if there is a low risk of conversion to COAG
- between 6 and 12 months if there is a high risk of conversion to COAG.

If no change in the parameters has been detected after 3–5 years (depending on perceived risk of conversion) the person should be discharged from active glaucoma care to community optometric care.

➢ At discharge advise people who are not recommended for treatment and whose condition is considered stable to visit their primary care optometrist annually so that any future changes in their condition can be detected.

➢ Monitor at regular intervals people with COAG according to their risk of progression to sight loss as illustrated in the following table:

Table: Monitoring intervals for people with COAG

Clinical assessment			Monitoring intervals (months)	
IOP at target [a]	**Progression [b]**	**Outcome [c]**	**IOP alone [d]**	**IOP, optic nerve head and visual field**
Yes	No [e]	No change in treatment plan	Not applicable	6 to 12
Yes	Yes	Review target IOP AND Change treatment plan	1 to 4	2 to 6
Yes	Uncertain	No change in treatment plan	Not applicable	2 to 6
No	No [e]	Review target IOP OR Change treatment plan	1 to 4	6 to 12
No	Yes / uncertain	Change treatment plan	1 to 2	2 to 6

[a] IOP at or below target.
For people started on treatment for the first time check IOP in 1 to 4 months after start of medication.
[b] Progression = increased optic nerve damage and/or visual field change confirmed by repeated test where clinically appropriate.

[c] *For change of treatment plan refer to treatment recommendations.*
[d] *For people started on treatment for the first time check IOP 1 to 4 months after start of medication.*
[e] *No = not detected or not assessed*

➢ Following full recovery from surgery or laser trabeculoplasty, restart monitoring according to IOP, optic nerve head appearance and visual field.

5.9 Research recommendation on monitoring patients with OHT, COAG and suspected COAG

See APPENDIX G

The GDG recommended the following research question:

➢ ➢ What is the clinical effectiveness and cost effectiveness of using different monitoring intervals to detect disease progression in people with COAG who are at risk of progression?

Why this is important

The answer to this question is key to the recommendations on chronic disease monitoring intervals in this guideline. There is currently no identifiable evidence from randomised controlled trials (RCTs) in this area. Once diagnosed, people with COAG face lifelong treatment and monitoring. Monitoring based on risk-guided intervals would allow people who have a high risk of progression to sight loss to have more intensive monitoring and would stop people with slowly progressing disease having to attend unnecessary appointments. It would also focus resources on the people at greatest risk, making early detection of progression more likely and allowing damage to vision over time to be minimised. A randomised comparative trial of three perceived risk strata (rapid, medium, slow) for progression randomised to two, three and two alternative monitoring intervals, respectively, is suggested. The outcome would be the progression events detected..

6 Overview of treatment

6.1 Introduction

Strategies for reduction of visual damage in COAG rely on reduction of intraocular pressure (IOP). When treating individual patients the short term objective is to reduce IOP to a clinically pre-determined 'target pressure', at or below which it may be anticipated that clinically significant progression of damage will be avoided. On a longer time scale clinical observation is maintained for signs of progression of visual field defects and optic nerve head damage. Provided IOP reduction is an effective way to protect against visual and nerve damage then IOP may be regarded as a useful and conveniently measured 'surrogate outcome' for treatment success. This approach may also be extended to prevention of visual damage by treatment of elevated IOP prior to development of manifest visual damage.

For these approaches to be valid, evidence is required which firstly links use of treatment to IOP reduction (does the treatment actually reduce the pressure?) and secondly links IOP reduction to control of disease progression (does lower pressure preserve vision?).

In the context of randomised trial evidence, treated patients should in the short term have lower average IOP (surrogate outcome) and in the longer term should have better preserved visual fields and less progressive disc damage. The true outcome is thus to stop or delay progression.

The mainstream treatments for COAG remain directed towards reduction of IOP. Other approaches to treatment have however been proposed and these are considered under Complementary and Alternative Treatments in Chapter 9. Neuroprotection is one such approach to COAG management. Despite significant interest and a clinical sense that there exist non-pressure related factors influencing COAG development and progression, there is as yet insufficient hard evidence to support recommending such approaches and further developments are awaited.

The aim of this section is to identify whether treatment overall is clinically and cost effective. By pooling results to compare the effectiveness of any treatment with no treatment we can identify whether IOP lowering treatments have an effect on COAG damage. Once clinical efficacy has been established, then cost effectiveness and acceptability to patients must be considered.

6.2 Any treatment vs. no treatment

Evidence comparing treatment with no treatment and meeting the inclusion criteria is presented here. Included are the RCTs analysed in chapter 7 (treatment of OHT and COAG suspects) and chapter 8 (treatment of COAG), and three additional RCTs: the Ocular Hypertension Study comparing any medication to no treatment[72]; the Early Manifest Glaucoma Trial comparing laser trabeculoplasty plus a beta-blocker to no treatment[59]; and the Collaborative Normal-Tension Study Group comparing any treatment (medication, laser or surgery) to no treatment[25].

6.2.1 Any treatment versus no treatment

See Evidence Tables 3, 4, 9 & 24, Appendix D and Figures 1 to 3, Appendix E

6.2.1.1 Clinical evidence

Table 6-30: Any treatment vs. no treatment – Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Number of ocular hypertensive patients developing COAG (follow up 5 to 6 years)[69,99]	2	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	
Number of COAG patients showing progressive damage (follow up 4 to 5 years)[25,59]	2	RCT	Serious limitations (a,c)	Serious inconsistency (b)	No serious indirectness	
Visual field progression in patients with ocular hypertension (follow up 2 to 10 years)[42,58,69,72,76,99,131,134]	8	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Visual field progression in COAG patients (follow up 4 to 5 years)[25,59]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Mean change in IOP from baseline (follow up 1 to 6 years)[42,69,72,131,134]	5	RCT	Serious limitations (e)	Serious inconsistency (f)	No serious indirectness	

(a) *One study was open label, the other study was placebo controlled*
(b) *The two studies produce different effect sizes and there is statistical heterogeneity in the results. The open label study shows a significant result and the placebo controlled study showed a non-significant result.*
(c) *The patients were not masked to treatment in either study*
(d) *Although no statistical heterogeneity in the results, the studies include different types of IOP lowering treatments, some shown to be better than others. This may have influenced the relative risk as the confidence intervals are quite wide and the upper confidence interval is close to the line of no effect.*
(e) *Only 2 of the 5 studies were masked to treatment.*

(f) *There is statistical heterogeneity within the results with IOP reduction varying from 1.70mmHg to 4.73mmHg. This does not appear to be due to the quality of the studies, type of intervention, follow up period or condition (i.e. OHT or COAG).*
(g) *The method of randomisation is not stated for most the studies and there is no mention of allocation concealment.*
(h) *The patients were not masked to treatment in two of the studies.*
(i) *The wide confidence intervals make the estimate of effect imprecise.*

Table 6-31: Any treatment vs no treatment - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of ocular hypertensive patients developing COAG (follow up 5 to 6 years)	82/1353 (6.1%)	149/1360 (11%)	RR 0.55 (0.43 to 0.72)	49 fewer per 1000 (from 31 fewer to 63 fewer)	Low
Number of COAG patients showing progressive damage (follow up 4 to 5 years)	80/190 (42.1%)	109/205 (53.2%)	RR 0.78 (0.63 to 0.95)	117 fewer per 1000 (from 27 fewer to 197 fewer)	Low
Visual field progression in patients with ocular hypertension (follow up 2 to 10 years)	81/1726 (4.7%)	124/1730 (7.2%)	RR 0.65 (0.5 to 0.86)	25 fewer per 1000 (from 10 fewer to 36 fewer)	Moderate
Visual field progression in COAG patients (follow up 4 to 5 years)	68/190 (35.8%)	102/205 (49.8%)	RR 0.69 (0.55 to 0.86)	154 fewer per 1000 (from 70 fewer to 224 fewer)	Moderate
Mean change in IOP from baseline (follow up 1 to 6 years)	1136	1137	Not applicable	MD -3.28 (-4.5 to -2.06)	Low

6.2.1.2 Cost-effectiveness evidence

We found two economic studies[80,144] matching the inclusion criteria for this question. They were both based on the results of the Ocular Hypertension Treatment Study[50]. In addition, in the NCC-AC economic model no treatment is compared to a range of definite treatments for OHT and COAG patients separately. See Chapter 7 and 8 and Appendix F – 1.3 for methods and results.

Table 6-32: Any treatment vs no treatment - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Kymes2006[80]	Minor limitations	Partially applicable (b, c)	
Stewart2008[144]	Minor limitations (a)	Partially applicable (b, c)	

(a) *Important outcomes (e.g. blindness) were omitted*
(b) *USA study*
(c) *Only OHT patients.*

Table 6-33: Any treatment vs no treatment- Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Kymes2006[80]	4,473	0.05 QALY	£89,460/QALY	Treating patients with annual risk of developing COAG ≥5% is more cost-effective than no treatment and more cost-effective than treating patient with annual risk of developing COAG ≥2%.
Stewart2008[144]	1,566	0.03 QALY	£52,200/QALY	Any treatment is cost-effective if vertical cup to disc ratio is ≥0.7 or corneal thickness ≤493µm.

6.2.1.3 Patient views evidence

No studies were identified.

6.2.1.4 Evidence statement (s) any treatment vs. no treatment

Clinical Treatment is more effective than no treatment in reducing the number of patients with ocular hypertension converting to COAG at 5 to 6 years follow up. However, there is significant heterogeneity between the two studies. (LOW QUALITY)

Treatment is more effective than no treatment in reducing the number of patients with COAG showing progressive damage at 4 to 5 years follow up. (LOW QUALITY)

Treatment is more effective than no treatment in reducing visual field progression in patients with ocular hypertension at 2 to 10 years follow up. (MODERATE QUALITY)

Treatment is more effective than no treatment in reducing visual field progression in patients with COAG at 4 to 5 years follow up. (MODERATE QUALITY)

Treatment is more effective than no treatment in reducing IOP from baseline at 1 to 6 years follow up. (LOW QUALITY)

Economic Treating every patient with OHT is not cost-effective. Treating patients on the basis of their risk of developing COAG is cost-effective. This evidence has minor limitations and partial applicability.

6.3 Conclusions

Pooling results from a range of pharmacological and laser treatments which aim to reduce IOP in COAG illustrates that these are clinically effective in both IOP reduction and reduction of visual and optic nerve damage from COAG. Furthermore, pharmacological treatments that reduce IOP in people with elevated pressure (OHT) reduce the incidence of future development of COAG.

Although treatment for all individuals with OHT was not cost effective, it was cost effective in preventing eventual vision loss from COAG in certain higher risk OHT

subgroups. This is confirmed by the results of our economic model (see Chapter 7 and Appendix F -1.3).

The clinical and cost effectiveness of individual treatment types will be examined in more detail in the following chapters and recommendations for treatments will be discussed there.

7 Treatment of ocular hypertension and suspected chronic open angle glaucoma

7.1 Introduction

When treatment is initiated for chronic open angle glaucoma (COAG) or ocular hypertension (OHT), topical glaucoma medications are the first choice of therapy. There are five main classes of drugs: prostaglandin derivatives, beta-blockers, carbonic anhydrase inhibitors, sympathomimetics and miotics. All these medications are licensed to treat COAG by reducing intraocular pressure. Currently prostaglandin analogues and beta-blockers are licensed for first and second line use, whilst the remainder are licensed for second line use only. Before offering any glaucoma medication contra-indications, comorbidities and drug interactions should be checked.

Prostaglandin derivatives lower intraocular pressure by increasing aqueous outflow. Systemic side effects are not common but local side effects include increased pigmentation of mixed colour irides, increased pigmentation of peri-ocular skin, and increased length and thickness of the eye lashes.

Beta-blockers reduce aqueous production within the eye. There are a number of topical preparations in this class and some are available in different strengths and formulations. Systemic side effects include broncho-constriction, bradycardia and central nervous system effects such as depression, fatigue and loss of libido. This class of drug is contraindicated for patients with asthma, chronic obstructive pulmonary disease, bradycardia or heart block. In addition they should not be used with calcium channel blockers because of the risk of inducing heart block. As a general prescribing principle the lowest effective concentration should be prescribed to minimise the risk of side effects.

Carbonic anhydrase inhibitors reduce aqueous production. Although available in both topical and systemic preparations only the topical drugs were considered for the purposes of this guideline. Systemic side effects are uncommon with the topical preparations but local side effects include burning, stinging and allergy. Drainage into the nasopharynx is often associated with a transient unpleasant taste.

The most commonly used sympathomimetic drugs used are alpha$_2$-adrenergic stimulants. They decrease aqueous production, and increase aqueous drainage. Commonly reported side effects are local to the eye and include marked hyperaemia and allergy, although central nervous system effects can also be significant including drowsiness. They are not recommended in those patients taking tri-cyclic antidepressants and monoamine oxidase inhibitors.

Miotics are no longer commonly used for the treatment of open angle glaucoma and ocular hypertension mainly because of poor tolerance of side effects of these drugs. These include pupil miosis, which is often accompanied by brow ache, loss of accommodation and blurring of vision. The use of miotics is almost exclusively confined to the treatment of narrow angle or angle closure glaucoma and some secondary glaucomas. For this reason this class of drugs has been given limited consideration in this guidance.

Fixed combination eye drops contain two drugs dispensed in one bottle. All currently marketed contain Timolol 0.5% and combinations are vailable with latanoprost, travoprost and bimatoprost for once daily use and with brimonidine and dorzolamide for twice daily use. When compared to prescribing the individual monotherapies, fixed combination therapies offer a simple and convenient dosing regimen, and may result in some cost saving for patients subject to prescription charges. However, fixed combinations also remove the possibility of titrating the individual components both in terms of concentration and timing of administration, and they might not always provide the same efficacy as proper use of the individual components. Unnecessary side effects may arise as a result of the higher concentration of Timolol in all currently available fixed combinations.

The Guideline Development Group is aware that new products may come onto the market before an update of this guideline is considered. The merits of these products should be based on evidence of effectiveness and post marketing experience of patients and healthcare professionals.

7.2 Matrix of treatments considered in our clinical questions

We searched for RCT evidence comparing the effectiveness of different pharmacological interventions for the treatment of OHT with a minimum follow up of 6 months. Below is a matrix showing where evidence was identified. A box filled with **Yes** represents where evidence was found and is reviewed in this chapter. A box filled with **No** represents the situation where no evidence was found and in this case no section on this comparison appears in the chapter. A box crossed out represents where the comparison was not considered for the review.

Most studies relating to pharmacological treatment included patients with OHT and COAG. It was not possible to separate out the effect sizes for these populations. Therefore, we used the same evidence to assess the IOP lowering effects of pharmacological treatment relating to patients with OHT as we used for patients with COAG (Chapter 8).

Data is also presented on adverse events related to topical medications at the end of the section on pharmacological treatments (see section 7.4)

Beta-blockers (BB)	Yes p. 122				
Prostaglandin analogues (PGA)	Yes p. 124				
Topical Carbonic Anhydrase Inhibitors (CAI)	Yes p. 131	Yes p. 127			
Sympathomimetics (Symp)	Yes p. 133	Yes p. 128	No		
Miotics	Yes p. 135	No	No	No	

Combination (fixed or separate) (Comb)	Yes p. 141, 143, 149	Yes p. 136, 138, 145, 146	No	No	No	No	
No treatment (NT)	Yes p. 119	Yes p. 123	Yes P. 130	No.	No	No	
	BB	PGA	CAI	Symp.	Miotics	Comb	NT

7.3 Pharmacological Treatment for OHT and suspected COAG

7.3.1 Beta-blockers versus no treatment

See Evidence Table 4, Appendix D, Forest Plots in Figures 4 to 8, Appendix E and Economic Model in Appendix F – 1.3

7.3.1.1 Clinical evidence

Table 7-34: Beta-blockers vs. no treatment - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression (follow up 2-6 years)[42,58,69,76,131,134]	6	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Mean change in IOP from baseline (follow up 2-6 years)[42,69,131,134]	4	RCT	Serious limitations (a)	Serious inconsistency (d)	No serious indirectness	Serious imprecision (e)
Number of patients with uncontrolled IOP (IOP >30mmHg) (follow up 2-10 years)[42,58,69,131]	4	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Number of patients with acceptable IOP	0					
Number of patients experiencing a respiratory adverse event (follow up 5 years)[42]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Number of patients experiencing a cardiovascular adverse event (follow up 5 years)[42]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)

(a) Randomisation method is unclear in most of the studies and allocation concealment is rarely addressed.
(b) Most of the studies are old and may have used less accurate methods of diagnosing visual field progression.
(c) Too few events and/or patients to give a significant estimate of effect.
(d) Significant unexplained statistical heterogeneity within the results.

(e) *The confidence interval of the pooled results cross the line of clinical significance making the result imprecise.*

Table 7-35: Beta-blockers vs. no treatment - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Visual field progression	37/373 (9.9%)	87/370 (23.5%)	RR 0.77 (0.52 to 1.14)	54 fewer per 1000 (from 113 fewer to 33 more)	Low
Mean change in IOP from baseline	319	318	not applicable	MD -2.88 (-4.14 to -1.61)	Very low
Number of patients with uncontrolled IOP (>30mmHg)	6/348 (1.7%)	11/342 (3.2%)	RR 0.56 (0.22 to 1.46)	14 fewer per 1000 (from 25 fewer to 15 more)	Low
Number of patients experiencing a respiratory adverse event	1/53 (1.9%)	0/54 (0%)	RR 3.06 (0.13 to 73.37)	not estimable (a)	Low
Number of patients experiencing a cardiovascular adverse event	4/53 (7.5%)	0/54 (0%)	RR 9.17 (0.51 to 166.18)	not estimable (a)	Low

(a) *An absolute effect calculation is not possible as there are no events in the control arm of the study.*

7.3.1.2 Economic evidence

No studies were identified. We conducted an original economic model to compare various strategies for the first-choice treatment of OHT patients, including beta-blockers and no treatment. This was based on clinical evidence (see 7.3.1.1). See Appendix F - 1.3 for methods and results.

Table 7-36: Beta-blockers vs. no treatment - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NCC-AC model	Minor limitations	Directly applicable	

Table 7-37: Beta-blockers vs. no treatment- Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER (£/QALY)	Uncertainty
IOP >21 – 25 mmHg and CCT >590 µm				
NCC-AC model	2,582	0.012	213,504	95% CI (£/QALY): 17,713 – dominated
IOP >25 - 32 mmHg and CCT >590 µm				
NCC-AC model	2,233	0.042	52,670	95% CI (£/QALY): 2,801 – 423,141
IOP >21 – 25 mmHg and CCT 555 - 590 µm				
NCC-AC model	2,008	0.061	32,749	95% CI (£/QALY):942 – 224,519
IOP >25 - 32 mmHg and CCT 555 - 590 µm				
NCC-AC model	1,732	0.083	20,864	95% CI (£/QALY): cost saving – 138,698 If age<60 BB more cost-effective.
IOP >21 – 25 mmHg and CCT <555 µm				
NCC-AC model	1,490	0.102	14,617 (a)	95% CI (£/QALY): cost saving – 89,068 If age>65 no treatment more cost-effective. Not sensitive to the cost of preservative-free preparations.
IOP >25 - 32 mmHg and CCT <555 µm				
NCC-AC model	703	0.153	4,605 (a)	95% CI (£/QALY): cost saving – 41,225 If age>80 no treatment more cost-effective. Not sensitive to cost of preservative-free preparations.

(a) *Prostaglandin analogues are more cost-effective for this group (See Table 7-45). This comparison refers to those patients for whom prostaglandin analogues are contraindicated.*

7.3.1.3 Patient views evidence

No studies were identified.

7.3.1.4 Evidence statements - Beta-blockers vs. no treatment

Clinical There is no statistically significant difference in the number of patients with visual field progression at 2 to 6 years follow up. (LOW QUALITY)

Beta-blockers are more effective than no treatment in reducing IOP from baseline at 2 to 6 years follow up. However, there is significant unexplained statistical heterogeneity within the results. (VERY LOW QUALITY)

There is no statistically significant difference in the number of patients with an uncontrolled intraocular pressure of over 30mmHg at 2 to 10 years follow up. (LOW QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

There is no statistically significant difference in the number of patients experiencing a respiratory or cardiovascular adverse event at 5 years follow up. (LOW QUALITY)

Economic No treatment is more cost-effective than beta-blockers in OHT patients with

the following exceptions:

- for patients with IOP>25 – 32 mmHg and CCT 555 - 590 μm until the age of 60 beta-blockers are more cost-effective
- for patients with IOP>21 – 25 mmHg until the age of 65 prostaglandin analogues are more cost-effective
- for patients with IOP>25 – 32 mmHg until the age of 80 prostaglandin analogues are more cost-effective

This evidence has minor limitations and direct applicability.

7.3.2 Timolol at 0.5% concentration versus timolol at 0.25% concentration

See Evidence Tables 5 and 24, Appendix D and Forest Plot in Figure 9, Appendix E

7.3.2.1 Clinical evidence

No studies were identified directly studying this comparison. Data relating to the treatment of primary open-angle glaucoma was used as evidence for the effectiveness in patients with ocular hypertension (see Section 8.3.2).

7.3.2.2 Economic evidence

We found a cost-effectiveness study comparing two different dosages of Timolol, sympathomimetics and miotics. We report the results of the comparison between Timolol 0.5% and Timolol 0.25% in this section, while the comparison between sympathomimetics and beta-blockers and between miotics and beta-blockers are reported in other sections (7.3.9.2 and 7.3.10.2). See economic evidence table in Appendix D for details.

Table 7-38: Timolol 0.5% vs. timolol 0.25% - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Cottle1998[27]	Serious limitations (a,b)	Directly applicable	In order for the study to be applicable, Canadian costs were modified using figures from the BNF54.

(a) *Very small sample size.*
(b) *The same eye could be included in more than one group when the treatment was changed.*

Table 7-39: Timolol 0.5% vs. timolol 0.25% - Economic summary of findings

Study	*Incremental cost (£)*	*Incremental effects*	*ICER*	*Uncertainty*
Cottle1998[27]	Cost saving	More effective in terms of IOP control (a,b) and fewer severe adverse events (a)	Timolol 0.5% is dominant	NR

(a) *Not significant*
(b) *See also clinical evidence (7.3.2.1)*

7.3.2.3 Patient views evidence

No studies were identified.

7.3.2.4 Evidence statements - Timolol 0.5% vs. timolol 0.25%

Clinical There were no studies which reported the number of patients with visual field

progression.

Timolol 0.5% is more effective than Timolol 0.25% in reducing IOP in the right eye, but not in the left eye. This evidence relates to patients with primary open angle glaucoma. (LOW QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

Economic Timolol 0.5% is less costly than Timolol 0.25% and more effective at reducing IOP without causing adverse events although this is not significant. However due to the small sample size and the cross over between interventions, the findings of this study were deemed unreliable.

7.3.3 Prostaglandin analogues versus no treatment

See Economic Model in Appendix F – 1.3

7.3.3.1 Clinical evidence

No studies were identified.

7.3.3.2 Economic evidence

No studies were identified. We constructed an original model to compare various strategies for the first-choice treatment of OHT patients, including prostaglandin analogues and no treatment. This was based on the clinical evidence comparing beta-blockers to no treatment (see 7.3.1.1) and prostaglandin analogues to beta-blockers (see 7.3.4.1). See Appendix F – 1.3 for methods and results.

Table 7-40: Prostaglandin analogues vs. no treatment - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
NCC-AC model	Minor limitations	Directly applicable	

Table 7-41: Prostaglandin analogues vs. no treatment - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER (£/QALY)	Uncertainty
IOP >21 – 25 mmHg and CCT >590 µm				
NCC-AC model	3,500	0.012	296,593	95% CI (£/QALY): 32,110 – dominated
IOP >25 - 32 mmHg and CCT >590 µm				
NCC-AC model	3,062	0.051	59,805	95% CI (£/QALY): 10,141 – 665,186
IOP >21 – 25 mmHg and CCT 555 - 590 µm				
NCC-AC model	2,778	0.075	36,598	95% CI (£/QALY): 6,154 – 271,632
IOP >25 - 32 mmHg and CCT 555 - 590 µm				
NCC-AC model	2,428	0.105	23,124 (a)	95% CI (£/QALY): 3,378 – 152,848 If age <55 PGA more cost-effective.
IOP >21 – 25 mmHg and CCT <555 µm				
NCC-AC model	2,119	0.130	16,307	95% CI (£/QALY): 1,417 – 93,199 If age >65 no treatment more cost-effective.
IOP >25 - 32 mmHg and CCT <555 µm				
NCC-AC model	1,091	0.201	5,429	95% CI (£/QALY): cost saving – 39,453 If age>80 no treatment more cost-effective.

(a) *BB are more cost-effective for this group (See Table 7-45). This comparison refers to those patients for whom BB are contraindicated.*

7.3.3.3 Patient views evidence

No studies were identified.

7.3.3.4 Evidence statements - Prostaglandin analogues vs. no treatment

Clinical No studies meeting the inclusion criteria were identified which compared prostaglandin analogues to no treatment.

Economic No treatment is more cost-effective than prostaglandin analogues in OHT patients with the following exceptions

- patients with IOP>21- 25 mmHg and CCT<555 µm until the age of 65
- patients with IOP>25 – 32 mmHg and CCT<555 µm until the age of 80

7.3.4 Prostaglandin analogues versus beta-blockers

See Evidence Tables 6 and 23, Appendix D, Forest Plots in Figures 10 to 15, Appendix E and Economic Model in Appendix F – 1.3

7.3.4.1 Clinical evidence

Table 7-42: Prostaglandin analogues vs. beta-blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 to 36 months)[4,17,44,47,62,93,95,110,116,150,156,158]	12	RCT	No serious limitations	Serious inconsistency (a)	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP (follow up 6 to 12 months)[4,44,47,62,93,110,116]	7	RCT	No serious limitations	Serious inconsistency (a)	No serious indirectness	No serious imprecision
Number of patients experiencing a respiratory adverse event (follow up 6 months)[4,116]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Number of patients experiencing a cardiovascular adverse event (follow up 6 to 12 months)[4,17,110,116,158]	5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Number of patients experiencing an allergic reaction (follow up 6 months)[4,158]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Number of patients with hyperaemia (follow up 6 to 12 months)[17,44,47,62,93,95,110,116,156,158]	10	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision

(a) *Significant heterogeneity found in overall result. No specific cause for heterogeneity identified.*
(b) *The confidence intervals are wide making the estimate of harm uncertain.*

Table 7-43: Prostaglandin analogues vs. beta-blockers - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	1342	1333	not applicable	MD -1.32 (-1.79 to -0.84)	Moderate
Number of patients with an acceptable IOP	546/971 (56.2%)	376/953 (39.5%)	RR 1.54 (1.21 to 1.96)	213 more per 1000 (from 83 more to 379 more)	Moderate
Number of patients experiencing a respiratory adverse event	25/330 (7.6%)	24/233 (10.3%)	RR 0.59 (0.35 to 1)	42 fewer per 1000 (from 67 fewer to 0 more)	Moderate
Number of patients experiencing a cardiovascular adverse event	99/997 (9.9%)	90/713 (12.6%)	RR 0.87 (0.67 to 1.13)	16 fewer per 1000 (from 42 fewer to 16 more)	Moderate
Number of patients experiencing an allergic reaction	7/332 (2.1%)	3/229 (1.3%)	RR 1.25 (0.31 to 5.09)	3 more per 1000 (from 9 fewer to 53 more)	Moderate
Number of patients with hyperaemia	582/1778 (32.7%)	108/1343 (8%)	RR 3.58 (2.97 to 4.32)	206 more per 1000 (from 158 more to 266 more)	High

7.3.4.2 Economic evidence

We constructed an original model to compare various strategies for the first-choice treatment of OHT patients, including prostaglandin analogues and beta-blockers. This was based on the clinical evidence (see 7.3.4.1). See Appendix F – 1.3 for methods and results.

We also found six economic studies[10,31,48,54,125,126] comparing beta-blockers to prostaglandin analogues in a mixed population of OHT and COAG patients. Since they had more limitations and less applicability compared to other evidence available (NCC-AC economic model), they were not included in the GRADE tables. Please see economic evidence table in Appendix D for details.

Table 7-44: Prostaglandin analogues vs. beta-blockers - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NCC-AC model	Minor limitations	Directly applicable	

Table 7-45: Prostaglandin analogues vs. beta-blockers - Economic summary of findings

Study	Incremental cost (£)	Incremental effects (QALY)	ICER (£/QALY)	Uncertainty
IOP >21 – 25 mmHg and CCT >590 µm				
NCC-AC model	916	0	PGA dominated (a)	95% CI (£/QALY): 64,402 - dominated
IOP >25 - 32 mmHg and CCT >590 µm				
NCC-AC model	829	0.009	94,182 (a)	95% CI (£/QALY): 23,334 - dominated
IOP >21 – 25 mmHg and CCT 555 - 590 µm				
NCC-AC model	770	0.014	52,760 (a)	95% CI (£/QALY): 15,892 – 11,180,850
IOP >25 - 32 mmHg and CCT 555 - 590 µm				
NCC-AC model	696	0.022	31,650	95% CI (£/QALY): 11,036 – 346,902
IOP >21 – 25 mmHg and CCT <555 µm				

Study	Incremental cost (£)	Incremental effects (QALY)	ICER (£/QALY)	Uncertainty
NCC-AC model	629	0.028	22,464	95% CI (£/QALY): 7,466 – 162,175 If age <58 PGA more cost-effective.
IOP >25 - 32 mmHg and CCT <555 µm				
NCC-AC model	387	0.048	8,056	95% CI (£/QALY): 1,460 – 52,186 If age >77 BB are more cost-effective

(a) *Neither prostaglandin analogues nor beta-blockers are cost-effective for this group (see Table 7-37 and Table 7-41).*

7.3.4.3 Patient views evidence

One study reporting the results of a validated questionnaire found that patient satisfaction scores for eye appearance significantly favour beta-blockers compared to prostaglandin analogues but there is no significant difference in patient scores on convenience of use.

7.3.4.4 Evidence statements - Prostaglandin analogues vs. beta-blockers

Clinical There were no studies which reported visual field progression.

Prostaglandin analogues are more effective than beta-blockers in reducing IOP from baseline at 6 to 36 months follow up, but the effect size is too small to be clinically significant. (MODERATE QUALITY)

Prostaglandin analogues are more effective than beta-blockers in increasing the number of patients with an acceptable IOP at 6 to 12 months follow up. (MODERATE QUALITY)

Significantly more patients using beta-blockers than prostaglandin analogues experienced a respiratory adverse event at 6 months follow up. (MODERATE QUALITY)

There was no statistically significant difference in patients experiencing cardiovascular adverse events or an allergic reaction at 6 to 12 months follow up. (MODERATE QUALITY)

Significantly more patients using prostaglandin analogues than beta-blockers experienced hyperaemia at 6 to 12 months follow up. (HIGH QUALITY)

Economic Beta-blockers are more cost-effective than prostaglandin analogues in patients with IOP>21 – 25 mmHg and CCT 555 – 590 µm.

Prostaglandin analogues are more cost-effective than beta-blockers in patients with IOP>21-25 mmHg and CCT <555µm until the age of 58, and in patients with IOP>25 – 32 mmHg and CCT <555µm until the age of 77. This evidence has minor limitations and direct applicability.

7.3.5 Prostaglandin analogues versus carbonic anhydrase inhibitors

See Evidence Table 23, Appendix D

7.3.5.1 Clinical evidence

No studies were identified.

7.3.5.2 Economic evidence

No studies were identified.

7.3.5.3 Patient views evidence

One study reporting the results of a validated questionnaire found no significant differences in patient satisfaction scores for eye appearance and convenience of use for prostaglandin analogues compared to carbonic anhydrase inhibitors.

7.3.5.4 Evidence statements - Prostaglandin analogues vs. carbonic anhydrase inhibitors

Clinical No studies meeting the inclusion criteria were identified which compared prostaglandin analogues to carbonic anhydrase inhibitors.

Economic No studies meeting the inclusion criteria were identified which compared prostaglandin analogues to carbonic anhydrase inhibitors.

7.3.6 Prostaglandin analogues versus sympathomimetics

See Evidence Tables 7 and 23, Appendix D and Forest Plots in Figures 16 to 18, Appendix E

7.3.6.1 Clinical evidence

Table 7-46: Prostaglandin analogues vs. sympathomimetics - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline (6-12 months follow up)[18,70]	2	RCT	Serious limitations (a,b)	Serious inconsistency (c)	No serious indirectness	None
Number of patients with an acceptable IOP	0					
Number of patients experiencing an allergic reaction (follow up mean 6 months)[70]	1	RCT	Serious limitations (d)	No serious inconsistency	No serious indirectness	None
Number of patients with hyperaemia (follow up 6 months)[70]	1	RCT	Serious limitations (d)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) *Only one study reported method of randomisation, neither mentioned allocation concealment.*
(b) *Patients were not masked to treatment although observers were.*
(c) *Some heterogeneity in the result with one study showing a greater than 2mmHg difference in IOP reduction with prostaglandins and the other showing less than 2mmHg. This could be due to the different follow up periods (one study - 12 months, the other - 6 months).*
(d) *Method of randomisation is not reported and there is no mention of allocation concealment.*

Table 7-47: Prostaglandin analogues vs. sympathomimetics - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	337	343	not applicable	MD -2.22 (-2.91 to -1.54)	Low
Number of patients experiencing an allergic reaction	0/187 (0%)	16/188 (8.5%)	RR 0.03 (0 to 0.5)	82 fewer per 1000 (from 42 fewer to 85 fewer)	Moderate
Number of patients with hyperaemia (follow up 6 months)	11/187 (5.9%)	11/188 (5.9%)	RR 1.01 (0.45 to 2.26)	1 more per 1000 (from 32 fewer to 74 more)	Moderate

7.3.6.2 Economic Evidence

No studies were identified.

7.3.6.3 Patient views evidence

One study reporting the results of a validated questionnaire found that patient satisfaction scores for convenience of use significantly favour prostaglandin analogues compared to sympathomimetics but there is no significant difference in patient scores for eye appearance.

7.3.6.4 Evidence statements - Prostaglandin analogues vs. sympathomimetics

Clinical There were no studies which reported the number of patients with visual field progression.

Prostaglandin analogues are more effective than sympathomimetics in reducing IOP from baseline at 6 to 12 months follow up. (LOW QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

Significantly more allergic reactions were experienced by patients using sympathomimetics compared to prostaglandin analogues at 6 months mean follow up. No patient using prostaglandin analogues experienced an allergic reaction. (MODERATE QUALITY)

There was no statistically significant difference in patients with hyperaemia at 6 months (MODERATE QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared prostaglandin analogues to sympathomimetics.

7.3.7 Carbonic anhydrase inhibitors versus no treatment

See Evidence Table 8, Appendix D and Forest Plots in Figures 19 to 21, Appendix E

7.3.7.1 Clinical evidence

Table 7-48: Carbonic anhydrase inhibitors vs. no treatment - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Conversion to COAG (follow up 5 years)[99]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Visual field progression (follow up 5 years)[99]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Mean change in IOP from baseline	0 (a)					
Number of patients with an acceptable IOP	0					
Number of patients with an IOP exceeding 35mmHg (follow up 5 years)[99]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Adverse events	0					

(a) The study reports % reduction in IOP from baseline rather than absolute values.
(b) Wide confidence intervals make the estimate of effect imprecise.

Table 7-49: Carbonic anhydrase inhibitors vs. no treatment - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Conversion to COAG	46/536 (8.6%)	60/541 (11.1%)	RR 0.77 (0.54 to 1.11)	26 fewer per 1000 (from 51 fewer to 12 more)	Moderate
Visual field progression	26/536 (4.9%)	38/541 (7%)	RR 0.69 (0.43 to 1.12)	22 fewer per 1000 (from 40 fewer to 8 more)	Moderate
Number of patients with an IOP exceeding 35mmHg	1/536 (0.2%)	12/541 (2.2%)	RR 0.08 (0.01 to 0.64)	20 fewer per 1000 (from 8 fewer to 22 fewer)	High

7.3.7.2 Economic evidence

No studies were identified.

7.3.7.3 Patient views evidence

No studies were identified.

7.3.7.4 Evidence statements - Carbonic anhydrase inhibitors vs. no treatment

Clinical There is no statistically significant difference between carbonic anhydrase inhibitors and no treatment in the number of patients converting to COAG at 5 years follow up. (MODERATE QUALITY)

There is no statistically significant difference between carbonic anhydrase inhibitors and no treatment in the number of patients with visual field progression at 5 years follow up. (MODERATE QUALITY)

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

Carbonic anhydrase inhibitors are more effective than no treatment in reducing the number of patients experiencing an IOP increase to in excess of 35mmHg at 5 years follow up. (HIGH QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

There were no studies which reported adverse events.

Economic No studies meeting the inclusion criteria were identified which compared carbonic anhydrase inhibitors to no treatment.

7.3.8 Carbonic anhydrase inhibitors versus beta-blockers

See Evidence Tables 9 and 23, Appendix D and Forest Plot in Figure 22, Appendix E

7.3.8.1 Clinical evidence

Table 7-50: Carbonic anhydrase inhibitors vs. beta-blockers - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline (follow up 12-18 months)[92,145]	2	RCT	Very serious limitations (a,b,c)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP	0					
Number of patients with hyperaemia (follow up 18 months)[92]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) *Not reported how patients were randomised or if there was allocation concealment.*
(b) *Not reported whether the clinicians and observers were masked to treatment.*
(c) *Outcomes were not reported properly. One study[92] does not report the standard deviations associated with the mean reductions, nor the IOP at the end of the study.*

Table 7-51: Carbonic anhydrase inhibitors vs. beta-blockers - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	463	178	Unable to pool results (a)	not estimable (a)	Low
Number of patients with hyperaemia	4/150 (2.7%)	0/75 (0%)	RR 4.53 (0.25 to 83.05)	not estimable (b)	Low

(a) *Not enough data provided to calculate the pooled weighted mean difference. Beta-blockers were significantly better than carbonic anhydrase inhibitors in both studies. In one[92] the difference was 2mmHg (confidence intervals not available), in the other 1.3mmHg (0.38, 2.22)[145].*
(b) *An absolute effect calculation is not possible as there are no events in the control arm of the study.*

7.3.8.2 Economic evidence

No studies were identified.

7.3.8.3 Patient views evidence

One study reporting the results of a validated questionnaire found that patient satisfaction scores for eye appearance significantly favour beta-blockers compared to carbonic anhydrase inhibitors but there is no significant difference in patient scores for convenience of use.

7.3.8.4 Evidence statements - Carbonic anhydrase inhibitors vs. beta-blockers

Clinical There were no studies which reported the number of patients with visual field progression.

Carbonic anhydrase inhibitors are less effective than beta-blockers in reducing IOP from baseline at 12 to 18 months follow up, but the effect size may be too small to be clinically significant. (LOW QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

There is no statistically significant difference between carbonic anhydrase inhibitors and beta-blockers in increasing the number of patients with hyperaemia at 18 months follow up. (LOW QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared carbonic anhydrase inhibitors to beta-blockers.

7.3.9 Sympathomimetics versus beta-blockers

See Evidence Tables 10, 23 and 24, Appendix D and Forest Plots in Figures 23 to 26, Appendix E

7.3.9.1 Clinical evidence

Table 7-52: Sympathomimetics vs. beta-blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression (follow up 12 months)[83,133]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Mean change in IOP from baseline (follow up 12 months)[152]	1	RCT	Very serious limitations (c,d)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP	0					
Number of patients experiencing an allergic reaction (follow up 12 months)[133]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients experiencing fatigue/ drowsiness (follow up 12 months)[133]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) Reporting of the methods within the studies was poor and the studies were not placebo controlled.
(b) Wide confidence intervals make the estimate of effect imprecise
(c) Method of randomisation was not reported. There was no mention of allocation concealment.
(d) Neither patients nor observers were masked to treatment.

Table 7-53: Sympathomimetics vs. beta-blockers - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Visual field progression	22/357 (6.2%)	29/294 (9.9%)	RR 0.92 (0.56 to 1.52)	8 fewer per 1000 (from 44 fewer to 51 more)	Low
Mean change in IOP from baseline	22	22	not applicable	MD -0.26 (-0.65, 0.13)	Low
Number of patients experiencing an allergic reaction	20/221 (9%)	0/222 (0%)	RR 41.18 (2.18 to 676.76)	not estimable (a)	Moderate
Number of patients experiencing fatigue/ drowsiness	44/221 (19.9%)	38/222 (17.1%)	RR 1.16 (0.79 to 1.72)	27 more per 1000 (from 36 fewer to 123 more)	Moderate

(a) An absolute effect calculation is not possible as there are no events in the control arm of the study.

7.3.9.2 Economic evidence

We identified a cost-effectiveness study where sympathomimetics were compared to beta-blockers. See economic evidence table in Appendix D for details.

Table 7-54: Sympathomimetics vs. beta-blockers - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Cottle1998[27]	Serious limitations (a, b)	Directly applicable	In order for the study to be applicable, Canadian costs were modified using figures from the BNF54.

(a) Very small sample size.
(b) The same eye could be included in more than one group when the treatment was changed.

Table 7-55: Sympathomimetics vs. beta-blockers - Economic summary of findings

Study	Incremental cost (£)per patient per year	Incremental effects (a)	ICER	Uncertainty
Cottle1998[27]	£10	10% (b)	£100/patient with controlled IOP and no adverse event.	NR

(a) Additional patients whose IOP is controlled with no severe adverse events
(b) Not statistically significant

7.3.9.3 Patient views evidence

One study reporting the results of a validated questionnaire found that patient satisfaction scores for convenience of use significantly favour beta-blockers compared to sympathomimetics but there is no statistically significant difference in patient scores for eye appearance.

7.3.9.4 Evidence statements - Sympathomimetics vs. beta-blockers

Clinical There is no statistically significant difference between sympathomimetics and beta-blockers in the number of people with visual field progression at 12 months follow up. (LOW QUALITY)

There is no statistically significant difference between sympathomimetics and beta-blockers in reducing IOP from baseline at 12 months follow up.

(LOW QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

Significantly more allergic reactions were experienced by patients using sympathomimetics than beta-blockers at 12 months follow up. No patient using beta-blockers experienced an allergic reaction. (MODERATE QUALITY)

There is no statistically significant difference between sympathomimetics and beta-blockers in the number of patients experiencing fatigue or drowsiness at 12 months follow up. (MODERATE QUALITY)

Economic Sympathomimetics are more costly than beta-blockers but they are more effective at controlling IOP without causing adverse events, although this is not significant. However due to the small sample size, the cross over between interventions, and the contradiction with the clinical evidence, the findings of this study were deemed unreliable.

7.3.10 Miotics versus beta-blockers

See Evidence Tables 11 and 24, Appendix D

7.3.10.1 Clinical evidence

Table 7-56: Miotics vs. beta-blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 17 to 24 months)[36,141,157]	3	RCT	very serious (a,b)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP	0					
Adverse events	0					

(a) *Method of randomisation is not described and there is no mention of allocation concealment.*
(b) *The studies do not provide standard deviations for IOP change from baseline and although visual field testing results are reported they are not valid as miotics constrict the pupil.*

Table 7-57: Miotics vs. beta-blockers - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Mean change in IOP from baseline	102	73	not estimable (a)	not estimable (a)	Low

(a) *Unable to provide a pooled estimate. The mean change in IOP from baseline between arms is similar suggesting no difference between miotics and beta-blockers.*

7.3.10.2 Economic evidence

We found a cost-effectiveness study comparing beta-blockers, sympathomimetics and miotics. We report the results of the comparison between beta-blockers and miotics in this section, while the comparison between sympathomimetics and beta-blockers is reported in another section (7.3.9.2). See economic evidence table in Appendix D for details.

Table 7-58: Miotics vs. beta-blockers - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Cottle1998[27]	Serious limitations (a,b)	Directly applicable	In order for the study to be applicable, Canadian costs were modified using figures from the BNF54.

(a) Very small sample size.
(b) The same eye could be included in more than one group when the treatment was changed.

Table 7-59: Miotics vs. beta-blockers - Economic summary of findings

Study	*Incremental cost (£)*	*Incremental effects*	*ICER*	*Uncertainty*
Cottle1998[27]	Cost saving	More effective in terms of IOP control (a,b) but more severe adverse events (a)	Pilocarpine 1.0% is dominant	NR

(a) Not significant
(b) See also clinical evidence (7.3.2.1)

7.3.10.3 Patient views evidence

No studies were identified.

7.3.10.4 Evidence statements - Miotics vs. beta-blockers

Clinical There were no studies which reported the number of patients with visual field progression.

There is no statistically significant difference between miotics and beta-blockers in reducing IOP from baseline at 17 to 24 months follow up. (LOW QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

There were no studies which reported adverse events.

Economic Miotics are less costly than beta-blockers and more effective at reducing IOP. However they could cause more adverse events although this is not significant. However due to the small sample size and the cross over between interventions, the findings of this study were deemed unreliable.

7.3.11 Fixed combination of carbonic anhydrase inhibitors plus beta-blockers versus prostaglandin analogues

See Evidence Table 12, Appendix D and Forest Plots in Figures 27 to 32, Appendix E

7.3.11.1 Clinical evidence

Table 7-60: Fixed combination of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[115]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP	0					
Number of patients experiencing a respiratory adverse event (follow up 6 months)[115]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Number of patients with hyperaemia (follow up 6 months)[115]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) *The study does not describe the method of randomisation nor whether there was allocation concealment.*
(b) *Only assessors of IOP measurements were masked to treatment.*
(c) *The confidence intervals are broad making the effect size imprecise.*

Table 7-61: Fixed combination of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Mean change in IOP from baseline	30	35	not applicable	MD -0.30 (-1.32 to 0.72)	Moderate
Number of patients experiencing a respiratory adverse event	1/30 (3.3%)	0/35 (0%)	RR 3.48 (0.15 to 82.48)	not estimable (a)	Low
Number of patients with hyperaemia	4/30 (13.3%)	18/35 (51.4%)	RR 0.26 (0.1 to 0.68)	380 fewer per 1000 (from 164 fewer to 463 fewer)	Moderate

(a) *An absolute effect calculation is not possible as there are no events in the control arm of the study.*

7.3.11.2 Economic evidence

No studies were identified.

7.3.11.3 Patient views evidence

No studies were identified.

7.3.11.4 Evidence statements - Fixed combination of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues

Clinical There were no studies which reported the number of patients with visual field progression.

There is no statistically significant difference between a fixed combination of carbonic anhydrase inhibitors + beta-blockers and prostaglandins alone in reducing IOP from baseline at 6 months follow up. (MODERATE QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

There is no statistically significant difference between a fixed combination of carbonic anhydrase inhibitors + beta-blockers and prostaglandins alone in the number of patients experiencing a respiratory adverse event at 6 months follow up. (LOW QUALITY)

Prostaglandins result in significantly more patients with hyperaemia than a fixed combination carbonic anhydrase inhibitor + beta-blockers at 6 month follow up. (MODERATE QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared a fixed combination of carbonic anhydrase inhibitors + beta-blockers to prostaglandin analogues alone.

7.3.12 Fixed combination of prostaglandin analogues plus beta-blockers versus prostaglandin analogues

See Evidence Table 12, Appendix D and Forest Plots in Figures 27 to 32, Appendix E

7.3.12.1 Clinical evidence

Table 7-62: Fixed combination of prostaglandin analogues + beta-blockers vs. prostaglandin analogues - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[61,116]	2	RCT	Serious limitations (a,b)	serious (c)	No serious indirectness	Serious imprecision (d)
Number of patients with an acceptable IOP of <18mmHg (follow up 6 months)[61,116]	2	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Number of patients experiencing a respiratory adverse event (follow up 6 months)[116]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Number of patients experiencing a cardiovascular adverse event (follow up 6 months)[116]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Number of patients with hyperaemia (follow up 6 months)[116]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (d)

(a) *One study did not report the method of randomisation*
(b) *Allocation concealment was not reported*
(c) *There is significant unexplained statistical heterogeneity within the results. In one study the fixed combination is statistically more effective than prostaglandin analogues in reducing IOP[61], in the other there is no statistical difference and the point estimate favours prostaglandin analogues[116].*
(d) *The confidence intervals are broad making the effect size imprecise.*

Table 7-63: Fixed combination of prostaglandin analogues + beta-blockers vs. prostaglandin analogues - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	278	287	not applicable	MD -0.34 (-1.81 to 1.13)	Very low
Number of patients with an acceptable IOP of <18mmHg	93/278 (33.5%)	90/287 (31.4%)	RR 1.07 (0.84 to 1.36)	22 more per 1000 (from 50 fewer to 113 more)	Low
Number of patients experiencing a respiratory adverse event	3/140 (2.1%)	6/147 (4.1%)	RR 0.53 (0.13 to 2.06)	19 fewer per 1000 (from 36 fewer to 43 more)	Low
Number of patients experiencing a cardiovascular adverse event	5/140 (3.6%)	1/147 (0.7%)	RR 5.25 (0.62 to 44.38)	30 more per 1000 (from 3 fewer to 304 more)	Low
Number of patients with hyperaemia	4/140 (2.9%)	2/147 (1.4%)	RR 2.10 (0.39 to 11.28)	15 more per 1000 (from 9 fewer to 144 more)	Low

7.3.12.2 Economic evidence

No studies were identified.

7.3.12.3 Patient views evidence

No studies were identified.

7.3.12.4 Evidence statements - Fixed combination of prostaglandin analogues + beta-blockers vs. prostaglandin analogues

Clinical There were no studies which reported the number of patients with visual field progression.

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and prostaglandins alone in reducing IOP from baseline at 6 months follow up. (VERY LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and prostaglandins alone in the number of patients with an acceptable IOP of <18mmHg at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and prostaglandins alone in the number of patients experiencing a respiratory adverse event at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and prostaglandins alone in the number of patients experiencing a cardiovascular adverse event at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and prostaglandins alone in the number of patients experiencing hyperaemia at 6 months follow up. (LOW QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared a fixed combination of prostaglandin analogues + beta-blockers to prostaglandin analogues alone.

7.3.13 Fixed combination of prostaglandin analogues plus beta-blockers versus beta-blockers

See Evidence Table 12, Appendix D and Forest Plots in Figures 27 to 32, Appendix E

7.3.13.1 Clinical evidence

Table 7-64: Fixed combination of prostaglandin analogues + beta-blockers vs. beta-blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[61,116]	2	RCT	Serious limitations (a,b)	Serious inconsistency (c,d)	No serious indirectness	Serious imprecision (e)
Number of patients with an acceptable IOP of <18mmHg (follow up 6 months) [61,116]	2	RCT	Serious limitations (a, b)	Serious inconsistency (c)	No serious indirectness	Serious imprecision (e)
Number of patients experiencing a respiratory adverse event (follow up 6 months)[116]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Number of patients experiencing a cardiovascular adverse event (follow up 6 months)[116]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Number of patients with hyperaemia (follow up 6 months)[116]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (e)

(a) One study did not report the method of randomisation.
(b) Allocation concealment was not reported.
(c) Significant unexplained statistical heterogeneity within the results.
(d) In one study the fixed combination is statistically and clinically more effective than beta-blockers in reducing IOP[61], in the other there is no statistical difference[116]. The confidence intervals do not overlap.
(e) The confidence intervals are broad making the effect size imprecise.

Table 7-65: Fixed combination of prostaglandin analogues + beta-blockers vs. beta-blockers - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	278	289	not applicable	MD -1.75 (-4.00 to 0.51)	Very low
Number of patients with an acceptable IOP of <18mmHg	93/278 (33.5%)	48/289 (16.6%)	RR 2.03 (1.50 to 2.75)	171 more per 1000 (from 83 more to 290 more)	Very low
Number of patients experiencing a respiratory adverse event	3/140 (2.1%)	7/149 (4.7%)	RR 0.46 (0.12 to 1.73)	25 fewer per 1000 (from 41 fewer to 34 more)	Low
Number of patients experiencing a cardiovascular adverse event	5/140 (3.6%)	2/149 (1.3%)	RR 2.66 (0.52 to 13.49)	22 more per 1000 (from 6 fewer to 162 more)	Low
Number of patients with hyperaemia	4/140 (2.9%)	1/149 (0.7%)	RR 4.26 (0.48 to 37.63)	23 more per 1000 (from 4 fewer to 256 more)	Low

7.3.13.2 Economic evidence

No studies were identified.

7.3.13.3 Patient views evidence

No studies were identified.

7.3.13.4 Evidence statements - Fixed combination of prostaglandin analogues + beta-blockers vs. beta-blockers

Clinical There were no studies which reported the number of patients with visual field progression.

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and beta-blockers alone in reducing IOP from baseline at 6 months follow up. (VERY LOW QUALITY)

A fixed combination of prostaglandin analogues + beta-blockers is significantly more effective than beta-blockers alone in increasing the number of patients with an acceptable IOP of <18mmHg at 6 months follow up. (VERY LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and beta-blockers alone in the number of patients experiencing a respiratory adverse event at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and beta-blockers alone in the number of patients experiencing a cardiovascular adverse event at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and beta-blockers alone in the number of patients experiencing hyperaemia at 6

months follow up. (LOW QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared a fixed combination of prostaglandin analogues + beta-blockers to beta-blockers alone.

7.3.14 Fixed combination of sympathomimetics plus beta-blockers versus beta-blockers

See Evidence Table 12, Appendix D and Forest Plots in Figures 27 to 32, Appendix E

7.3.14.1 Clinical evidence

Table 7-66: Fixed combination of sympathomimetics + beta-blockers vs. beta-blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an acceptable IOP of <17.5mmHg (mean follow up across all visits)[135]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	(a)
Number of patients experiencing a respiratory adverse event (follow up 12 months)[135]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	None
Number of patients experiencing a cardiovascular adverse event (follow up 12 months)[135]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	None

(a) *Outcomes are not reported properly. Mean diurnal IOP pressures are not reported. Standard deviations for each mean are not reported.*

Table 7-67: Fixed combination of sympathomimetics + beta-blockers vs. beta-blockers - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an acceptable IOP <17.5mHg	202/385 (52.5%)	127/392 (32.4%)	RR 1.62 (1.36 to 1.92)	201 more per 1000 (from 117 more to 298 more)	High
Number of patients experiencing an allergic reaction	100/385 (26%)	47/392 (12%)	RR 2.17 (1.58 to 2.97)	140 more per 1000 (from 70 more to 236 more)	High
Number of patients with hyperaemia	56/385 (14.5%)	29/392 (7.4%)	RR 1.97 (1.28 to 3.01)	72 more per 1000 (from 21 more to 149 more)	High

7.3.14.2 Economic evidence

No studies were identified.

7.3.14.3 Patient views evidence

No studies were identified.

7.3.14.4 Evidence statements - Fixed combination of sympathomimetics + beta-blockers vs. beta-blockers

Clinical

There were no studies which reported the number of patients with visual field progression.

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

A fixed combination of sympathomimetics + beta-blockers is more effective than beta-blockers alone in increasing the number of patients with an acceptable IOP of <17.5mmHg at a mean follow up across all visits. (HIGH QUALITY)

A fixed combination of sympathomimetics + beta-blockers resulted in significantly more people experiencing an allergic reaction than beta-blockers alone at 12 months follow up. (HIGH QUALITY)

A fixed combination of sympathomimetics + beta-blockers resulted in significantly more patients experiencing hyperaemia than beta-blockers alone at 12 months follow up. (HIGH QUALITY)

Economic

No studies meeting the inclusion criteria were identified which compared fixed combination of sympathomimetics + beta-blockers to beta-blockers alone.

7.3.15 Separate combination of carbonic anhydrase inhibitors plus beta-blockers versus prostaglandin analogues

See Evidence Table 13, Appendix D and Forest Plots in Figures 33 to 36, Appendix E

7.3.15.1 Clinical evidence

Table 7-68: Separate combination of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[117,121]	2	RCT	Very serious limitations (a,b,c)	Serious inconsistency (d)	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP of <21mmHg (follow up 24 months)[117]	1	RCT	Very serious limitations (a,b,c)	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Adverse events	0					

(a) *Method of randomisation is not mentioned.*
(b) *Allocation concealment is not mentioned.*
(c) *Masked outcome assessment was not mentioned in one study*[117]
(d) *Serious statistical heterogeneity was observed between studies which may have been due to different dosages of CAI applied. One study*[121] *applied CAI at a dosage of 3/day rather than the recommended 2/day for use alongside a beta-blocker.*
(e) *The confidence intervals are broad making the effect size imprecise.*

Table 7-69: Separate combination of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	90	91	not applicable	MD 0.28 (-0.42 to 0.99)	Low
Number of patients with an acceptable IOP of <21mmHg	17/30 (56.7%)	37/45 (82.2%)	RR 0.69 (0.49 to 0.97)	255 fewer per 1000 (from 25 fewer to 419 fewer)	Very low

7.3.15.2 Economic evidence

No studies were identified.

7.3.15.3 Patient views evidence

No studies were identified.

7.3.15.4 Evidence statements - Separate combination of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues

Clinical There were no studies which reported the number of patients with visual field progression.

There is no statistically significant difference between a separate combination of carbonic anhydrase inhibitors + beta-blockers and prostaglandin analogues alone in reducing IOP from baseline at 6 months follow up. (LOW QUALITY)

A separate combination of carbonic anhydrase inhibitors + beta-blockers is less effective than prostaglandin analogues alone in increasing the number of patients with an acceptable IOP of <21mmHg at 24 months follow up. (VERY LOW QUALITY)

There were no studies which reported adverse events.

Economic No studies meeting the inclusion criteria were identified which compared a separate combination of carbonic anhydrase inhibitors + beta-blockers to prostaglandin analogues alone.

7.3.16 Separate combination of prostaglandin analogues plus beta-blockers versus prostaglandin analogues

See Evidence Tables 13 and 24, Appendix D and Forest Plots in Figures 33 to 36, Appendix E

7.3.16.1 Clinical evidence

Table 7-70: Separate combination of prostaglandin analogues + beta-blockers versus prostaglandin analogues - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[13,91]	2	RCT	Very serious limitations (a,b,c)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Number of patients with an acceptable IOP of approx<18 mmHg (follow up 6 months)[13]	1	RCT	Very serious limitations (b,c,e)	No serious inconsistency	No serious indirectness	None
Number of patients experiencing a respiratory adverse event (follow up 6 months)[13]	1	RCT	Very serious limitations (b,c,e)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Number of patients with hyperaemia (follow up 6 months)[13,91]	2	RCT	Very serious limitations (a,b,c)	No serious inconsistency	No serious indirectness	Serious imprecision (d)

(a) Only one study reports the method of randomisation. This study has a 90% weighting on the estimate of effect.
(b) Allocation concealment is not mentioned in either study.
(c) Only observers were masked to treatment.
(d) The confidence intervals are broad making the effect size imprecise.
(e) Method of randomisation is not reported.

Table 7-71: Separate combination of prostaglandin analogues + beta-blockers versus prostaglandin analogues - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	79	81	not applicable	MD -0.66 (-1.44 to 0.13)	Very low
Number of patients with an acceptable IOP of approx <18mmHg	30/45 (66.7%)	32/46 (69.6%)	RR 0.96 (0.72 to 1.27)	28 fewer per 1000 (from 195 fewer to 188 more)	Low
Number of patients experiencing a respiratory adverse event	1/49 (2%)	0/50 (0%)	RR 3.06 (0.13 to 73.34)	not estimable (a)	Very low
Number of patients with hyperaemia	27/79 (34.2%)	18/81 (22.2%)	RR 1.54 (0.98 to 2.44)	120 more per 1000 (from 4 fewer to 320 more)	Very low

(a) An absolute effect calculation is not possible as there are no events in the control arm of the study.

7.3.16.2 Economic evidence

We found a cost-effectiveness analysis based on a retrospective cohort study[143]. Patients who failed treatment with beta-blockers were either treated with a prostaglandin analogue in monotherapy or this was added to the beta-blocker already prescribed. Two studies based on the same cohort study reported the cost-effectiveness analysis after one year[125] and two year[126] follow-up of patients treated with either beta-blockers, prostaglandin analogues or an unfixed combination of a prostaglandin analogue plus beta-blocker. The comparison of beta-blockers with the fixed combination is reported in 7.3.17.2. See economic evidence table in Appendix D for details of the studies.

Table 7-72: Separate combination of prostaglandin analogues plus beta-blockers versus prostaglandin analogues - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Stewart2002[143]	Serious limitations (a, b, c)	Partially applicable (d, e)	
Rouland2003[125]	Serious limitations (a, b)	Partially applicable (d, f)	
Rouland2005[126]	Serious limitations (a, b)	Partially applicable (d, f)	Same study as above but different outcomes reported.

a) *Not based on RCT clinical evidence.*
b) *Short follow-up.*
c) *Small sample size*
d) *Not UK cost figures.*
e) *Patients were previously prescribed a topical beta-blocker as monotherapy.*
f) *Second-line treatment*

Table 7-73: Separate combination of prostaglandin analogues plus beta-blockers versus prostaglandin analogues - Economic summary of findings

Study	*Incremental cost (£)*	*Incremental effects*	*ICER*	*Uncertainty*
Stewart2002[143]	£221 per year	1.7mmHg mean change in IOP from baseline (a)	£130 per mmHg of mean change in IOP from baseline	NR
Rouland2003[125]	£39 per year	2.3 mmHg mean change in IOP from baseline (b)	£24 per mmHg of mean change in IOP from baseline	NR
Rouland2005[126]	£117/2years	1.1 mmHg mean change in IOP from baseline after 2 years(b)	£106 per mmHg of mean change in IOP from baseline	NR

(a) *Not statistically significant.*
(b) *Significance not reported.*

7.3.16.3 Patient views evidence

No studies were identified.

7.3.16.4 Evidence statements - Separate combination of prostaglandin analogues + beta-blockers versus prostaglandin analogues

Clinical There were no studies which reported the number of patients with visual field

progression.

There is no statistically significant difference between a separate combination of prostaglandin analogues + beta-blockers and prostaglandin analogues alone in reducing IOP from baseline at 6 months follow up. (VERY LOW QUALITY)

There is no statistically significant difference between a separate combination of prostaglandin analogues + beta-blockers and prostaglandin analogues alone in increasing the number of patients with an IOP of approx <18 mmHg at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a separate combination of prostaglandin analogues + beta-blockers and prostaglandin analogues alone in the number of patients experiencing a respiratory adverse event at 6 months follow up. (VERY LOW QUALITY)

There is no statistically significant difference between a separate combination of prostaglandin analogues + beta-blockers and prostaglandin analogues alone in the number of patients experiencing hyperaemia at 6 months follow up. (VERY LOW QUALITY)

Economic Separate combinations of prostaglandin analogues plus beta-blockers are more effective (not statistically significant) but more costly than prostaglandin analogues alone. This evidence has serious limitations and partial applicability.

7.3.17 Separate combination of prostaglandin analogues plus beta-blockers versus beta-blockers

See Evidence Table 13, Appendix D and Forest Plots in Figures 33 to 36, Appendix E

7.3.17.1 Clinical evidence

Table 7-74: Separate combinations of prostaglandin analogues + beta-blockers vs. beta-blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an acceptable IOP of approx <17mmHg (follow up 6 months) [114]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients with hyperaemia (follow up 6 months)[114]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) Outcomes not reported properly. Mean diurnal IOP pressures are not reported. Standard deviations for each mean are not reported.

(b) Only 77% of those randomised were included in the analysis..

Table 7-75: Separate combination of prostaglandin analogues + beta-blockers vs. beta-blockers - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Number of patients with an acceptable IOP of approx <17mmHg	55/114 (48.2%)	11/112 (9.8%)	RR 4.91 (2.72 to 8.88)	383 more per 1000 (from 169 more to 772 more)	High
Number of patients with hyperaemia	52/145 (35.9%)	13/145 (9%)	RR 4.00 (2.28 to 7.02)	270 more per 1000 (from 115 more to 542 more)	Moderate

7.3.17.2 Economic evidence

We found two studies based on the same cohort study reporting the cost-effectiveness analysis after one year[125] and two year[126] follow-up of patients treated with either beta-blockers, prostaglandin analogues or an unfixed combination of a prostaglandin analogue plus beta-blocker. The comparison of prostaglandin analogues with the fixed combination is reported in 7.3.16.2. See economic evidence table in Appendix D for details of the studies.

Table 7-76: Separate combination of prostaglandin analogues + beta-blockers vs. beta-blockers - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Rouland2003[125]	Serious limitations (a, b)	Partially applicable (c, d)	
Rouland2005[126]	Serious limitations (a, b)	Partially applicable (c, d)	Same study as above but different outcomes reported.

a) Not based on RCT clinical evidence.

b) Short follow-up.

c) *Not UK cost figures.*
d) *Second-line treatment*

Table 7-77: Separate combination of prostaglandin analogues + beta-blockers vs. beta-blockers - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Rouland2003[125]	£104 per year	3.2 mmHg mean change in IOP from baseline (a)	£33 per mmHg of mean change in IOP from baseline	NR
Rouland2005[126]	£230/2years	1.8 mmHg mean change in IOP from baseline after 2 years (a)	£128 per mmHg of mean change in IOP from baseline	NR

(a) *Significance not reported.*

7.3.17.3 Patient views evidence

No studies were identified.

7.3.17.4 Evidence statements - Separate combination of prostaglandin analogues + beta-blockers vs. beta-blockers

Clinical There were no studies which reported the number of patients with visual field progression.

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

A separate combination of prostaglandin analogues + beta-blockers is more effective than beta-blockers alone in increasing the number of patients who reach an IOP of approx <17mmHg at 6 months follow up. (HIGH QUALITY)

Significantly more patients using a separate combination of prostaglandin analogues + beta-blockers compared to beta-blockers alone experienced hyperaemia at 6 months follow up. (MODERATE QUALITY)

Economic Separate combinations of prostaglandin analogues plus beta-blockers are more effective (significance not reported) but more costly than beta-blockers alone. This evidence has serious limitations and partial applicability.

7.4 Adverse Events associated with pharmacological treatments

Some important adverse events were not well reported in the randomised controlled trials. This is particularly the case for beta-blockers where an association has been suggested for serious respiratory or cardiovascular adverse events[109], a change in respiratory or cardiovascular function[35,139], depression[137] or falls and syncope[46,103]. Although there is greater potential for bias with observational studies, to supplement the sparse data found from RCTs, we decided to review these studies. We reviewed evidence from comparative observational studies where patients had been using medications for a minimum of six months, the same time period used for the RCT reviews.

A summary of the evidence identified from both RCTs and observational studies are included below.

See Evidence Table 14, Appendix D

Table 7-78: Summary of adverse events evidence associated with topical medications

Adverse event	*Evidence from reviewed RCTs*	*Evidence from observational studies*
Respiratory adverse events	Some evidence in studies of beta-blockers reviewed earlier in this chapter but these are mostly too small to show an effect.	Large observational study shows evidence of increased harm with beta-blockers
Cardiovascular adverse events	Some evidence in studies of beta-blockers but these are mostly too small to show an effect.	No studies
Change in respiratory or cardiovascular function	No studies	No studies
Depression	No studies	Large observation study shows no difference between beta-blockers & other medications
Syncope and falls	No studies	No studies

7.4.1.1 Clinical evidence

Table 7-79: Adverse events associated with topical medications - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
New prescription for reversible airways obstruction (follow up 6 months)[74,75]	1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	None
New prescription for reversible airways obstruction (follow up 12 months)[74,75]	1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	None
New prescription for reversible airways obstruction AND a new Read code for asthma or COPD (follow up 6 months)[74,75]	1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	None
New prescription for reversible airways obstruction AND a new Read code for asthma or COPD (follow up 12 months)[74,75]	1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	None
Number of patients taking at least 4 prescriptions of anti-depressants	1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	None

Table 7-80: Adverse events associated with topical medications - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
New prescription for reversible airways obstruction (follow up 6 months)	49/2645 (1.9%)	55/9094 (0.6%)	HR 2.79 (1.88 to 4.15) (a)	11 more per 1000 (from 5 more to 19 more)	Low
New prescription for reversible airways obstruction (follow up 12 months)	81/2645 (3.1%)	112/9094 (1.2%)	HR 2.29 (1.71 to 3.07) (a)	15 more per 1000 (from 8 more to 24 more)	Low
New prescription for reversible airways	115/2645 (4.3%)	172/9094 (1.9%)	HR 2.18 (1.71 to 2.79) (a)	22 more per 1000 (from 13	Low

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
obstruction AND a new Read code for asthma or COPD (follow up 6 months)				more to 33 more)	
New prescription for reversible airways obstruction AND a new Read code for asthma or COPD (follow up 12 months)	191/2645 (7.2%)	354/9094 (3.9%)	HR 1.77 (1.48 to 2.12) (a)	29 more per 1000 (from 18 more to 42 more)	Low
Number of patients taking at least 4 prescriptions of antidepressants	715/5846 (12.2%)	95/752 (12.6%)	OR 0.96 (0.77 to 1.21)	5 fewer per 1000 (from 27 fewer to 23 more)	Low

(a) *Adjusted analysis used a proportional hazards model, corrected for age, sex, use of systemic beta-blockers, use of non-steroidal anti-inflammatory drugs, use of nitrates, smoking, season of presentation, and number of visits to general practitioners.*

7.4.1.2 Economic evidence

No economic studies were identified which compared the cost implications of adverse events with different treatments. The cost of asthma was included in the NCC-AC model on treatment. It was estimated as £147 per year[11]. See Appendix F – 1.3 for details.

7.4.1.3 Evidence Statements – adverse events

Clinical Significantly more patients using beta-blockers compared to those not using beta-blockers required a new prescription for reversible airways obstruction and/or a new Read code for asthma or COPD. (LOW QUALITY)

There is no statistically significant difference between beta-blockers and other medications in the number of patients who are prescribed anti-depressants. (LOW QUALITY)

Economic No economic studies were identified which compared the cost implications of adverse events with different treatments. The annual cost of asthma was estimated and used in the NCC-AC model on treatment (Appendix F).

7.5 The risk of conversion from ocular hypertension to chronic open-angle glaucoma

Several factors have been associated with increased risk of developing COAG in the general population[14,43]. These include:

- Age (risk increases with years)
- Ethnicity (increased risk in people of black Caribbean descent)
- Raised intraocular pressure
- Exfoliation in patients over the age of 65 years
- Myopia

- Diabetes
- Family history of glaucoma

Some of the RCTs included in our reviews analysed these risk factors within their study populations. One study[51] analysed the risk factors for the untreated patients with ocular hypertension in two of the trials together[72,99].

Five factors were found to be significant risk factors for the development of COAG from OHT in multivariate analyses:

- age (per decade)
- mean IOP (per mmHg)
- central corneal thickness (per 40µm thinner)
- pattern standard deviation (per 0.2dB greater)
- vertical cup-to-disc ratio (per 0.1 larger).

Age, central corneal thickness and IOP were included in the economic model. Pattern standard deviation and vertical cup-to-disc ratio were not included in the model as these parameters are related to diagnostic criteria for COAG itself.

7.6 Recommendations and link to evidence

Recommendation

Offer people with OHT or suspected COAG with high IOP treatment based on estimated risk of conversion to COAG using IOP, CCT and age as illustrated in the following table:

Table: Treatment of people with OHT or suspected COAG

CCT	More than 590 micrometres		555 to 590 micrometres		Less than 555 micrometres		Any
Untreated IOP	**>21-25 mmHg**	**>25-32 mmHg**	**>21-25 mmHg**	**>25-32 mmHg**	**>21-25 mmHg**	**>25-32 mmHg**	**>32 mmHg**
Age threshold [a]	**None**	**None**	**None**	**up to 60 years**	**up to 65 years**	**up to 80 years**	**None**
Treatment	No Treatment	No Treatment	No Treatment	BB [b]	PGA [c]	PGA [c]	PGA [c]

[a] *Treatment should not be routinely offered to people over the age threshold unless there are likely to be benefits from the treatment over an appropriate time scale. Once a person being treated for OHT reaches the age threshold for stopping treatment but has not developed COAG, healthcare professionals should discuss the option of stopping treatment.*
[b] *If beta-blockers (BB) are contraindicated offer a prostaglandin analogue (PGA)*
[c] *PGA, prostaglandin analogue*

Relative values of different outcomes

It is important that patients with significant risk of developing COAG should have treatment initiated before visual loss occurs. Patients with low risk of developing COAG should not be given unnecessary long term therapy.

Trade off between clinical benefits and harms

Both beta-blockers and prostaglandin analogues are effective at reducing intraocular pressure. The systemic side effects of beta-blockers on the respiratory and cardiovascular system may have serious consequences for the health of some patients. Pooled multivariate analyses showed age, IOP and CCT to be significant factors in risk of progression to conversion to glaucoma. Other suspected risk factors for conversion to COAG (e.g. family history, race) were not significant in the multivariate model after adjustment for age, IOP & CCT.

Economic considerations

The cost-effectiveness of treatment for OHT depends on the risk of developing COAG and on the likelihood of consequently developing visual impairment within a person's lifetime. If a patient recommended to receive a beta-blocker has contraindications to the medication then prostaglandins are the most cost-effective alternative.

Quality of evidence

Most of the clinical evidence is of low quality. The economic evidence has only minor limitations and direct applicability.

Other considerations

Patients should be counselled about their risk factors for COAG and the potential side effects of the medication to be able to make an informed choice about treatment. This guidance only considered the variation in concentration of the most commonly prescribed beta-blocker, Timolol and at the concentrations of 0.25% and 0.5%. Timolol is available in a number of different preparations (with and without preservatives, and as drops, a gel and as long acting preparations), and in a range of strengths from 0.1% to 0.5%. Although there is a lack of evidence, clinicians should consider the possibility of greater side effects from the higher concentration preparations.

Recommendation	**Do not treat people with suspected COAG and normal IOP.**
Relative values of different outcomes	These patients have a low risk of developing COAG and therefore should not be given unnecessary long term medications.
Trade off between clinical benefits and harms	The risk of developing significant visual loss in these patients is low. Patients may have side effects from medications.
Economic considerations	The overall cost of long term unnecessary treatment for all such patients in the population would be high.
Quality of evidence	Evidence is unavailable as COAG suspects with normal IOP are not included in any RCTs and any possible long term benefit of treating such individuals remains unknown. The economic evidence has minor limitations and direct applicability.
Other considerations	Where there is a high perceived risk of future visual loss it may be necessary to consider offering treatment on a case by case basis.

Recommendation	**Offer alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to people with OHT or suspected COAG and high IOP who are intolerant of the current medication.**
Relative values of different outcomes	The surrogate outcome is IOP reduction which in turn reduces the risk of future conversion to COAG in people with elevated IOP. Intolerance to one medication may require use of an alternative provided costs are broadly similar.
Trade off between clinical benefits and harms	Side effects of topical glaucoma medications may cause significant morbidity for patients. Intolerance to medications is likely to lead to poor persistence.
Economic considerations	Beta-blockers are cost-effective for patients with IOP 21-32 mmHg, CCT <555 µm who cannot be treated with PGA. PGA are cost-effective for patients with IOP 25 - 32 mmHg, CCT 555 – 590 µm who cannot be treated with BB only up to the age of 60.
Quality of evidence	There is no direct clinical evidence. The economic evidence has minor limitations and direct applicability.
Other considerations	None

Recommendation	**Offer a preservative-free preparation to people with OHT or suspected COAG who are at high risk of conversion to COAG (IOP more than 25–32 mmHg and CCT less than 555 micrometres; or IOP more than 32 mmHg) and an allergy to preservatives.**
Relative values of different outcomes	The surrogate outcome is IOP reduction which in turn reduces the risk for future conversion to COAG in people with elevated IOP. Intolerance to preservative requires the use of a preservative free preparation which alters cost effectiveness.

Trade off between clinical benefits and harms	Side effects of topical glaucoma medications may cause significant morbidity for patients. Intolerance to medications is likely to lead to poor persistence.
Economic considerations	Treatment with preservative-free preparations is cost-effective only for patients with CCT <555µm and any IOP.
Quality of evidence	There is no direct clinical evidence. The economic evidence has minor limitations and direct applicability.
Other considerations	None

7.7 Supporting recommendations

Recommendation	**Check that there are no relevant comorbidities or potential drug interactions before offering medication.**
Trade off between clinical benefits and harms	Some pharmacological treatments that are effective at lowering IOP may have serious systemic side effects, particularly worsening of chronic obstructive pulmonary disease and asthma by beta blocker eye drops. There are many potential drug interactions with beta-blockers and alpha receptor agonists. The patient's general health should not be compromised by any pharmacological treatment as alternative treatments for COAG are available.
Economic considerations	None
Other considerations	Older people are more likely to experience adverse reactions to medications

Recommendation	**Offer alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to treated patients with OHT or suspected COAG whose IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss. More than one agent may be needed concurrently to achieve target IOP.**
Trade off between clinical benefits and harms	When a first choice medication is not effective at reducing the IOP the risk of progression to COAG remains.
Economic considerations	Progression to COAG is related to IOP (see Chapter 6). Therefore it is cost-effective to offer a treatment that effectively reduces IOP.
Other considerations	Whenever there appears to be no reduction in IOP with a glaucoma medication, adherence and drop instillation technique should be checked with the patient.

Recommendation	**Refer treated patients with OHT or suspected COAG whose intraocular pressure cannot be reduced sufficiently to prevent the risk of progression to sight loss to a consultant ophthalmologist to discuss other options.**
Trade off between clinical benefits and harms	The trade off between the benefits and harms of having surgery in these patients is unclear. Therefore, the next step in the clinical pathway should be discussed between the ophthalmologist and the patient to determine on a case by case basis.
Economic considerations	None
Other considerations	None

7.8 Summary of all recommendations on treatment for patients with OHT and suspected COAG

The recommendations have been reordered to reflect the patient's pathway.

➢ Offer people with OHT or suspected COAG with high IOP treatment based on estimated risk of conversion to COAG using IOP, CCT and age as illustrated in the following table:

Table: Treatment of people with OHT or suspected COAG

CCT	More than 590 micrometres		555 to 590 micrometres		Less than 555 micrometres		Any
Untreated IOP	**>21-25 mmHg**	**>25-32 mmHg**	**>21-25 mmHg**	**>25-32 mmHg**	**>21-25 mmHg**	**>25-32 mmHg**	**>32 mmHg**
Age threshold [a]	**None**	**None**	**None**	**up to 60 years**	**up to 65 years**	**up to 80 years**	**None**
Treatment	No Treatment	No Treatment	No Treatment	BB [b]	PGA [c]	PGA [c]	PGA [c]

[a] *Treatment should not be routinely offered to people over the age threshold unless there are likely to be benefits from the treatment over an appropriate time scale. Once a person being treated for OHT reaches the age threshold for stopping treatment but has not developed COAG, healthcare professionals should discuss the option of stopping treatment.*

[b] *If beta-blockers (BB) are contraindicated offer a prostaglandin analogue (PGA)*

[c] *PGA, prostaglandin analogue*

➢ Check that there are no relevant comorbidities or potential drug interactions before offering medication.

➢ Do not treat people with suspected COAG and normal IOP.

➢ Offer alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to treated patients with OHT or suspected COAG whose IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss. More than one agent may be needed concurrently to achieve target IOP.

➢ Offer alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to people with OHT or suspected COAG and high IOP who are intolerant of the current medication.

➢ Offer a preservative-free preparation to people with OHT or suspected COAG who are at high risk of conversion to COAG (IOP more than 25–32 mmHg and CCT less than 555 micrometres; or IOP more than 32 mmHg) and an allergy to preservatives.

➢ Refer treated people with OHT or suspected COAG whose IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss to a consultant ophthalmologist to discuss other options.

8 Treatment of chronic open angle glaucoma

8.1 Introduction

In this chapter we consider the clinical and cost effectiveness of treatments for COAG. We examine various pharmacological treatments (as in the previous chapter) as well as laser treatments and surgical procedures.

Pharmacological treatment

Eye drops are the most commonly used treatment for COAG. There are five main classes of drug available as eye drops to lower intraocular pressure (IOP); prostaglandin analogues, beta-blockers (beta receptor antagonists), carbonic anhydrase inhibitors, sympathomimetics (alpha receptor agonists), and miotics (cholinergic agonists).

Tablets of the oral carbonic anhydrase inhibitor acetazolamide are only rarely used to treat COAG. For more information on specific classes of pharmacological treatment see the introduction of chapter 7.

Laser treatment

The laser treatments under consideration in this guideline are argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT).

Argon laser trabeculoplasty is an outpatient procedure. A contact lens is placed on the eye to focus an aiming beam onto the trabecular meshwork (TM) and half of the TM is treated (180 degrees) at one sitting. ALT is thought to work by activating cells called trabeculocytes and thus improving TM function. It may take up to six weeks for treatment to have the full effect and after this, if further IOP lowering is needed, the second 180 degrees of the TM is treated. Re-treatments in the same area can cause scarring of the TM and raised IOP.

Selective laser trabeculoplasty is similar to ALT but uses a different laser with a discharge of a very short duration. The spot size of the laser beam is much larger than that used for ALT so accurate identification of the TM is not as critical and the procedure is technically simpler. The mechanism of action is thought to be the same as ALT but re-treatments are said to be less likely to cause raised IOP because there is less photocoagulative damage to adjacent tissue.

Surgical treatment

The surgical treatments are classified as penetrating and non-penetrating surgery. In this guideline the penetrating surgical procedure under consideration is trabeculectomy, and the non-penetrating surgical procedures are deep sclerectomy and viscocanalostomy.

During trabeculectomy a flap of conjunctiva is dissected under the upper eyelid and a partial thickness flap of sclera is raised. A block of tissue is excised from the inner sclera exposing the iris beneath and a portion of iris is removed with the scleral flap and conjunctiva sutured back in place. Fluid from within the eye cavity filters around the edges of the scleral flap forming a fluid lake or 'bleb' under the conjunctiva below the upper eye lid from where it is absorbed by blood vessels of the sclera and conjunctiva into the bloodstream.

Deep sclerectomy is a variant of trabeculectomy. Instead of removing a piece of the iris and inner sclera, only a thin strip of inner sclera overlying Schlemm's canal is removed. Fluid from the exposed canal filters slowly around the loosely applied scleral flap and a bleb is not formed.

Viscocanalostomy is a variant of deep sclerectomy. After Schlemm's canal is deroofed it is cannulated and viscoelastic solution injected to break open the inner wall to allow easier egress of fluid from the TM into Schlemm's canal over a larger circumference than just the area beneath the scleral flap.

8.2 Matrix of treatments considered in our clinical questions

We searched for RCT evidence comparing the effectiveness of different interventions (pharmacological, laser or surgical) for the treatment of COAG with a minimum follow up of 6 months. Below is a matrix showing where evidence was identified. A box filled with **Yes** represents where evidence was found and is reviewed in this chapter. A box filled with **No** represents where no evidence was found. In this case, no section on this comparison is included in the chapter. A box crossed out represents where the comparison was not considered for review.

Most studies relating to pharmacological treatment included patients with OHT and COAG. It was not possible to separate out the effect sizes for these populations. Therefore, we used the same evidence to assess the IOP lowering effects of pharmacological treatment relating to patients with COAG as we used for patients with OHT (Chapter 7).

Data is also presented on adverse events related to topical medications at the end of the section on pharmacological treatments (see section 8.4)

BB	Yes p. 165														
PGA	Yes p. 167														
CAI	Yes p. 173	Yes p. 170													
Symp.	Yes p. 175	Yes p. 171	No												
Miotics	Yes p. 177	No	No	No											
Comb.	Yes p. 183, 185, 191	Yes p. 178, 180, 186, 188	No	No	No	No									
Any pharm.	No	No	No	No	No	No									
Any (pharm, surg or laser)	No	No	No	No	No	No	Yes p. 198								
ALT	No	No	No	No	No	No	Yes* p. 197	No							
SLT	No	Yes* p. 197	No	No	No	No	No	No	Yes p. 195						
Trab.	Yes p. 202	Yes p. 202	No	No	No	No	Yes p. 200	No	Yes p. 199	No					
N-P Surg.	No	No	No	No	No	No	No	No	No	No	Yes p. 208	Yes p. 208			
Surg + Aug.	No	No	No	No	No	No	No	No	No.	No	Yes p. 204	Yes p. 211	Yes p. 206		
Laser Irid (PDS)															
NT	Yes p. 164	Yes p. 166	Yes P. 172	No.	No	No	No.	Yes p. 113	No	No	No	No	No	No	
	BB	PGA	CAI	Symp.	Miotics	Comb.	Any pharm.	Any	ALT	SLT	Trab.	N-P Surg.	Surg + Aug.	Laser irid (PDS)	NT

BB – beta-blockers; PGA – prostaglandin analogues; CAI – topical carbonic anhydrase inhibitors; Symp – sympathomimetics; Comb. – combination of pharmacological treatments (in separate bottles or as a 'fixed' combination in one bottle); Any pharm. – any pharmacological treatment; Any – any treatment (i.e. pharmacological, laser trabeculoplasty or surgery); ALT – argon laser trabeculoplasty; SLT – selective laser trabeculoplasty; Trab – trabeculectomy; N-P Surg – non-penetrating surgery; Surg + Aug – surgery augmented with pharmacological agents; Laser Irid (PDS) – laser iridotomy (only considered for pigment dispersion syndrome); NT – no treatment (includes placebo studies).

* review includes SLT vs. PGA and ALT vs. any pharmacological treatment reported together

8.3 Pharmacological Treatment for COAG

8.3.1 Beta-blockers versus no treatment

See Evidence Table 4, Appendix D, Forest Plots in Figures 4 to 8, Appendix E and Economic Model in Appendix F – 1.3

8.3.1.1 Clinical evidence

No studies were identified directly studying this comparison. Data relating to the treatment of OHT was used as evidence for the effectiveness in chronic open angle glaucoma (see Section 7.3.1). The data should be considered with caution for patients with normal tension glaucoma as they have a different baseline intraocular pressure to patients with ocular hypertension.

8.3.1.2 Economic evidence

No studies were identified. We conducted original modelling to compare various strategies for the first-choice treatment of COAG patients, including beta-blockers and no treatment. This was based on clinical evidence (see 8.3.1.1). See Appendix F – 1.3 for methods and results.

Table 8-81: Beta-blockers vs. no treatment - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
NCC-AC model	Minor limitations (a)	Directly applicable	

(a) Based on clinical evidence which has serious limitations (see 8.3.1.1)

Table 8-82: Beta-blockers vs. no treatment- Economic summary of findings

Study	*Incremental cost (£)*	*Incremental effects*	*ICER (£/QALY)*	*Uncertainty*
NCC-AC model	cost saving	0.079 QALY	cost saving (a)	95% CI: cost saving – £9,461/QALY Not sensitive to the cost of preservative-free preparations. Not sensitive to the stage of COAG.

a) *Prostaglandin analogues are more cost-effective for this group (see Table 8-92). This comparison refers to those patients for whom Prostaglandin analogues are contraindicated.*

8.3.1.3 Patient views evidence

No studies were identified.

8.3.1.4 Evidence statements on beta-blockers vs. no treatment

Clinical There is no statistically significant difference in the number of patients with visual field progression at 2 to 6 years follow up. (LOW QUALITY)

Beta-blockers are more effective than no treatment in reducing IOP from baseline at 2 to 6 years follow up. However, there is significant unexplained statistical heterogeneity within the results. This evidence relates to patients with ocular hypertension. (VERY LOW QUALITY)

There is no statistically significant difference in the number of patients with

an uncontrolled intraocular pressure of over 30mmHg at 2 to 10 years follow up. This evidence relates to patients with ocular hypertension. (LOW QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

There is no statistically significant difference in the number of patients experiencing a respiratory or cardiovascular adverse event at 5 years follow up. (LOW QUALITY)

Economic Beta-blockers are more cost-effective than no treatment for any stage of COAG. This evidence has minor limitations and direct applicability.

8.3.2 Timolol at 0.5% concentration versus timolol at 0.25% concentration

See Evidence Tables 5 and 24, Appendix D and Forest Plot in Figure 9, Appendix E

8.3.2.1 Clinical evidence

Table 8-83: Timolol 0.5% vs. timolol 0.25% - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 12 months)[101]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
No. of patients with an acceptable IOP	0					
Adverse events	0					

(a) Method of randomisation is not reported.
(b) Not clear who was masked to treatment.
(c) There were too few patients in the study to show a clear estimate of effect.

Table 8-84: Timolol 0.5% vs. timolol 0.25% - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Mean change in IOP from baseline (right eye)	15	15	not applicable	MD -2.10 (-3.82 to -0.38)	Low
Mean change in IOP from baseline (left eye)	15	15	not applicable	MD -0.90 (-3.01 to 1.21)	Low

8.3.2.2 Economic evidence

We found a cost-effectiveness study comparing two different concentrations of Timolol and sympathomimetics. We report the results of the comparison between Timolol 0.5% and Timolol 0.25% in this section, while the comparison between sympathomimetics and beta-blockers is reported in another section (8.3.9.2). See economic evidence table in Appendix D for details.

Table 8-85: Timolol 0.5% vs. timolol 0.25% - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Cottle1988[27]	Serious (a,b)	Directly applicable	In order for the study to be applicable, Canadian costs were modified using figures from the BNF54.

(a) *Very small sample size.*
(b) *The same eye could be included in more than one group when the treatment was change.*

Table 8-86: Timolol 0.5% vs. timolol 0.25% - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Cottle1988[27]	Cost saving	More effective in terms of IOP control (a, b) and fewer severe adverse events (a)	Timolol 0.5% is dominant	NR

(a) *Not statistically significant.*
(b) *See also clinical evidence (Table 8-84).*

8.3.2.3 Patient views evidence

No studies were identified.

8.3.2.4 Evidence statements - Timolol 0.5% vs. timolol 0.25%

Clinical There were no studies which reported the number of patients with visual field progression.

The effectiveness of Timolol 0.5% and 0.25% at reducing IOP from baseline are similar when assessed at 12 months follow-up (results for right and left eyes inconsistent but confidence intervals overlap. There is a weak suggestion of a greater effect with the higher concentration) (LOW QUALITY).

There were no studies which reported the number of patients with an acceptable IOP.

There were no studies which reported adverse events.

Economic Timolol 0.5% is less costly than Timolol 0.25% and more effective at reducing IOP without causing adverse events although this is not significant. This evidence has direct applicability but severe limitations due to the small sample size and the cross over between interventions.

8.3.3 Prostaglandin analogues versus no treatment

See Economic Model in Appendix F – 1.3

8.3.3.1 Clinical evidence

No studies were identified.

8.3.3.2 Economic evidence

No studies were identified. We constructed an original model to compare various strategies for the first-choice treatment of COAG patients, including prostaglandin analogues and no treatment. This was based on the clinical evidence comparing beta-

blockers to no treatment (see 8.3.1.1) and prostaglandin analogues to beta-blockers (see 8.3.4.1). See Appendix F – 1.3 for methods and results.

Table 8-87: Prostaglandin analogues vs. no treatment - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NCC-AC model	Minor limitations (a)	Directly applicable	

(a) *Partially based on clinical evidence which has serious limitations (see 8.3.1.1)*

Table 8-88: Prostaglandin analogues vs. no treatment - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER (£/QALY)	Uncertainty
NCC-AC model	cost saving	0.110 QALY	cost saving	95% CI (£/QALY): cost saving – 13,836. Not sensitive to the stage of COAG.

8.3.3.3 Patient views evidence

No studies were identified.

8.3.3.4 Evidence statements - Prostaglandin analogues vs. no treatment

Clinical No studies meeting the inclusion criteria were identified which compared prostaglandin analogues to no treatment.

Economic Prostaglandin analogues are more cost-effective than no treatment for any stage of COAG. This evidence has minor limitations and direct applicability.

8.3.4 Prostaglandin analogues versus beta-blockers

See Evidence Tables 6 and 23, Appendix D, Forest Plots in Figures 10 to 15, Appendix E and Economic Model in Appendix F – 1.3

8.3.4.1 Clinical evidence

Table 8-89: Prostaglandin analogues vs. beta-blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 to 36 months)[4,17,44,47,62,93,95,110,116,150,156,158]	12	RCT	No serious limitations	Serious inconsistency (a)	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP (follow up 6 to 12 months)[4,44,47,62,93,110,116]	7	RCT	No serious limitations	Serious inconsistency (a)	No serious indirectness	No serious imprecision
Number of patients experiencing a respiratory adverse event (follow up 6 months)[4,116]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Number of patients experiencing a cardiovascular adverse event (follow up 6 to 12 months)[4,17,110,116,158]	5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Number of patients experiencing an allergic reaction (follow up 6 months)[4,158]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Number of patients with hyperaemia (follow up 6 to 12 months)[17,44,47,62,93,95,110,116,156,158]	10	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision

(c) Significant heterogeneity found in overall result. No specific cause for heterogeneity identified.
(d) The confidence intervals are wide making the estimate of harm uncertain.

Table 8-90: Prostaglandin analogues vs. beta-blockers - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	1342	1333	not applicable	MD -1.32 (-1.79 to -0.84)	Moderate
Number of patients with an acceptable IOP	546/971 (56.2%)	376/953 (39.5%)	RR 1.54 (1.21 to 1.96)	213 more per 1000 (from 83 more to 379 more)	Moderate
Number of patients experiencing a respiratory adverse event	25/330 (7.6%)	24/233 (10.3%)	RR 0.59 (0.35 to 1)	42 fewer per 1000 (from 67 fewer to 0 more)	Moderate
Number of patients experiencing a cardiovascular adverse event	99/997 (9.9%)	90/713 (12.6%)	RR 0.87 (0.67 to 1.13)	16 fewer per 1000 (from 42 fewer to 16 more)	Moderate
Number of patients experiencing an allergic reaction	7/332 (2.1%)	3/229 (1.3%)	RR 1.25 (0.31 to 5.09)	3 more per 1000 (from 9 fewer to 53 more)	Moderate
Number of patients with hyperaemia	582/1778 (32.7%)	108/1343 (8%)	RR 3.58 (2.97 to 4.32)	206 more per 1000 (from 158 more to 266 more)	High

8.3.4.2 Economic evidence

We found a cost-utility analysis[82] comparing prostaglandin analogues to beta-blockers in a Markov Model. See economic evidence table in Appendix D for details.

We also found six economic studies[10,31,48,54,125,126] comparing beta-blockers to prostaglandin analogues in a mixed population of OHT and COAG patients. Since they had more limitations and less applicability compared to other evidence available (Le Pen et al (2005)[82] and NCC-AC economic model), they were not included in the GRADE tables. However, a description is reported in the economic evidence table in Appendix D.

We constructed an original model to compare various strategies for the first-choice treatment of COAG patients, including prostaglandin analogues and beta-blockers. This was based on the clinical evidence comparing prostaglandin analogues to beta-blockers (see 8.3.4.1). See Appendix F – 1.3 for methods and results.

Table 8-91: Prostaglandin analogues vs. beta-blockers - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Le Pen 2005	Serious limitations (a, b, c)	Partially applicable (d)	
NCC-AC model	Minor limitations	Directly applicable	

a) *Limited time horizon (5 years).*
b) *Clinical outcomes were not derived from a systematic search.*
c) *Possible underestimation in the utilisation of ophthalmologic resources.*
d) *Patients had advanced COAG. Discount of costs was 5%*

Table 8-92: Prostaglandin analogues vs. beta-blockers - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Le Pen 2005	203	0.021 QALY	£6,767/QALY	PSA = 98.8%
NCC-AC model	96	0.031 QALY	£3,100/QALY	95% CI (£/QALY): cost saving – 23,258 Not sensitive to the stage of COAG.

8.3.4.3 Patient views evidence

One study reporting the results of a validated questionnaire found that patient satisfaction scores for eye appearance are significantly more favourable for beta-blockers compared to prostaglandin analogues but there is no statistically significant difference in patient scores for convenience of use.

8.3.4.4 Evidence statements on prostaglandin analogues vs. beta-blockers

Clinical There were no studies which reported visual field progression.

Prostaglandin analogues are more effective than beta-blockers in reducing IOP from baseline at 6 to 36 months follow up, but the effect size is too small to be clinically effective. (MODERATE QUALITY)

Prostaglandin analogues are more effective than beta-blockers in increasing the number of patients with an acceptable IOP at 6 to 12 months follow up. (MODERATE QUALITY)

Significantly more patients using beta-blockers than prostaglandin analogues experienced a respiratory adverse event at 6 months follow up. (MODERATE QUALITY)

There was no statistically significant difference in patients experiencing cardiovascular adverse events or an allergic reaction at 6 to 12 months follow up. (MODERATE QUALITY)

Significantly more patients using prostaglandin analogues than beta-blockers experienced hyperaemia at 6 to 12 months follow up. (HIGH QUALITY)

Economic Prostaglandin analogues are more cost-effective than beta-blockers for any stage of COAG. This evidence has minor limitations and direct applicability.

8.3.5 Prostaglandin analogues versus carbonic anhydrase inhibitors

See Evidence Table 23, Appendix D

8.3.5.1 Clinical evidence

No studies were identified.

8.3.5.2 Economic evidence

No studies were identified.

8.3.5.3 Patient views evidence

One study reporting the results of a validated questionnaire found no statistically significant differences between patient satisfaction scores for eye appearance and convenience of use for prostaglandin analogues compared to carbonic anhydrase inhibitors.

8.3.5.4 Evidence statements on prostaglandin analogues vs. carbonic anhydrase inhibitors

Clinical No studies meeting the inclusion criteria were identified which compared prostaglandin analogues to carbonic anhydrase inhibitors.

Economic No studies meeting the inclusion criteria were identified which compared prostaglandin analogues to carbonic anhydrase inhibitors.

8.3.6 Prostaglandin analogues versus sympathomimetics

See Evidence Tables 7 and 23, Appendix D and Forest Plots in Figures 16 to 18, Appendix E

8.3.6.1 Clinical evidence

Table 8-93: Prostaglandin analogues vs. sympathomimetics - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (6 to 12 months follow up)[18,70]	2	RCT	Serious limitations (a,b)	Serious inconsistency (c)	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP	0					
Number of patients experiencing an allergic reaction (follow up mean 6 months)[70]	1	RCT	Serious limitations (d)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients with hyperaemia (follow up 6 months)[70]	1	RCT	Serious limitations (d)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) Only one study reported method of randomisation, neither mentioned allocation concealment.
(b) Patients were not masked to treatment although observers were.
(c) Some heterogeneity in the result with one study showing a greater than 2mmHg difference in mean change in IOP from baseline with prostaglandins and the other showing less than 2mmHg. This could be due to the different follow up periods (one study - 12 months, the other - 6 months).
(d) Method of randomisation is not reported and there is no mention of allocation concealment.

Table 8-94: Prostaglandin analogues vs. sympathomimetics - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	337	343	not applicable	MD -2.22 (-2.91 to -1.54)	Low
Number of patients experiencing an allergic reaction	0/187 (0%)	16/188 (8.5%)	RR 0.03 (0 to 0.5)	82 fewer per 1000 (from 42 fewer to 85 fewer)	Moderate
Number of patients with hyperaemia (follow up 6 months)	11/187 (5.9%)	11/188 (5.9%)	RR 1.01 (0.45 to 2.26)	1 more per 1000 (from 32 fewer to 74 more)	Moderate

8.3.6.2 Economic evidence

No studies were identified.

8.3.6.3 Patient views evidence

One study reporting the results of a validated questionnaire found that patient satisfaction scores for convenience of use significantly favour prostaglandin analogues compared to sympathomimetics but there is no statistically significant difference in patient scores for eye appearance.

8.3.6.4 Evidence statements on prostaglandin analogues vs. sympathomimetics

Clinical There were no studies which reported the number of patients with visual field progression.

Prostaglandin analogues are more effective than sympathomimetics in reducing IOP from baseline at 6 to 12 months follow up. (LOW QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

Significantly more allergic reactions were experienced by patients using sympathomimetics compared to prostaglandin analogues at 6 months mean follow up. No patient using prostaglandin analogues experienced an allergic reaction. (MODERATE QUALITY)

There was no statistically significant difference in patients with hyperaemia at 6 months (MODERATE QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared prostaglandin analogues to sympathomimetics.

8.3.7 Carbonic anhydrase inhibitors versus no treatment

See Evidence Table 8, Appendix D and Forest Plots in Figures 19 to 21, Appendix E

8.3.7.1 Clinical evidence

No studies were identified that directly studied this comparison. Data relating to the treatment of OHT was used as evidence for the effectiveness in chronic open angle glaucoma (see Section 7.3.7). The data should be considered with caution for patients with normal tension glaucoma as they have a different baseline intraocular pressure to patients with ocular hypertension.

8.3.7.2 Economic evidence

No studies were identified.

8.3.7.3 Patient views evidence

No studies were identified.

8.3.7.4 Evidence statements on carbonic anhydrase inhibitors vs. no treatment

Clinical There is no statistically significant difference between carbonic anhydrase inhibitors and no treatment in the number of patients converting to COAG at 5 years follow up. (MODERATE QUALITY)

There is no statistically significant difference between carbonic anhydrase inhibitors and no treatment in the number of patients with visual field progression at 5 years follow up. (MODERATE QUALITY)

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

Carbonic anhydrase inhibitors are more effective than no treatment in reducing the number of patients experiencing an IOP increase to in excess of 35mmHg at 5 years follow up. (HIGH QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

There were no studies which reported adverse events.

Economic No studies meeting the inclusion criteria were identified which compared carbonic anhydrase inhibitors to no treatment.

8.3.8 Carbonic anhydrase inhibitors versus beta-blockers

See Evidence Tables 9 and 23, Appendix D and Forest Plot in Figure 22, Appendix E

8.3.8.1 Clinical evidence

Table 8-95: Carbonic anhydrase inhibitors vs. beta-blockers - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline (follow up 12-18 months)[92,145]	2	RCT	Very serious limitations (a,b,c)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP	0					
Number of patients with hyperaemia (follow up 18 months)[92]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) *Not reported how patients were randomised or if there was allocation concealment.*
(b) *Not reported whether the clinicians and observers were masked to treatment.*
(c) *Outcomes not reported properly. One study[92] does not report the standard deviations associated with the mean reductions, nor the IOP at the end of the study.*

Table 8-96: Carbonic anhydrase inhibitors vs. beta-blockers - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	463	178	Unable to pool results (a)	not estimable (a)	Low
Number of patients with hyperaemia	4/150 (2.7%)	0/75 (0%)	RR 4.53 (0.25 to 83.05)	not estimable (b)	Low

(a) *Not enough data provided to calculate the pooled weighted mean difference. Beta-blockers were significantly better than carbonic anhydrase inhibitors in both studies. In one[92] the difference was 2mmHg (confidence intervals not available), in the other 1.3mmHg (0.38, 2.22)[145].*
(b) *An absolute effect calculation is not possible as there are no events in the control arm of the study.*

8.3.8.2 Economic evidence

No studies were identified.

8.3.8.3 Patient views evidence

One study reporting the results of a validated questionnaire found that patient satisfaction scores for eye appearance significantly favour beta-blockers compared to carbonic anhydrase inhibitors but there is no statistically significant difference in patient scores for convenience of use.

8.3.8.4 Evidence statements - Carbonic anhydrase inhibitors vs. beta-blockers

Clinical There were no studies which reported the number of patients with visual field progression.

Carbonic anhydrase inhibitors are less effective than beta-blockers in reducing IOP from baseline at 12 to 18 months follow up, but the effect size maybe too small to be clinically significant. (LOW QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

There is no statistically significant difference between carbonic anhydrase inhibitors and beta-blockers in the number of patients experiencing hyperaemia at 18 months follow up. (LOW QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared carbonic anhydrase inhibitors to beta-blockers.

8.3.9 Sympathomimetics versus beta-blockers

See Evidence Tables 10, 23 and 24, Appendix D and Forest Plots in Figures 23 to 26, Appendix E

8.3.9.1 Clinical evidence

Table 8-97: Sympathomimetics vs. beta-blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression (follow up 12 months)[83,133]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Mean change in IOP from baseline (follow up 12 months)[152]	1	RCT	Very serious limitations (c,d)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP	0					
Number of patients experiencing an allergic reaction (follow up 12 months)[133]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients experiencing fatigue/ drowsiness (follow up 12 months)[133]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) The reporting of the methods within the studies was poor and the studies were not placebo controlled.
(b) The wide confidence intervals make the estimate of effect imprecise
(c) The method of randomisation was not reported. There was no mention of allocation concealment.
(d) Neither patients nor observers were masked to treatment.

Table 8-98: Sympathomimetics vs. beta-blockers - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Visual field progression	22/357 (6.2%)	29/294 (9.9%)	RR 0.92 (0.56 to 1.52)	8 fewer per 1000 (from 44 fewer to 51 more)	Low
Mean change in IOP from baseline	22	22	not applicable	MD -0.26 (-0.65, 0.13)	Low
Number of patients experiencing an allergic reaction	20/221 (9%)	0/222 (0%)	RR 41.18 (2.18 to 676.76)	not estimable (a)	Moderate
Number of patients experiencing fatigue/ drowsiness	44/221 (19.9%)	38/222 (17.1%)	RR 1.16 (0.79 to 1.72)	27 more per 1000 (from 36 fewer to 123 more)	Moderate

(a) An absolute effect calculation is not possible as there are no events in the control arm of the study.

8.3.9.2 Economic evidence

We identified a cost-effectiveness study where sympathomimetics were compared to beta-blockers. See economic evidence table in Appendix D for details.

Table 8-99: Sympathomimetics vs. beta-blockers - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Cottle1998[27]	Serious limitations (a, b)	Directly applicable	In order for the study to be applicable, Canadian costs were modified using figures from the BNF.

a) Very small sample size.
b) The same eye could be included in more than one group when the treatment was change.

Table 8-100: Sympathomimetics vs. beta-blockers - Economic summary of findings

Study	Incremental cost (£)per patient per year	Incremental effects (a)	ICER	Uncertainty
Cottle1998[27]	£10	10% (b)	£100/patient with controlled IOP and no adverse event.	NR

a) Additional patients whose IOP is controlled with no severe adverse events
b) Not statistically significant

8.3.9.3 Patient views evidence

One study reporting the results of a validated questionnaire found that patient satisfaction scores for convenience of use significantly favour beta-blockers compared to sympathomimetics but there is no statistically significant difference in patient scores for eye appearance.

8.3.9.4 Evidence statements - Sympathomimetics vs. beta-blockers

Clinical There is no statistically significant difference between sympathomimetics and beta-blockers in the number of people with visual field progression at 12 months follow up. (LOW QUALITY)

There is no statistically significant difference between sympathomimetics and beta-blockers in reducing IOP from baseline at 12 months follow up. (LOW QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

Significantly more allergic reactions were experienced by patients using sympathomimetics than beta-blockers at 12 months follow up. No patient using beta-blockers experienced an allergic reaction. (MODERATE QUALITY)

There is no statistically significant difference between sympathomimetics and beta-blockers in the number of patients experiencing fatigue or drowsiness at 12 months follow up. (MODERATE QUALITY)

Economic Sympathomimetics are more costly than beta-blockers but more effective at controlling IOP without causing adverse events, although this is not significant. However due to the small sample size, the cross over between interventions, and the contradiction with the clinical evidence, the findings of this study were deemed unreliable.

8.3.10 Miotics versus beta-blockers

See Evidence Table 11, Appendix D

8.3.10.1 Clinical evidence

Table 8-101: Miotics vs. beta-blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 17 to 24 months)[36,141,157]	3	RCT	Very serious limitations (a,b,c)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP	0					
Adverse events	0					

(a) *Method of randomisation is not described and there is no mention of allocation concealment.*
(b) *The studies do not provide standard deviations for IOP change from baseline and although visual field testing results are reported they are not valid as miotics constrict the pupil..*
(c) *One study*[141] *was very old.*

Table 8-102: Miotics vs. beta-blockers - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Mean change in IOP from baseline	102	73	not estimable (a)	not estimable (a)	Low

(a) *Unable to provide a pooled estimate. The mean change in IOP from baseline between arms is similar suggesting no difference between miotics and beta-blockers.*

8.3.10.2 Economic evidence

We found a cost-effectiveness study comparing beta-blockers, sympathomimetics and miotics. We report the results of the comparison between beta-blockers and miotics in this section, while the comparison between sympathomimetics and beta-blockers is reported in another section (8.3.9.2). See economic evidence table in Appendix D for details.

Table 8-103: Miotics vs. beta-blockers - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Cottle1998[27]	Serious limitations (a,b)	Directly applicable	In order for the study to be applicable, Canadian costs were modified using figures from the BNF54.

(a) Very small sample size.
(b) The same eye could be included in more than one group when the treatment was changed.

Table 8-104: Miotics vs. beta-blockers - Economic summary of findings

Study	*Incremental cost (£)*	*Incremental effects*	*ICER*	*Uncertainty*
Cottle1998[27]	Cost saving	More effective in terms of IOP control (a,b) but more severe adverse events (a)	Pilocarpine 1.0% is dominant	NR

(a) Not significant
(b) See also clinical evidence (7.3.2.1)

8.3.10.3 Patient views evidence

No studies were identified.

8.3.10.4 Evidence statements - Miotics vs. beta-blockers

Clinical There were no studies which reported the number of patients with visual field progression.

There is no statistically significant difference between miotics and beta-blockers in reducing IOP from baseline at 17 to 24 months follow up. (LOW QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

There were no studies which reported adverse events.

Economic Miotics are less costly than beta-blockers and more effective at reducing IOP. However they could cause more adverse events although this finding is not statistically significant. Due to the small sample size and the cross over between interventions, the findings of this study were deemed unreliable.

8.3.11 Fixed combination of carbonic anhydrase inhibitors plus beta-blockers versus prostaglandin analogues

See Evidence Table 12, Appendix D and Forest Plots in Figures 27 to 32, Appendix E

8.3.11.1 Clinical evidence

Table 8-105: Fixed combination of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[115]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients with an acceptable IOP	0					
Number of patients experiencing a respiratory adverse event (follow up 6 months)[115]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Number of patients with hyperaemia (follow up 6 months)[115]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) *The study does not describe the method of randomisation nor whether there was allocation concealment.*
(b) *Only assessors of IOP measurements were masked to treatment.*
(c) *The confidence intervals are broad making the effect size imprecise.*

Table 8-106: Fixed combination of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	30	35	not applicable	MD -0.30 (-1.32 to 0.72)	Moderate
Number of patients experiencing a respiratory adverse event	1/30 (3.3%)	0/35 (0%)	RR 3.48 (0.15 to 82.48)	not estimable (a)	Low
Number of patients with hyperaemia	4/30 (13.3%)	18/35 (51.4%)	RR 0.26 (0.1 to 0.68)	380 fewer per 1000 (from 164 fewer to 463 fewer)	Moderate

(a) *An absolute effect calculation is not possible as there are no events in the control arm of the study.*

8.3.11.2 Economic evidence

No studies were identified.

8.3.11.3 Patient views evidence

No studies were identified.

8.3.11.4 Evidence statements - Fixed combinations of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues

Clinical There were no studies which reported the number of patients with visual field progression.

There is no statistically significant difference between a fixed combination of carbonic anhydrase inhibitors + beta-blockers and prostaglandins alone in reducing IOP from baseline at 6 months follow up. (MODERATE QUALITY)

There were no studies which reported the number of patients with an acceptable IOP.

There is no statistically significant difference between a fixed combination of carbonic anhydrase inhibitors + beta-blockers and prostaglandins alone in the number of patients experiencing a respiratory adverse event at 6 months follow up. (LOW QUALITY)

Prostaglandins result in significantly more patients with hyperaemia than a fixed combination carbonic anhydrase inhibitor + beta-blockers at 6 month follow up. (MODERATE QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared fixed combinations of carbonic anhydrase inhibitors + beta-blockers to prostaglandin analogues alone.

8.3.12 Fixed combination of prostaglandin analogues plus beta-blockers versus prostaglandin analogues

See Evidence Table 12, Appendix D and Forest Plots in Figures 27 to 32, Appendix E

8.3.12.1 Clinical evidence

Table 8-107: Fixed combination of prostaglandin analogues + beta-blockers vs. prostaglandin analogues - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[61,116]	2	RCT	Serious limitations (a,b)	serious (c)	No serious indirectness	Serious imprecision (d)
Number of patients with an acceptable IOP of <18mmHg (follow up 6 months)[61,116]	2	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Number of patients experiencing a respiratory adverse event (follow up 6 months)[116]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Number of patients experiencing a cardiovascular adverse event (follow up 6 months)[116]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Number of patients with hyperaemia (follow up 6 months)[116]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	Serious imprecision (d)

(a) *One study did not report the method of randomisation*
(b) *Allocation concealment was not reported*
(c) *There is significant unexplained statistical heterogeneity within the results. In one study the fixed combination is statistically more effective than prostaglandin analogues in reducing IOP[HIGGINBOTHAM2002A}, in the other there is no statistical difference and the point estimate favours prostaglandin analogues[116].*
(d) *The confidence intervals are broad making the effect size imprecise.*

Table 8-108: Fixed combination of prostaglandin analogues + beta-blockers vs. prostaglandin analogues - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	278	287	not applicable	MD -0.34 (-1.81 to 1.13)	Very low
Number of patients with an acceptable IOP of <18mmHg	93/278 (33.5%)	90/287 (31.4%)	RR 1.07 (0.84 to 1.36)	22 more per 1000 (from 50 fewer to 113 more)	Low
Number of patients experiencing a respiratory adverse event	3/140 (2.1%)	6/147 (4.1%)	RR 0.53 (0.13 to 2.06)	19 fewer per 1000 (from 36 fewer to 43 more)	Low
Number of patients experiencing a cardiovascular adverse event	5/140 (3.6%)	1/147 (0.7%)	RR 5.25 (0.62 to 44.38)	30 more per 1000 (from 3 fewer to 304 more)	Low
Number of patients with hyperaemia	4/140 (2.9%)	2/147 (1.4%)	RR 2.10 (0.39 to 11.28)	15 more per 1000 (from 9 fewer to 144 more)	Low

8.3.12.2 Economic evidence

No studies were identified.

8.3.12.3 Patient views evidence

No studies were identified.

8.3.12.4 Evidence statements - Fixed combination of prostaglandin analogues + beta-blockers vs. prostaglandin analogues

Clinical There were no studies which reported the number of patients with visual field progression.

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and prostaglandins alone in reducing IOP from baseline at 6 months follow up. (VERY LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and prostaglandins alone in the number of patients with an acceptable IOP of <18mmHg at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and prostaglandins alone in the number of patients experiencing a respiratory adverse event at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and prostaglandins alone in the number of patients experiencing a cardiovascular adverse event at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and prostaglandins alone in the number of patients experiencing hyperaemia at 6 months follow up. (LOW QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared fixed combinations of prostaglandin analogues + beta-blockers to prostaglandin analogues alone.

8.3.13 Fixed combination of prostaglandin analogues plus beta-blockers versus beta-blockers

See Evidence Table 12, Appendix D and Forest Plots in Figures 27 to 32, Appendix E

8.3.13.1 Clinical evidence

Table 8-109: Fixed combination of prostaglandin analogues + beta-blockers vs. beta-blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[61,116]	2	RCT	Serious limitations (a, b)	Serious inconsistency (c,d)	No serious indirectness	Serious imprecision (e)
Number of patients with an acceptable IOP of <18mmHg (follow up 6 months) [61,116]	2	RCT	Serious limitations (a, b)	Serious inconsistency (c)	No serious indirectness	Serious imprecision (e)
Number of patients experiencing a respiratory adverse event (follow up 6 months)[116]	1	RCT	Serious limitations (a, b)	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Number of patients experiencing a cardiovascular adverse event (follow up 6 months)[116]	1	RCT	Serious limitations (a, b)	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Number of patients with hyperaemia (follow up 6 months)[116]	1	RCT	Serious limitations (a, b)	No serious inconsistency	No serious indirectness	Serious imprecision (e)

(a) One study did not report the method of randomisation.
(b) Allocation concealment was not reported.
(c) There is significant unexplained statistical heterogeneity within the results.
(d) In one study the fixed combination is statistically and clinically more effective than beta-blockers in reducing IOP[61], in the other there is no statistical difference[116]. The confidence intervals do not overlap.
(e) The confidence intervals are broad making the effect size imprecise.

Table 8-110: Fixed combination of prostaglandin analogues + beta-blockers vs. beta-blockers - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	278	289	not applicable	MD -1.75 (-4.00 to 0.51)	Very low
Number of patients with an acceptable IOP of <18mmHg	93/278 (33.5%)	48/289 (16.6%)	RR 2.03 (1.50 to 2.75)	171 more per 1000 (from 83 more to 290 more)	Very low
Number of patients experiencing a respiratory adverse event	3/140 (2.1%)	7/149 (4.7%)	RR 0.46 (0.12 to 1.73)	25 fewer per 1000 (from 41 fewer to 34 more)	Low
Number of patients experiencing a cardiovascular adverse event	5/140 (3.6%)	2/149 (1.3%)	RR 2.66 (0.52 to 13.49)	22 more per 1000 (from 6 fewer to 162 more)	Low
Number of patients with hyperaemia	4/140 (2.9%)	1/149 (0.7%)	RR 4.26 (0.48 to 37.63)	23 more per 1000 (from 4 fewer to 256 more)	Low

8.3.13.2 Economic evidence

No studies were identified.

8.3.13.3 Patient views evidence

No studies were identified.

8.3.13.4 Evidence statements on fixed combination of prostaglandin analogues + beta-blockers vs. beta-blockers

Clinical

There were no studies which reported the number of patients with visual field progression.

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and beta-blockers alone in reducing IOP from baseline at 6 months follow up. (VERY LOW QUALITY)

A fixed combination of prostaglandin analogues + beta-blockers is significantly more effective than beta-blockers alone in increasing the number of patients with an acceptable IOP of <18mmHg at 6 months follow up. (VERY LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and beta-blockers alone in the number of patients experiencing a respiratory adverse event at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and beta-blockers alone in the number of patients experiencing a cardiovascular adverse event at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a fixed combination of prostaglandin analogues + beta-blockers and beta-blockers alone in the number of patients experiencing hyperaemia at 6 months follow up. (LOW QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared fixed combinations of prostaglandin analogues + beta-blockers to beta-blockers alone.

8.3.14 Fixed combination of sympathomimetics plus beta-blockers versus beta-blockers

See Evidence Table 12, Appendix D and Forest Plots in Figures 27 to 32, Appendix E

8.3.14.1 Clinical evidence

Table 8-111: Fixed combination of sympathomimetics + beta-blockers vs. beta-blockers - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an acceptable IOP of <17.5mmHg (mean follow up across all visits)[135]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	(a)
Number of patients experiencing a respiratory adverse event (follow up 12 months)[135]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	None
Number of patients experiencing a cardiovascular adverse event (follow up 12 months)[135]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	None

(a) *Outcomes are not reported properly. Mean diurnal IOP pressures are not reported. Standard deviations for each mean are not reported.*

Table 8-112: Fixed combination of sympathomimetics + beta-blockers vs. beta-blockers - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an acceptable IOP of <17.5mHg	202/385 (52.5%)	127/392 (32.4%)	RR 1.62 (1.36 to 1.92)	201 more per 1000 (from 117 more to 298 more)	High
Number of patients experiencing an allergic reaction	100/385 (26%)	47/392 (12%)	RR 2.17 (1.58 to 2.97)	140 more per 1000 (from 70 more to 236 more)	High
Number of patients with hyperaemia	56/385 (14.5%)	29/392 (7.4%)	RR 1.97 (1.28 to 3.01)	72 more per 1000 (from 21 more to 149 more)	High

8.3.14.2 Economic evidence

No studies were identified.

8.3.14.3 Patient views evidence

No studies were identified.

8.3.14.4 Evidence statements on fixed combination of sympathomimetics + beta-blockers vs. beta-blockers

Clinical There were no studies which reported the number of patients with visual field progression.

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

A fixed combination of sympathomimetics + beta-blockers is more effective than beta-blockers alone in increasing the number of patients with an acceptable IOP of <17.5mmHg at a mean follow up across all visits. (HIGH QUALITY)

A fixed combination of sympathomimetics + beta-blockers resulted in significantly more people experiencing an allergic reaction than beta-blockers alone at 12 months follow up. (HIGH QUALITY)

A fixed combination of sympathomimetics + beta-blockers resulted in significantly more patients experiencing hyperaemia than beta-blockers alone at 12 months follow up. (HIGH QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared fixed combination of sympathomimetics + beta-blockers to beta-blockers alone.

8.3.15 Separate combination of carbonic anhydrase inhibitors plus beta-blockers versus prostaglandin analogues

See Evidence Table 13, Appendix D and Forest Plots in Figures 33 to 36, Appendix E

8.3.15.1 Clinical evidence

Table 8-113: Separate combination of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[117,121]	2	RCT	Very serious limitations (a,b,c)	Serious inconsistency (d)	No serious indirectness	No serious imprecision (e)
Number of patients with an acceptable IOP of <21mmHg (follow up 24 months)[117]	1	RCT	Very serious limitations (a,b,c)	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Adverse events	0					

(a) *Method of randomisation is not mentioned.*
(b) *Allocation concealment is not mentioned.*
(c) *Masked outcome assessment was not mentioned in one study*[117]
(d) *Serious statistical heterogeneity was observed between studies which may have been due to different dosages of CAI applied. One study*[121] *applied CAI at a dosage of 3/day rather than the recommended 2/day for use alongside a beta-blocker.*
(e) *The confidence intervals are broad making the effect size imprecise.*

Table 8-114: Separate combination of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Mean change in IOP from baseline	90	91	not applicable	MD 0.28 (-0.42 to 0.99)	Low
Number of patients with an acceptable IOP of <21mmHg	17/30 (56.7%)	37/45 (82.2%)	RR 0.69 (0.49 to 0.97)	255 fewer per 1000 (from 25 fewer to 419 fewer)	Very low

8.3.15.2 Economic evidence

No studies were identified.

8.3.15.3 Patient views evidence

No studies were identified.

8.3.15.4 Evidence statements - Separate combination of carbonic anhydrase inhibitors + beta-blockers vs. prostaglandin analogues

Clinical There were no studies which reported the number of patients with visual field progression.

There is no statistically significant difference between a separate combination of carbonic anhydrase inhibitors + beta-blockers and prostaglandin analogues alone in reducing IOP from baseline at 6 months follow up. (LOW QUALITY)

A separate combination of carbonic anhydrase inhibitors + beta-blockers is less effective than prostaglandin analogues alone in increasing the number of patients with an acceptable IOP of <21mmHg at 24 months follow up. (VERY LOW QUALITY)

There were no studies which reported adverse events.

Economic No studies meeting the inclusion criteria were identified which compared separate combinations of carbonic anhydrase inhibitors plus beta-blockers to prostaglandin analogues alone.

8.3.16 Separate combination of prostaglandin analogues plus beta-blockers versus prostaglandin analogues

See Evidence Tables 13 and 24, Appendix D and Forest Plots in Figures 33 to 36, Appendix E

8.3.16.1 Clinical evidence

Table 8-115: Separate combination of prostaglandin analogues plus beta-blockers versus prostaglandin analogues - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[13,91]	2	RCT	Very serious limitations (a,b,c)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Number of patients with an acceptable IOP of approx <18mmHg (follow up 6 months)[13]	1	RCT	Very serious limitations (b,c,e)	No serious inconsistency	No serious indirectness	None
Number of patients experiencing a respiratory adverse event (follow up 6 months)[13]	1	RCT	Very serious limitations (b,c,e)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Number of patients with hyperaemia (follow up 6 months)[13,91]	2	RCT	Very serious limitations (a,b,c)	No serious inconsistency	No serious indirectness	Serious imprecision (d)

(a) *Only one study reports the method of randomisation. This study has a 90% weighting on the estimate of effect.*
(b) *Allocation concealment is not mentioned in either study.*
(c) *Only observers were masked to treatment.*
(d) *The confidence intervals are broad making the effect size imprecise.*
(e) *Method of randomisation is not reported.*

Table 8-116: Separate combination of prostaglandin analogues plus beta-blockers versus prostaglandin analogues - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	79	81	not applicable	MD -0.66 (-1.44 to 0.13)	Very low
Number of patients with an acceptable IOP of approx <18mmHg	30/45 (66.7%)	32/46 (69.6%)	RR 0.96 (0.72 to 1.27)	28 fewer per 1000 (from 195 fewer to 188 more)	Low
Number of patients experiencing a respiratory adverse event	1/49 (2%)	0/50 (0%)	RR 3.06 (0.13 to 73.34)	not estimable (a)	Very low
Number of patients with hyperaemia	27/79 (34.2%)	18/81 (22.2%)	RR 1.54 (0.98 to 2.44)	120 more per 1000 (from 4 fewer to 320 more)	Very low

(a) An absolute effect calculation is not possible as there are no events in the control arm of the study.

8.3.16.2 Economic evidence

We found a cost-effectiveness analysis based on a retrospective cohort study[143]. Patients who failed treatment with beta-blockers were either treated with a prostaglandin analogue in monotherapy or this was added to the beta-blocker already prescribed. Two studies based on the same cohort study reported the cost-effectiveness analysis after one year[125] and two year[126] follow-up of patients treated with either beta-blockers, prostaglandin analogues or an unfixed combination of a prostaglandin analogue plus beta-blocker. The comparison of beta-blockers with the fixed combination is reported in 8.3.17.2. See economic evidence table in Appendix D for details of the studies.

Table 8-117: Separate combination of prostaglandin analogues plus beta-blockers versus prostaglandin analogues - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Stewart2002[143]	Serious limitations (a, b, c)	Partially applicable (d, e)	
Rouland2003[125]	Serious limitations (a, b)	Partially applicable (d, f)	
Rouland2005[126]	Serious limitations (a, b)	Partially applicable (d, f)	Same study as above but different outcomes reported.

a) Not based on RCT clinical evidence.
b) Short follow-up.
c) Small sample size
d) Not UK cost figures.
e) Patients were previously prescribed a topical beta-blocker as monotherapy.
f) Second-line treatment

Table 8-118: Separate combination of prostaglandin analogues plus beta-blockers versus prostaglandin analogues - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Stewart2002[143]	£221 per year	1.7mmHg mean change in IOP from baseline (a)	£130 per mmHg of mean change in IOP from baseline	NR
Rouland2003[125]	£39 per year	2.3 mmHg mean change in IOP from baseline (b)	£24 per mmHg of mean change in IOP from baseline	NR
Rouland2005[126]	£117/2years	1.1 mmHg mean change in IOP from baseline after 2 years(b)	£106 per mmHg of mean change in IOP from baseline	NR

(a) Not statistically significant.
(b) Significance not reported.

8.3.16.3 Patient views evidence

No studies were identified

8.3.16.4 Evidence statements - Separate combination of prostaglandin analogues plus beta-blockers versus prostaglandin analogues

Clinical There were no studies which reported the number of patients with visual field progression.

There is no statistically significant difference between a separate combination of prostaglandin analogues + beta-blockers and prostaglandin analogues alone in reducing IOP from baseline at 6 months follow up. (VERY LOW QUALITY)

There is no statistically significant difference between a separate combination of prostaglandin analogues + beta-blockers and prostaglandin analogues alone in increasing the number of patients with an IOP of approx <18 mmHg at 6 months follow up. (LOW QUALITY)

There is no statistically significant difference between a separate combination of prostaglandin analogues + beta-blockers and prostaglandin analogues alone in the number of patients experiencing a respiratory adverse event at 6 months follow up. (VERY LOW QUALITY)

There is no statistically significant difference between a separate combination of prostaglandin analogues + beta-blockers and prostaglandin analogues alone in the number of patients experiencing hyperaemia at 6 months follow up. (VERY LOW QUALITY)

Economic Separate combinations of prostaglandin analogues plus beta-blockers are more effective (not statistically significant) but more costly than prostaglandin analogues alone. This evidence has serious limitations and partial applicability.

8.3.17 Separate combination of prostaglandin analogues plus beta-blockers versus beta-blockers

See Evidence Table 13, Appendix D and Forest Plots in Figures 33 to 36, Appendix E

8.3.17.1 Clinical evidence

Table 8-119: Separate combination of prostaglandin analogues + beta-blockers vs. beta-blockers - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months) [114]	0					
Number of patients with an acceptable IOP of approx <17mmHg (follow up 6 months) [114]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	No serious imprecision
Number of patients with hyperaemia (follow up 6 months)[114]	1	RCT	Serious limitations (a,b)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) *Outcomes not reported properly. Mean diurnal IOP pressures are not reported. Standard deviations for each mean are not reported.*

(b) *Only 77% of those randomised were included in the analysis.*

Table 8-120: Separate combination of prostaglandin analogues + beta-blockers vs. beta-blockers - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an acceptable IOP of approx <17mmHg	55/114 (48.2%)	11/112 (9.8%)	RR 4.91 (2.72 to 8.88)	383 more per 1000 (from 169 more to 772 more)	High
Number of patients with hyperaemia	52/145 (35.9%)	13/145 (9%)	RR 4.00 (2.28 to 7.02)	270 more per 1000 (from 115 more to 542 more)	Moderate

8.3.17.2 Economic evidence

We found two studies based on the same cohort study reporting the cost-effectiveness analysis after one year[125] and two year[126] follow-up of patients treated with either beta-blockers, prostaglandin analogues or an unfixed combination of a prostaglandin analogue plus beta-blocker. The comparison of prostaglandin analogues with the fixed combination is reported in 8.3.16.2. See economic evidence table in Appendix D for details of the studies.

Table 8-121: Separate combination of prostaglandin analogues + beta-blockers vs. beta-blockers - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Rouland2003[125]	Serious limitations (a, b)	Partially applicable (c, d)	
Rouland2005[126]	Serious limitations (a, b)	Partially applicable (c, d)	Same study as above but different outcomes reported.

a) *Not based on RCT clinical evidence.*
b) *Short follow-up.*
c) *Not UK cost figures.*
d) *Second-line treatment*

Table 8-122: Separate combination of prostaglandin analogues + beta-blockers vs. beta-blockers - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Rouland2003[125]	£104 per year	3.2 mmHg mean change in IOP from baseline (a)	£33 per mmHg of mean change in IOP from baseline	NR
Rouland2005[126]	£230/2years	1.8 mmHg mean change in IOP from baseline after 2 years (a)	£128 per mmHg of mean change in IOP from baseline	NR

(a) *Significance not reported.*

8.3.17.3 Patient views evidence

No studies were identified.

8.3.17.4 Evidence statements - Separate combination of prostaglandin analogues + beta-blockers vs. beta-blockers

Clinical There were no studies which reported the number of patients with visual field progression.

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

A separate combination of prostaglandin analogues + beta-blockers is more effective than beta-blockers alone in increasing the number of patients who reach an IOP of approx <17mmHg at 6 months follow up. (HIGH QUALITY)

Significantly more patients using a fixed combination of prostaglandin analogues + beta-blockers compared to beta-blockers alone experienced hyperaemia at 6 months follow up. (MODERATE QUALITY)

Economic Separate combinations of prostaglandin analogues plus beta-blockers are more effective (significance not reported) but more costly than beta-blockers alone. This evidence has serious limitations and partial applicability.

8.4 Adverse Events associated with pharmacological treatments

Some important adverse events were not well reported in the randomised controlled trials. This is particularly the case for beta-blockers which have been associated, or an association has been suggested, with serious respiratory or cardiovascular adverse events[109], a change in respiratory or cardiovascular function[35,139], depression[137] or falls and syncope[46,103]. Further evidence is reviewed here from comparative observational studies where patients had been using medications for a minimum of six months, the same time period used for the RCT reviews. A summary of the evidence identified from both RCTs and observational studies are included below.

See Evidence Table 14, Appendix D

Table 8-123: Summary of adverse events evidence associated with topical medications

Adverse event	*Evidence from reviewed RCTs*	*Evidence from observational studies*
Respiratory adverse events	Some evidence in studies of beta-blockers reviewed earlier in this chapter but these are mostly too small to show an effect.	Large observational study shows evidence of increased harm with beta-blockers
Cardiovascular adverse events	Some evidence in studies to beta-blockers but these are mostly too small to show an effect.	No studies
Change in respiratory or cardiovascular function	No studies	No studies
Depression	No studies	Large observation study shows no difference between beta-blockers & other medications
Syncope and falls	No studies	No studies

8.4.1.1 Clinical evidence

Table 8-124: Adverse events associated with topical medications - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
New prescription for reversible airways obstruction (follow up 6 months)[74,75]	1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	None
New prescription for reversible airways obstruction (follow up 12 months)[74,75]	1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	None
New prescription for reversible airways obstruction AND a new Read code for asthma or COPD (follow up 6 months)[74,75]	1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	None
New prescription for reversible airways obstruction AND a new Read code for asthma or COPD (follow up 12 months)[74,75]	1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	None
Number of patients taking at least 4 prescriptions of anti-depressants	1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	None

Table 8-125: Adverse events associated with topical medications - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
New prescription for reversible airways obstruction (follow up 6 months)	49/2645 (1.9%)	55/9094 (0.6%)	HR 2.79 (1.88 to 4.15) (a)	11 more per 1000 (from 5 more to 19 more)	Low
New prescription for reversible airways obstruction (follow up 12 months)	81/2645 (3.1%)	112/9094 (1.2%)	HR 2.29 (1.71 to 3.07) (a)	15 more per 1000 (from 8 more to 24 more)	Low

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
New prescription for reversible airways obstruction AND a new Read code for asthma or COPD (follow up 6 months)	115/2645 (4.3%)	172/9094 (1.9%)	HR 2.18 (1.71 to 2.79) (a)	22 more per 1000 (from 13 more to 33 more)	Low
New prescription for reversible airways obstruction AND a new Read code for asthma or COPD (follow up 12 months)	191/2645 (7.2%)	354/9094 (3.9%)	HR 1.77 (1.48 to 2.12) (a)	29 more per 1000 (from 18 more to 42 more)	Low
Number of patients taking at least 4 prescriptions of antidepressants	715/5846 (12.2%)	95/752 (12.6%)	OR 0.96 (0.77 to 1.21)	5 fewer per 1000 (from 27 fewer to 23 more)	Low

(a) *Adjusted analysis used a proportional hazards model, corrected for age, sex, use of systemic beta-blockers, use of non-steroidal anti-inflammatory drugs, use of nitrates, smoking, season of presentation, and number of visits to general practitioners.*

8.4.1.2 Economic evidence

No economic studies were identified which compared the cost implications of adverse events with different treatment. The cost of asthma was included in the NCC-AC model on treatment. It was estimated as £147 per year[11]. See Appendix F – 1.3 for details.

8.4.1.3 Evidence Statements – adverse events

Clinical Significantly more patients using beta-blockers compared to those not using beta-blockers required a new prescription for reversible airways obstruction and/or a new Read code for asthma or COPD. (LOW QUALITY)

There is no statistically significant difference between beta-blockers and other medications in the number of patients who are prescribed anti-depressants. (LOW QUALITY)

Economic No economic studies were identified which compared the cost implications of adverse events with different treatment. The annual cost of asthma was estimated and used in the NCC-AC model on treatment (Appendix F – 1.3).

8.5 Laser treatment for COAG

8.5.1 Selective laser trabeculoplasty versus argon laser trabeculoplasty

See Evidence Table 15, Appendix D and Forest Plots in Figures 37 to 39

8.5.1.1 Clinical evidence

Table 8-126 Selective laser trabeculoplasty vs. argon laser trabeculoplasty - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline (follow up 12 months)[30]	1	RCT (a)	Serious limitations (b)	No Serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)
Number of patients with an unacceptable IOP (follow up 12 months)[30]	1	RCT (a)	Serious limitations (b)	No Serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)
Complications: PAS formation [30]	1	RCT (a)	Serious limitations (b)	No Serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)

(a) *Studies are supplemented by data from the Cochrane systematic reviews Rolim 2007[124].*
(b) *Randomisation and allocation concealment are adequate but masking of outcome assessment is not reported.*
(c) *Wide confidence interval making estimate of effect uncertain.*
(d) *All patients were maintained on current IOP lowering medications throughout study and some patients previously received ALT treatment.*

Table 8-127: Selective laser trabeculoplasty vs. argon laser trabeculoplasty - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	89	87	not applicable	MD 0.18 (-1.45 to 1.81)	Moderate
Number of patients with an unacceptable IOP	35/89 (39.3%)	27/87 (31%)	1.27 (0.84 to 1.90)	84 more per 1000 (from 50 fewer to 249 more)	Low
Complications: PAS formation	1/89 (1.1%)	1/87 (1.1%)	0.98 (0.06 to 15.38	0 fewer per 1000 (from 10 fewer to 158 more)	Low

8.5.1.2 Economic evidence

No studies were identified.

8.5.1.3 Patient views evidence

No studies were identified.

8.5.1.4 Evidence statements - Selective laser trabeculoplasty vs. argon laser trabeculoplasty

Clinical

There were no studies which reported number of patients with visual field progression.

There is no statistically significant difference between SLT and ALT in reducing IOP from baseline at 12 months follow up. (MODERATE QUALITY)

There is no statistically significant difference between SLT and ALT in number of patients with an unacceptable IOP at 12 months follow up. (LOW QUALITY)

There is no statistically significant difference between SLT and ALT in PAS formation at 12 months follow up. (LOW QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared argon laser trabeculoplasty to selective laser trabeculoplasty.

8.5.2 Laser trabeculoplasty versus pharmacological treatment

See Evidence Table 15, Appendix D and Forest Plot in Figure 40

8.5.2.1 Clinical evidence

Table 8-128 Laser trabeculoplasty vs. pharmacological treatment - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an unacceptable IOP (follow up 2 to 48 months)[45,98,104]	3	RCT (a)	Serious limitations (b)	No serious inconsistency	Serious indirectness (c)	Serious imprecision (d) Additional notes (e)
Complications	0					

(a) *Studies are supplemented by data from the Cochrane systematic review Rolim 2007[124].*
(b) *Allocation concealment and randomisation methods are not reported in one study[45] and masking of outcome assessment is not reported in any of the studies.*
(c) *One study[104] included 51% OHT patients.*
(d) *Wide confidence interval making estimate of effect uncertain.*
(e) *Although there was no statistical heterogeneity observed other differences between studies were noted in length of follow up, IOP failure criteria, laser modality, laser degrees of treatment, class of medications, mean baseline IOP and COAG population (previously untreated or treated). One study[104] tested different in laser degrees of treatment against prostaglandin analogues. For the purposes of comparison the 360 degree was selected.*

Table 8-129: Laser trabeculoplasty vs. pharmacological treatment - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Number of patients with an unacceptable IOP	32/115 (27.8%)	22/111 (19.8%)	1.37 (0.86 to 2.17)	73 more per 1000 (from 28 fewer to 232 more)	Very Low

8.5.2.2 Economic evidence

No studies were identified.

8.5.2.3 Patient views evidence

No studies were identified.

8.5.2.4 Evidence statements - Laser trabeculoplasty vs. pharmacological treatment

Clinical There were no studies which reported number of patients with visual field progression.

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

There is no statistically significant difference between laser trabeculoplasty and pharmacological treatment in terms of number of patients with an unacceptable IOP at 2 to 48 months follow up. (VERY LOW QUALITY)

There were no studies which reported complications lasting longer than 1 week.

Economic No studies meeting the inclusion criteria were identified which compared laser trabeculoplasty to pharmacological treatment.

8.5.3 Laser trabeculoplasty plus pharmacological treatment versus pharmacological treatment

See Evidence Table 15, Appendix D and Forest Plot in Figure 41

8.5.3.1 Clinical evidence

Table 8-130 Laser trabeculoplasty + pharmacological treatment vs. pharmacological treatment- Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an unacceptable IOP (follow up 12 months) [102,136]	2	RCT (a)	Serious limitations (b)	Serious inconsistency (c)	No serious indirectness	Serious imprecision (d)
Complications	0					

(a) *Studies are supplemented by data from the Cochrane systematic reviews Rolim 2007*[124].
(b) *Allocation concealment, randomisation methods and masking of outcome assessment are not reported in one study*[102].
(c) *I-squared value of 81% indicates high statistical heterogeneity which may have been due to the studies being from very different populations. One study*[102] *is exclusively in Afro-Caribbean patients. Variations between studies are also noted in laser degrees of treatment and mean baseline IOP.*
(d) *Wide confidence interval making estimate of effect uncertain.*

Table 8-131 Laser trabeculoplasty + pharmacological treatment vs. pharmacological treatment - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Number of patients with an unacceptable IOP	10/49 (20.4%)	41/46 (89.1%)	0.22 (0.05 to 1.00)	695 fewer per 1000 (from 846 fewer to 0 more)	Very Low

8.5.3.2 Economic evidence

No studies were identified.

8.5.3.3 Patient views evidence

No studies were identified.

8.5.3.4 Evidence statements - Laser trabeculoplasty + pharmacological treatment vs. pharmacological treatment

Clinical

There were no studies which reported number of patients with visual field progression.

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

There is no statistically significant difference between laser trabeculoplasty + pharmacological treatment and pharmacological treatment alone in terms of number of patients with an unacceptable IOP at 12 months follow up. (VERY LOW QUALITY)

There were no studies which reported complications lasting longer than 1 week.

Economic

No studies meeting the inclusion criteria were identified which compared laser trabeculoplasty + pharmacological treatment to pharmacological treatment.

8.5.4 Laser trabeculoplasty versus trabeculectomy

See Evidence Table 15, Appendix D and Forest Plot in Figure 42

8.5.4.1 Clinical evidence

Table 8-132 Laser trabeculoplasty vs. trabeculectomy - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an unacceptable IOP (follow up 0 - 6 months)[2,98]	2	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)
Number of patients with an unacceptable IOP (follow up 3 - 24 months)[2,98]	2	RCT (a)	No serious limitations (b)	Serious inconsistency (c)	No serious indirectness	No serious imprecision Additional notes (d)
Complications	0					

(a) *Studies are supplemented by data from the Cochrane systematic reviews Rolim 2007[124].*
(b) *One study[98] does not report masking of outcome assessment.*
(c) *Although there is no statistical heterogeneity observed at 0 – 6 months follow up, the I-squared value is high (51%) for 3 – 24 months follow up.*

(d) Differences between studies are noted in IOP failure criteria, laser degrees of treatment and mean baseline IOP.

Table 8-133 Laser trabeculoplasty vs. trabeculectomy - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an unacceptable IOP (follow up 0 - 6 months)	34/419 (8.1%)	10/400 (2.5%)	3.14 (1.60 to 6.18)	54 more per 1000 (from 15 more to 130 more)	Moderate
Number of patients with an unacceptable IOP (follow up 3 - 24 months)	72/459 (15.7%)	34/442 (7.7%)	2.03 (1.38 to 2.98)	79 more per 1000 (from 29 more to 152 more)	Low

8.5.4.2 Economic evidence

No studies were identified.

8.5.4.3 Patient views evidence

No studies were identified

8.5.4.4 Evidence statements - Laser trabeculoplasty vs. trabeculectomy

Clinical

There were no studies which reported number of patients with visual field progression.

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

Laser trabeculoplasty is less effective than trabeculectomy in reducing the number of patients with an unacceptable IOP at 0 to 6 months follow up. (MODERATE QUALITY)

Laser trabeculoplasty is less effective than trabeculectomy in reducing the number of patients with an unacceptable IOP at 3 to 24 months follow up. However, there is significant unexplained statistical heterogeneity within the results. (LOW QUALITY)

There were no studies which reported complications lasting longer than 1 week.

Economic

No studies meeting the inclusion criteria were identified which compared laser trabeculoplasty to trabeculectomy.

8.6 Surgical Treatment for COAG

8.6.1 Trabeculectomy versus pharmacological treatment

Evidence Table 16, Appendix D, Forest Plots in Figures 43 to 47 and Economic Model in Appendix F - 1.3

8.6.1.1 Clinical evidence

Table 8-134: Trabeculectomy vs. pharmacological treatment- Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression (follow up 1 to 5 years) [65,98]	2	RCT (a)	Serious limitations (b)	Serious inconsistency (c)	No serious indirectness	Serious imprecision (d) Additional notes (e)
Mean change in IOP from baseline (follow up 12 months)[65,89,98]	3	RCT (a)	Serious limitations (b)	Serious inconsistency (c)	No serious indirectness	No serious imprecision Additional notes (e)
Mean change in IOP from baseline (follow up 1 to 5 years)[89,98]	2	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (d) Additional notes (e)
Mean change in IOP from baseline (follow up >5 years)[89,98]	2	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (d) Additional notes (e)
Number of patients with an unacceptable IOP (follow up 12 months)[65]	1	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Complications: Cataract formation [65,89,98]	3	RCT (a)	Serious limitations (b)	Not estimable as individual study data not reported	No serious indirectness	No serious imprecision Additional notes (e)

(a) *Studies are supplemented by data from the Cochrane systematic review Burr 2004*[15].
(b) *Randomisation and allocation concealment are adequate for all studies but masking of outcome assessment is not attempted. Attrition bias is noted for 2 studies*[65,98] *where treatment failures are excluded from the analysis.*
(c) *Statistically significant heterogeneity possibly due to differences in types of medications, classification methods for visual field changes and length of follow up.*
(d) *For visual field progression in the medium term and IOP failure at 12 months wide confidence intervals make estimate of effect uncertain. For mean change in IOP from baseline in the medium and long term the lower confidence interval is clinically insignificant.*
(e) *Other differences in study populations are noted in baseline IOP, severity of COAG and race.*

Table 8-135: Trabeculectomy vs. pharmacological treatment - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Visual field progression	47/98 (48%)	52/97 (53.6%)	0.81 (0.38 to 1.73)	102 fewer per 1000 (from 332 fewer to 391 more)	Very Low
Mean change in IOP from baseline (follow up 12 months)	397	388	not applicable	MD -4.92 (-6.93 to -2.91)	Low
Mean change in IOP from baseline (follow up 1 to 5 years)	326	285	not applicable	MD -2.04 (-2.85 to -1.23)	Low
Mean change in IOP from baseline (follow up >5 years)	257	229	not applicable	MD -2.15 (-3.10 to -1.19)	Low

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an unacceptable IOP	7/46 (15.2%)	17/53 (32.1%)	0.47 (0.22 to 1.04)	170 fewer per 1000 (from 250 fewer to 13 more)	Low
Complications: Cataract formation	57/403 (14.1%)	24/406 (5.8%)	2.45 (1.55 to 3.87	82 more per 1000 (from 32 more to 166 more)	Not estimable (a)

(a) Figures taken from the systematic review[15]. Data not provided for individual studies consequently no forest plot is provided in this guideline's appendices.

8.6.1.2 Economic evidence

We found a cost analysis comparing early trabeculectomy (within 4 weeks of diagnosis) to medical management. See economic evidence table in Appendix D for details.

We also constructed an original model to compare various strategies for the first-choice treatment of COAG patients, including trabeculectomy and pharmacological treatment with beta-blockers and prostaglandin analogues. This was based on clinical evidence comparing trabeculectomy to beta-blockers (see 8.6.1.1). See Appendix F – 1.3 for methods and results.

Table 8-136: Trabeculectomy vs. pharmacological treatment - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Ainsworth1991[3] (a)	Serious limitations (b)	Partially applicable (c)	Early trabeculectomy was compared to conventional management: up to a maximum of three different topical or systemic drugs and late trabeculectomy if medical therapy has failed.
NCC-AC model	Minor limitations	Directly applicable	

a) Based on the RCT Jay1988[65] – see clinical evidence in 8.6.1.1.
b) Not a full economic evaluation.
c) Average length of stay after surgery was 7.6 days and therefore longer than the current average.

Table 8-137: Trabeculectomy vs. pharmacological treatment - Economic summary of findings

Study	*Incremental cost (£)*	*Incremental effects*	*ICER (£/QALY)*	*Uncertainty*
Ainsworth1991[3]	cost saving (a)	NR	NA	Incremental cost per unilateral COAG patient is £219.
Early COAG				
NCC-AC model *Trabeculectomy vs BB*	1,230	0.135 QALY	9,113	95% CI (£/QALY): cost saving – 85,631 Results sensitive to probability of progression: if <6% per year (~0.18 dB/year) treatment with BB is more cost effective. Results also sensitive to cost of surgery and age.
NCC-AC model *Trabeculectomy vs PGA*	1,134	0.104 QALY	10,906	95% CI (£/QALY): cost saving – 122,050 Results sensitive to probability of progression: if <6% per year (~0.18 dB/year) treatment with PGA is more cost effective. Results also sensitive to cost of surgery and age.
Moderate COAG				
NCC-AC model *Trabeculectomy vs BB*	397	0.218	1,822	If progression is <2% per year (~0.08dB/year) treatment with BB is more cost-effective. Results are sensitive to age.
NCC-AC model *Trabeculectomy vs PGA*	363	0.165 QALY	2,194	If progression is <2% per year (0.08dB/year) treatment with PGA is more cost-effective. Results are sensitive to age.
Advanced COAG				
NCC-AC model *Trabeculectomy vs BB*	cost saving	0.307 QALY	cost saving	Results are not sensitive to progression rate or age. .
NCC-AC model *Trabeculectomy vs PGA*	cost saving	0.233 QALY	cost saving	Results are not sensitive to progression rate or age.

a) *In bilateral COAG patients.*

8.6.1.3 Patient views evidence

No studies were identified.

8.6.1.4 Evidence statements - Trabeculectomy vs. pharmacological treatment

Clinical

There is no statistically significant difference between visual field progression for the comparison of trabeculectomy and pharmacological treatment. (VERY LOW QUALITY)

Trabeculectomy is more effective than pharmacological treatment in reducing IOP from baseline at 12 months follow up. (LOW QUALITY)

Trabeculectomy is more effective than pharmacological treatment in reducing IOP from baseline at 1 to 5 years follow up but the effect size may be too small to be clinically significant. (LOW QUALITY)

Trabeculectomy is more effective than pharmacological treatment in reducing IOP from baseline at >5 years follow up but the effect size may be too small to be clinically significant. (LOW QUALITY)

There is no statistically significant difference in number of patients with an unacceptable IOP for the comparison of trabeculectomy and pharmacological treatment at 12 months follow up. (LOW QUALITY)

Trabeculectomy causes more cataracts than pharmacological treatment (QUALITY NOT ESTIMABLE)

Economic In COAG patients, trabeculectomy is more cost-effective than pharmacological treatment. However, this result is sensitive to the progression rate for patients in the early stages of COAG. This evidence has minor limitations and direct applicability.

8.6.2 Trabeculectomy plus pharmacological augmentation versus trabeculectomy

Evidence Table 17, Appendix D and Forest Plots in Figures 48 to 52

8.6.2.1 Clinical evidence

Table 8-138: Trabeculectomy + pharmacological augmentation vs. trabeculectomy - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an unacceptable IOP (follow up 12 months) [26,39,49,94,113,118,123,147]	8	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)
Complications: Cataract Formation (follow up 9-18 months) [26,39,49,88,94,118,123,147]	8	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)
Complications: Persistent hypotony (follow up 9-18 months) [26,39,49,88,94,118,147]	7	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)
Complications: Wound leak (follow up 9-18 months) [26,39,49,88,118,147]	6	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)
Complications: Corneal epithelial defects (follow up 9-18 months) [39,49,88,113,147]	5	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)

(a) *Studies are supplemented by data from the Cochrane systematic reviews Wilkins 2005[161] and Wormald 2001[162].*

(b) *For the antimetabolite MMC: 3 studies do not report details of randomisation method[26,123,147]. 3 studies do not report details of allocation concealment[94,118,147]. 3 studies do not report masking of outcome assessment[26,118,147]. Only 2 studies were placebo controlled[26,147]. For the antimetabolite 5-FU: 2 studies do not report details of* randomisation method[39,113]. *3 studies do not report details of allocation concealment, masking of outcome assessment and are not placebo controlled[39,49,113]. One study[88] is a placebo controlled double blind design.*

(c) *Wide confidence intervals making estimate of effect uncertain.*

(d) *Although there is no statistical heterogeneity observed other differences between studies are noted in type of antimetabolite (MMC or 5-FU) used and dosage, delivery method of 5-FU (intraoperative or postoperative injections), IOP failure criteria, length of follow up, reporting of complications, proportion of patients with closed-angle glaucoma of <50%, mean baseline IOP and whether patients received previous laser treatment. One study[39] is exclusively in Afro-Caribbean patients and one study[123] is exclusively in patients from the Indian sub-continent.*

Table 8-139: Trabeculectomy + pharmacological augmentation vs. trabeculectomy - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an unacceptable IOP	35/337 (10.4%)	82/218 (37.6%)	0.33 (0.23 to 0.47)	252 fewer per 1000 (from 199 fewer to 290 fewer)	Moderate
Complications: Cataract Formation	56/335 (16.7%)	19/210 (9.0%)	1.61 (0.96 to 2.70)	55 more per 1000 (from 4 fewer to 153 more)	Low
Complications: Persistent hypotony	12/169 (7.1%)	3/155 (1.9%)	2.60 (0.97 to 6.97)	30 more per 1000 (from 1 fewer to 113 more)	Low
Complications: Wound leak	26/139 (18.7%)	11/125 (8.8%)	2.02 (1.06 to 3.84)	90 more per 1000 (from 5 more to 250 more)	Low
Complications: Corneal epithelial defects	32/125 (25.6%)	6/111 (5.4%)	3.75 (1.76 to 7.99	149 more per 1000 (from 41 more to 337 more)	Low

8.6.2.2 Economic evidence

No studies were identified.

8.6.2.3 Patient views evidence

No studies were identified.

8.6.2.4 Evidence statements - Trabeculectomy + pharmacological augmentation vs. trabeculectomy

Clinical

There were no studies which reported number of patients with visual field progression.

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

Trabeculectomy + pharmacological augmentation is more effective than trabeculectomy alone in reducing the number of eyes with an unacceptable IOP at 12 months follow up. (MODERATE QUALITY).

There is no statistically significant difference between trabeculectomy + pharmacological augmentation and trabeculectomy alone in causing cataract formation at 9 to 18 months follow up. (LOW QUALITY).

There is no statistically significant difference between trabeculectomy + pharmacological

augmentation and trabeculectomy alone in causing persistent hypotony at 9 to 18 months follow up. (LOW QUALITY)

Trabeculectomy + pharmacological augmentation is more likely to cause wound leaks than trabeculectomy alone at 9 to 18 months follow up. (LOW QUALITY)

Trabeculectomy + pharmacological augmentation is more likely to cause corneal epithelial defects than trabeculectomy alone at 9 to 18 months follow up. (LOW QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared trabeculectomy + pharmacological augmentation to trabeculectomy alone.

8.6.3 Trabeculectomy plus antimetabolite drug MMC versus antimetabolite drug 5-FU

Evidence Table 18, Appendix D and Forest Plots in Figures 53 to 57

8.6.3.1 Clinical evidence

Table 8-140: Trabeculectomy + antimetabolite drug MMC versus antimetabolite drug 5-FU - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an unacceptable IOP (follow up 12 months)[138,165]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b) Additional notes (c)
Complications: Cataract Formation IOP (follow up 12 months)[138]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b) Additional notes (c)
Complications: Persistent hypotony IOP (follow up 12 months)[138,165]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b) Additional notes (c)
Complications: Wound leak IOP (follow up 12 months)[138,165]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b) Additional notes (c)
Complications: Corneal epithelial defects IOP (follow up 12 months)[165]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b) Additional notes (c)

(a) *One study[138] reports adequate randomisation methods but neither study reports allocation concealment. Masking of outcome assessment is only performed in one study[165].*

(b) *Wide confidence intervals make estimate of effect uncertain.*

(c) *Although there no statistical heterogeneity is observed other differences between studies are noted in antimetabolite dosage, delivery method of 5-FU (intraoperative or postoperative injections), IOP failure criteria, length of follow up, reporting of complications and mean baseline IOP. One study[138] was exclusively in Afro-Caribbean patients.*

Table 8-141: Trabeculectomy + antimetabolite drug MMC versus antimetabolite drug 5-FU - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an unacceptable IOP	5/54 (9.3%)	13/47 (27.7%)	0.34 (0.13 to 0.88)	183 fewer per 1000 (from 33 fewer to 241 fewer)	Low
Complications: Cataract Formation	3/44 (6.8%)	3/37 (8.1%)	0.84 (0.18 to 3.92)	13 fewer per 1000 (from 66 fewer to 237 more)	Low
Complications: Persistent hypotony	2/54 (3.7%)	3/47 (6.4%)	0.63 (0.13 to 3.11)	24 fewer per 1000 (from 56 fewer to 135 more)	Low
Complications: Wound leak	2/54 (3.7%)	2/47 (4.3%)	1.00 (0.17 to 5.77)	0 fewer per 1000 (from 36 fewer to 205 more)	Low
Complications: Corneal epithelial defects	0/10 (0%)	3/10 (30%)	0.14 (0.01 to 2.45)	258 fewer per 1000 (from 297 fewer to 435 more)	Low

8.6.3.2 Economic evidence

No studies were identified.

8.6.3.3 Patient views evidence

No studies were identified.

8.6.3.4 Evidence statements - Trabeculectomy + antimetabolite drug MMC versus antimetabolite drug 5-FU

Clinical

There were no studies which reported number of patients with visual field progression.

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

Trabeculectomy + antimetabolite drug MMC is more effective than antimetabolite drug 5-FU in reducing the number of patients with an unacceptable IOP at 12 months follow up. (LOW QUALITY)

There is no statistically significant difference between trabeculectomy + antimetabolite drug MMC and antimetabolite drug 5-FU in cataract formation at 12 months follow up. (LOW QUALITY)

There is no statistically significant difference between trabeculectomy + antimetabolite drug MMC and antimetabolite drug 5-FU in causing persistent hypotony at 12 months follow up. (LOW QUALITY)

There is no statistically significant difference between trabeculectomy + antimetabolite drug MMC and antimetabolite drug 5-FU in causing wound leaks at 12 months follow up. (LOW QUALITY)

There is no statistically significant difference between trabeculectomy + antimetabolite drug MMC and antimetabolite drug 5-FU in causing corneal epithelial defects at 12 months follow up. (LOW QUALITY)

Economic

No studies meeting the inclusion criteria were identified which compared trabeculectomy + antimetabolite drug MMC to antimetabolite drug 5-FU.

8.6.4 Viscocanalostomy versus deep sclerectomy

Evidence Table 19, Appendix D and Forest Plot in Figure 58

8.6.4.1 Clinical evidence

Table 8-142: Viscocanalostomy versus deep sclerectomy - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[40]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Number of patients with an unacceptable IOP	0					
Complications	0					

(a) *Randomisation method, allocation concealment and masking of outcome assessment are not reported.*
(b) *Confidence intervals are wide making estimate of effect uncertain.*

Table 8-143: Viscocanalostomy versus deep sclerectomy - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Mean change in IOP from baseline	12	10	not applicable	MD 2.79 (-2.95 to 8.53)	Low

8.6.4.2 Economic evidence

No studies were identified.

8.6.4.3 Patient views evidence

No studies were identified.

8.6.4.4 Evidence statements - Viscocanalostomy versus deep sclerectomy

Clinical

There were no studies which reported number of patients with visual field progression.

There is no statistically significant difference between viscocanalostomy and deep sclerectomy in reducing IOP from baseline at 6 months follow up. (LOW QUALITY)

There were no studies which reported number of patients with an unacceptable IOP.

There were no studies which reported complications.

Economic

No studies meeting the inclusion criteria were identified which compared viscocanalostomy to deep sclerectomy.

8.6.5 Non-penetrating surgery versus trabeculectomy

Evidence Table 20, Appendix D and Forest Plots in Figures 59 to 64

8.6.5.1 Clinical evidence

Table 8-144: Non-penetrating surgery versus trabeculectomy - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[19,20,22,40,41,67,77,90,163,164]	10	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c) Additional notes (d)
Mean change in IOP from baseline (follow up 12 months)[19,20,22,41,77,90,163,164]	8	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c) Additional notes (d)
Number of eyes with an unacceptable IOP (follow up 6 or 12 months)[19,20,22,41,67,77,90,163,164]	9	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)
Complications: Cataract Formation (follow up 12 – 36 months)[20,22,41,77,90,163,164]	7	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)
Complications: Persistent hypotony (follow up 12 – 36 months)[19,22,41,77,90,163,164]	7	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)
Complications: Wound leak (follow up 6 - 12 months)[41,67]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)

(a) *Only 3 studies report adequate randomisation methods[22,77,164] and only 2 studies report allocation concealment[19,164]. Only 2 studies report masking of outcome assessment[20,22], but all studies report low or zero dropout rates.*

(b) *Some statistical heterogeneity is noted in mean change in IOP from baseline at 6 and 12 months which is not satisfactorily explained by subgroup analysis for type of non-penetrating surgery, use of augmentation or presence of PXF in population.*

(c) *For mean change in IOP from baseline from baseline at 6 and 12 months the lower confidence interval is clinically insignificant. For complications: wound leak wide confidence intervals make estimate of effect uncertain.*

(d) *Other differences between studies are noted in non-penetrating surgery type (viscocanalostomy or deep sclerectomy with or without implant); use of augmentation; study design where 3 studies[20,77,164] randomised fellow eyes to treatment; IOP failure criteria; length of follow up from 6 months to 2 years; reporting of complications and mean baseline IOP. 5 studies[19,22,40,90,164] included a proportion of patients diagnosed with PXF and one study[164] included some CACG patients but <50%.*

Table 8-145: Non-penetrating surgery versus trabeculectomy - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline (follow up 6 months)	222	226	not applicable	MD 2.57 (1.35 to 3.80) (e)	VERY LOW
Mean change in IOP from baseline (follow up 12 months)	202	204	not applicable	MD 2.45 (1.46 to 3.44)	VERY LOW
Number of eyes with an unacceptable IOP	88/208 (42.3%)	52/210 (24.8%)	1.70 (1.30 to 2.23)	174 more per 1000 (from 74 more to 305 more)	MODERATE
Complications: Cataract Formation	4/177 (2.3%)	31/179 (17.3%)	0.20 (0.09 to 0.44)	138 fewer per 1000 (from 97 fewer to 157 fewer)	MODERATE
Complications: Persistent hypotony	8/184 (4.3%)	39/187 (20.9%)	0.25 (0.13 to 0.48)	157 fewer per 1000 (from 109 fewer to 182 fewer)	MODERATE
Complications: Wound leak	1/49 (2%)	4/49 (8.2%)	0.33 (0.05 to 2.02)	55 fewer per 1000 (from 78 fewer to 84 more)	LOW

(e) *One study[40] included 3 arms, viscocanalostomy, deep sclerectomy and trabeculectomy. The data for trabeculectomy is added twice meaning there is some double counting. The overall effect to the weighted mean difference is around 0.1mmHg.*

8.6.5.2 Economic evidence

No studies were identified.

8.6.5.3 Patient views evidence

No studies were identified.

8.6.5.4 Evidence statements - Non-penetrating surgery versus trabeculectomy

Clinical

There were no studies which reported number of patients with visual field progression.

Trabeculectomy is more effective than non-penetrating surgery in reducing IOP from baseline at 6 months follow up but the effect size may be too small to be clinically significant. (VERY LOW QUALITY)

Trabeculectomy is more effective than non-penetrating surgery in reducing IOP from baseline at 12 months follow up but the effect size may be too small to be clinically significant. (VERY LOW QUALITY)

Trabeculectomy is more effective than non-penetrating surgery in reducing the number of eyes with an unacceptable IOP at either 6 or 12 months follow up. (MODERATE QUALITY)

Trabeculectomy is more likely to cause cataract formation than non-penetrating surgery at 12 to 36 months follow up. (MODERATE QUALITY)

Trabeculectomy is more likely to cause persistent hypotony than non-penetrating surgery at 12 to 36 months follow up. (MODERATE QUALITY)

There is no statistically significant difference between trabeculectomy and non-penetrating surgery in causing wound leaks at 6 to 12 months follow up. (LOW QUALITY)

Economic

No studies meeting the inclusion criteria were identified which compared non-penetrating surgery to trabeculectomy.

8.6.6 Non-penetrating surgery plus pharmacological augmentation versus non-penetrating surgery

Evidence Table 21, Appendix D and Forest Plot in Figure 65

8.6.6.1 Clinical evidence

Table 8-146: Non-penetrating surgery + pharmacological augmentation vs. non-penetrating surgery - Clinical study characteristics

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Directness*	*Other considerations*
Visual field Progression	0					
Mean change in IOP from baseline	0					
Number of patients with an unacceptable IOP (follow up 12 months)[111]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Number of patients with an unacceptable IOP (follow up 24 months)[111]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Complications: Persistent hypotony (follow up 24 months)[111]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Complications: Wound leak (follow up 24 months)[111]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)

(a) Randomisation method, allocation concealment and masking of outcome assessment are not reported and the study is not placebo controlled. Despite randomisation baseline IOP was 5 mmHg higher in the MMC group.

(b) Wide confidence intervals make estimate of effect uncertain.

Table 8-147: Non-penetrating surgery + pharmacological augmentation vs. non-penetrating surgery - Clinical summary of findings

Outcome	*Intervention*	*Control*	*Relative risk*	*Absolute effect*	*Quality*
Number of patients with an unacceptable IOP (follow up 12 months)	0/13 (0%)	2/13 (15.4%)	0.2 (0.01 to 3.80)	123 fewer per 1000 (from 152 fewer to 431 more)	Low
Number of patients with an unacceptable IOP (follow up 24 months)	1/13 (7.7%)	1/13 (7.7%)	1.00 (0.07 to 14.34)	0 fewer per 1000 (from 72 fewer to 1000 more)	Low
Complications: Persistent hypotony	0/13 (0%)	0/13 (0%)	Not estimable	Not estimable	Low
Complications: Wound leak	0/13 (0%)	0/13 (0%)	Not estimable	Not estimable	Low

8.6.6.2 Economic evidence

No studies were identified.

8.6.6.3 Patient views evidence

No studies were identified.

8.6.6.4 Evidence statements - Non-penetrating surgery plus pharmacological augmentation vs. non-penetrating surgery

Clinical

There were no studies which reported number of patients with visual field progression.

There were no studies which reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

There is no statistically significant difference between non-penetrating surgery + pharmacological augmentation and non-penetrating surgery alone in reducing the number of patients with unacceptable IOP at 12 months follow up. (LOW QUALITY)

There is no statistically significant difference between non-penetrating surgery + pharmacological augmentation and non-penetrating surgery alone in reducing the number of patients with an unacceptable IOP at 24 months follow up. (LOW QUALITY)

There were no studies which reported number of patients with cataract progression.

There is no statistically significant difference between non-penetrating surgery + pharmacological augmentation and non-penetrating surgery alone in causing persistent hypotony at 24 months follow up. (LOW QUALITY)

There is no statistically significant difference between non-penetrating surgery + pharmacological augmentation and non-penetrating surgery alone in causing wound leaks at 24 months follow up. (LOW QUALITY)

There were no studies which reported corneal epithelial defects.

Economic

No studies meeting the inclusion criteria were identified which compared non-penetrating surgery + pharmacological augmentation to non-penetrating surgery alone.

8.7 Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion

Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion were included in the scope for this guideline. We searched for evidence of effectiveness of treatments but no studies were found either in these groups alone, or as part of subgroup analysis within the comparisons listed above. Therefore, the GDG decided not to make a specific recommendation regarding these patients. Patients should be treated according to the recommendations used for COAG patients.

8.8 Recommendations and link to evidence

Recommendation	**Offer people newly diagnosed with early or moderate COAG, and at risk of significant visual loss in their lifetime, treatment with a prostaglandin analogue.**
Relative values of different outcomes	Prevention of blindness is the most important outcome. Cosmetic side effects of treatment with prostaglandin analogues may be unacceptable to some patients who may prefer an alternative treatment.
Trade off between clinical benefits and harms	Prostaglandin analogues are effective at lowering IOP. They may affect the pigmentation of the iris and periorbital skin and cause lash growth but rarely have systemic side effects
Economic considerations	The cost-effectiveness of trabeculectomy is dependent on a rapid progression in visual field loss. Therefore in the absence of any evidence of progression, pharmacological treatment is cost-effective. Among the pharmacological treatments PGA are the most cost-effective.
Quality of evidence	Clinical evidence was generally of low quality. The economic evidence has minor limitations but direct applicability.
Other considerations	Patient preference (see Relative values of different outcomes above).

Recommendation	**Offer surgery with pharmacological augmentation (MMC or 5FU)* as indicated to people with COAG who are at risk of progressing to sight loss despite treatment. Information should be provided on the risks and benefits associated with surgery.** **MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*
Relative values of different outcomes	Progression is the most important outcome.
Trade off between clinical benefits and harms	There is a balance to be found. On the one hand there is a higher risk of progression to blindness if the target pressure is not achieved. On the other hand there is a higher risk of side effects with more aggressive interventions. For example the risks of surgery are greater than the risks from medical treatment.
Economic considerations	Trabeculectomy is cost-effective in cases of a detectable progression despite topical treatment.
Quality of evidence	Clinical evidence was generally of low quality. The economic evidence has minor limitations but direct applicability.
Other considerations	Patients may not be fit for surgery or may not wish to proceed to surgery because of anxiety or other issues. Where this situation arises alternative attempts at IOP lowering may be necessary. Options which may need to be considered include laser treatments, or multiple topical pharmacological treatments.

Recommendation	**Offer people with severe COAG surgery with pharmacological augmentation (MMC or 5FU)* as indicated. Information should be provided on the risks and benefits associated with surgery.** **MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*
Relative values of different outcomes	Surgery is the most potent treatment for lowering IOP and can save remaining sight. If there are complications of surgery sight could be lost more quickly than if there had been persistence with pharmacological treatment. If surgery is successful the risk of losing further sight and progressing to complete blindness is reduced.
Trade off between clinical benefits and harms	There is a risk of progression to complete blindness if COAG is not adequately treated. Although surgery has a higher risk than pharmacological treatment in the short term of causing blindness, it reduces this risk in the long term. If pharmacological treatment causes a satisfactory fall in IOP, surgery may be deferred.
Economic considerations	Trabeculectomy is cost-effective for this group of patients even if the progression rate is very low. Blindness has a large personal and social cost (see calculation of cost of blindness in Appendix F – 1.3)
Quality of evidence	Clinical evidence was generally of low quality. The economic evidence has minor limitations but direct applicability.
Other considerations	There were no trials due to the ethical implications of not treating patients with severe COAG.

Recommendation	**Consider offering people with COAG who are intolerant to a prescribed medication:** • **alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) or** • **a preservative-free preparation if there is evidence that the person is allergic to the preservative.** **After trying two alternative pharmacological treatments consider offering surgery with pharmacological augmentation (MMC or 5FU)* as indicated or laser trabeculoplasty.** **MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*
Trade off between clinical benefits and harms	Prescribing an alternative medication should reduce the risk of progression to blindness. If there is intolerance, allergy or an inadequate IOP lowering effect surgery should be offered as an alternative treatment.
Economic considerations	Offering a more costly BB (preservative-free preparation) is still more cost-

	effective than no treatment in patients with COAG.
Quality of evidence	There was no clinical evidence. The economic evidence has minor limitations but direct applicability.
Other considerations	Patients may not be fit for surgery or may not wish to proceed to surgery because of anxiety or other issues. In such instances laser treatment may be helpful in improving IOP control.

8.9 Supporting recommendations

Recommendation	**Offer people who present with severe COAG and who are listed for surgery interim treatment with a prostaglandin analogue.**
Trade off between clinical benefits and harms	If COAG is severe when first diagnosed, treatment to lower IOP should be started immediately as any amount of progression could cause additional severe visual disability. There is a risk of progression to complete blindness if COAG is not adequately treated.
Economic considerations	Blindness has a large personal and social cost (see NICE's social value judgements document)
Other considerations	None

Recommendation	**Check that there are no relevant comorbidities or potential drug interactions before offering medication.**
Trade off between clinical benefits and harms	Some pharmacological treatments that are effective at lowering IOP may have serious systemic side effects, particularly worsening of chronic obstructive pulmonary disease and asthma by beta blocker eye drops. There are many potential drug interactions with beta-blockers and alpha receptor agonists. The patient's general health should not be compromised by any pharmacological treatment as alternative treatments for COAG are available.
Economic considerations	None
Other considerations	Older people are more likely to experience adverse reactions to medications

Recommendation	**Encourage people using the prescribed pharmacological treatment to continue with the same treatment unless:** • **their IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss** • **there is progression of optic nerve head damage** • **there is progression of visual field defect** • they are intolerant to the drug.
Trade off between clinical benefits and harms	Persisting with medication will reduce the risk of progression to blindness. If the medication is causing harm because of allergy or intolerance a different medication can be offered.

Economic considerations	Changes in therapy are associated with additional costs of visits. If a change is unnecessary then these costs should be avoided.
Other considerations	None

Recommendation	**Check the person's adherence to their treatment and eye drop instillation technique in people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss despite pharmacological treatment. If adherence and eye drop instillation technique are satisfactory offer one of the following:** • **alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP** • **laser trabeculoplasty** • **surgery with pharmacological augmentation (MMC or 5FU)*as indicated** **If the pharmacological treatment option is chosen, after trying two alternative pharmacological treatments consider offering surgery with pharmacological augmentation (MMC or 5FU)* or laser trabeculoplasty.** **MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*
Trade off between clinical benefits and harms	Complications of surgery may cause harm but if alternative treatments fail then surgery offers the least risk of progression to blindness.
Economic considerations	None.
Other considerations	Patients may not be fit for surgery or may prefer not to proceed to surgery because of anxiety or other issues.

Recommendation	**Offer people with COAG who prefer not to have surgery or who are not suitable for surgery:** • **alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP,** • **laser trabeculoplasty or cyclo-diode laser treatment.** *f.*
Trade off between clinical benefits and harms	Alternative treatments to surgery are less effective but have a lower risk of immediate loss of sight. Some patients may choose a higher long term risk of sight loss to a low risk of immediate sight loss.

Economic considerations	None.
Other considerations	Patients may prefer certain options ahead of others.

Recommendation	**After surgery offer people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss one of the following:** • **pharmacological treatment (a prostaglandin analogues, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP** • **further surgery** • **Laser trabeculoplasty or cyclo-diode laser treatment.**
Trade off between clinical benefits and harms	If surgery fails to control IOP topical medical treatment should be restarted. Repeat surgery may be required and if so should be offered. Cyclodiode laser treatment may need to be considered.
Economic considerations	None.
Other considerations	Patients may prefer certain options ahead of others.

8.10 Summary of all recommendations on treatment for patients with COAG

The recommendations have been reordered to reflect the patient's pathway.

➢ Offer people newly diagnosed with early or moderate COAG, and at risk of significant visual loss in their lifetime, treatment with a prostaglandin analogue.

➢ Check that there are no relevant comorbidities or potential drug interactions before offering medication.

➢ Offer people with severe COAG surgery with pharmacological augmentation (MMC or 5FU)* as indicated. Information should be provided on the risks and benefits associated with surgery.

**MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*

➢ Offer people who present with severe COAG and who are listed for surgery interim treatment with a prostaglandin analogue.

➢ Encourage people using the prescribed pharmacological treatment to continue with the same treatment unless:

- their IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss
- there is progression of optic nerve head damage
- there is progression of visual field defect
- they are intolerant to the drug.

➢ Check the person's adherence to their treatment and eye drop instillation technique in people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss despite pharmacological treatment. If adherence and eye drop instillation technique are satisfactory offer one of the following:

- alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP
- laser trabeculoplasty
- surgery with pharmacological augmentation (MMC or 5FU)* as indicated

If the pharmacological treatment option is chosen, after trying two alternative pharmacological treatments consider offering surgery with pharmacological augmentation (MMC or 5FU)* as indicated or laser trabeculoplasty.

**MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*

➢ Offer surgery with pharmacological augmentation (MMC or 5FU)* as indicated to people with COAG who are at risk of progressing to sight loss despite treatment. Information should be provided on the risks and benefits associated with surgery.

**MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*

➢ Consider offering people with COAG who are intolerant to a prescribed medication:

- alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) or
- a preservative-free preparation if there is evidence that the person is allergic to the preservative.

After trying two alternative pharmacological treatments consider offering surgery with pharmacological augmentation (MMC or 5FU)* as indicated or laser trabeculoplasty.

**MMC or 5FU are not licensed for the stated use and informed consent should be obtained and documented. Both drugs should be handled with caution and in accordance with guidance issued by the Health and Safety Executive. It is recommended that local protocols be approved by pharmacists for preparation, use and disposal of cytotoxic drugs used as adjuncts in glaucoma surgery.*

➢ After surgery offer people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss one of the following:

- pharmacological treatment (a prostaglandin analogues, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP
- further surgery
- Laser trabeculoplasty or cyclo-diode laser treatment.

➢ Offer people with COAG who prefer not to have surgery or who are not suitable for surgery:

- alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP,
- laser trabeculoplasty or cyclo-diode laser treatment.

8.11 Research recommendations on treatment for patients with COAG

See APPENDIX G

8.11.1 Update of National survey of trabeculectomy

The GDG recommended the following research question:

➢ What are the current NHS national benchmarks for surgical success and complications in people with COAG undergoing trabeculectomy drainage surgery with and without pharmacological augmentation?

Why this is important

The answer to this question would provide more accurate and up-to-date evidence for surgical treatment in COAG. Surgical success and complication rates could then be used to update benchmarks for clinical audit and assist in planning service provision. It would also then be possible to inform people having surgery of the chances of success and complications. The current evidence base is the National Survey of Trabeculectomy. However, this is now 10 years old and techniques have changed. The benchmarks created from the new survey would set a standard against which newer techniques could be evaluated. The study design would be similar to the audit of 10 years ago, to allow comparison of outcomes now in the light of changes in technique and the recommendations made by that audit..

8.11.2 Laser treatment

The GDG recommended the following research question:

➢ What is the clinical effectiveness and cost effectiveness of initial argon, diode or selective laser trabeculoplasty compared with prostaglandin analogues alone or laser trabeculoplasty plus prostaglandin analogues in combination in people with COAG?

Why this is important

The answer to this question would provide data on the comparative clinical effectiveness and cost effectiveness of laser treatment versus modern ocular hypotensive agents, particularly prostaglandin analogues. Laser treatment may control IOP in some people for a time without the need for topical medications, and in others, it may offer additional benefit to topical medications. In either case there may be cost savings and improved prevention of progression. Existing trials of laser trabeculoplasty compared with pharmacological treatment use outdated pharmacological agents. Because of the lack of evidence, the role of laser trabeculoplasty in COAG management cannot be clearly defined. An RCT should be used to answer this research question, and sham laser treatment would be needed to enable double masking or at least single masking.

9 Complementary and alternative interventions

9.1 Introduction

This chapter addresses approaches other than the mainstream interventions that are directed towards the lowering of IOP. The GDG decided to investigate the effectiveness of neuroprotective agents as a possible alternative to IOP lowering treatments. These agents attempt to preserve those cells which have been adversely affected by a glaucoma 'insult' and remain vulnerable to damage[73]. A variety of pharmacological agents, growth factors, and other compounds have been reported to be neuroprotective in vitro, and in a number of neurologic and neurodegenerative disorders.

An initial search was also undertaken to identify other candidate complementary and alternative treatments for OHT and COAG. Two reviews[120,122] suggested that a range of treatments may be of value for glaucoma patients.

We conducted a subsequent search for evidence on the following interventions and approaches in patients with OHT and COAG.:

- neuroprotective agents (i.e. memantine)
- acupuncture
- megavitamins
- special diets
- herbal remedies (including cannabis and cannabinoids)
- ginkgo biloba
- exercise
- spinal manipulation
- homeopathy
- meditation (including relaxation techniques)
- therapeutic touch

9.2 Complementary and alternative treatments

We searched for RCT evidence investigating the effectiveness of these interventions using the same criteria which were applied for evidence supporting the medical, laser and surgical interventions.

9.2.1 Comparison of complementary and alternative treatments used alone or as an adjuvant

9.2.1.1 Clinical evidence

No studies meeting the inclusion criteria for any of the treatments mentioned above were identified

9.2.1.2 Economic evidence

No studies meeting the inclusion criteria for any of the treatments mentioned above were identified

9.2.1.3 Patient views evidence

No studies were identified

9.3 Conclusions

In the absence of objective scientific evidence supporting the use of these approaches the consensus view of the GDG was sought. It was decided that without either supportive evidence or accepted practice it was not possible to form an opinion either in support of or against the use of the identified candidate complementary and alternative treatments for glaucoma. As such, no recommendations on these interventions have been made.

10 Service Provision

10.1 Introduction

The majority of patients in the UK who develop COAG are initially identified when they present to their own optometrist for routine eye examination. Optometrists employ a case-finding approach to identifying individual patients who either exhibit signs consistent with COAG, or appear to be at risk of COAG development. Traditionally, individuals identified in this manner are then referred, via their General Practitioner, for comprehensive specialist examination by Ophthalmologists within the Hospital Eye Service (HES). Within the HES setting patients receive a formal diagnosis and ongoing management, if required, by ophthalmology staff. Patients with no evidence of COAG are typically discharged, whilst those diagnosed with COAG receive appropriate treatment and ongoing monitoring. Individuals with ocular hypertension or COAG suspect status that are considered at sufficient risk of COAG development receive either treatment and HES monitoring, HES monitoring alone or discharge, dependent upon the specific clinical scenario of risk of COAG development.

Over the past decade, increasing demand for care of patients with COAG, ocular hypertension and COAG suspect status has led to involvement of non-medical and non-ophthalmologist medical healthcare professionals in COAG care beyond traditional roles. NHS service developments have also supported and encouraged changes to provision of COAG care. This has resulted in deviations from the traditional patient pathway in which non-ophthalmologist healthcare professionals participate in roles previously undertaken by ophthalmologists. In some locations, revised pathways now provide for parts of COAG-related patient care in non-HES locations. In the future it is possible that an increasing proportion of these patients will need to be managed by non-medical and non-ophthalmologist healthcare professionals to meet the burgeoning demands on COAG service provision.

In this chapter we examine evidence on effectiveness of care delivered by different healthcare professionals. For the purposes of this guideline the term 'healthcare professional' refers to a trained individual involved in glaucoma related care including: ophthalmologists, optometrists, orthoptists, pharmacists, nurses and general practitioners. We have reviewed the evidence for diagnosis, monitoring and treatment.

10.2 Matrices of healthcare professionals considered in our clinical questions

Below are the matrices showing where evidence was identified which compared agreement between different groups of healthcare professionals in the management of ocular hypertension and COAG. A box filled with **Yes** represents where evidence was found and is reviewed in this chapter. A box filled with **No** represents where no evidence was found or where the resulting statistical measure for agreement between comparisons was less than moderate. In this case no section on this comparison is included in the chapter. A box crossed out represents where the comparison was not considered for review.

Matrix 1: Effectiveness of diagnosis by different healthcare professionals

General ophthalmologist						
Specialist ophthalmologist	Yes p. 228					
Certified optometrist with specialist interest	Yes p. 229	No				
Non specialist optometrist	Yes p. 225	Yes p. 226	No			
Orthoptist with specialist interest + training	No	No	No	No		
Nurse with specialist interest + training	No	No	No	No	No	
	General ophthalmologist	Specialist ophthalmologist	Certified optometrist with specialist interest	Non specialist optometrist	Orthoptist with specialist interest + training	Nurse with specialist interest + training

Matrix 2: Effectiveness of monitoring by different healthcare professionals

General ophthalmologist						
Specialist ophthalmologist	No					
Certified optometrist with specialist interest	No	No				
Non specialist optometrist	Yes p. 232	No	No			
Orthoptist with specialist interest + training	No	No	No	No		
Nurse with specialist interest + training	No	No	No	No	No	
	General ophthalmologist	Specialist ophthalmologist	Certified optometrist with specialist	Non specialist optometrist	Orthoptist with specialist interest +	Nurse with specialist interest + training

			interest		training	

Matrix 3: Effectiveness of treatment by different healthcare professionals

General ophthalmologist						
Specialist ophthalmologist	Yes p. 239					
Certified optometrist with specialist interest	No	Yes p. 240				
Non specialist optometrist	Yes p. 237	Yes p. 238	No			
Orthoptist with specialist interest + training	No	No	No	No		
Nurse with specialist interest + training	No	No	No	No	No	
	General ophthalmolo-gist	Specialist Ophthalmolo-gist	Certified optometrist with specialist interest	Non specialist optometrist	Orthoptist with specialist interest + training	Nurse with specialist interest + training

10.3 Effectiveness of diagnosis by different healthcare professionals

We searched for any studies comparing the agreement in the diagnosis of ocular hypertension or COAG between the different groups of healthcare professionals listed in the matrix at the beginning of this chapter. We did not compare agreement within groups.

10.3.1 Non specialist optometrist compared to general ophthalmologist

See Evidence Table 22, Appendix D

10.3.1.1 Clinical evidence

Table 10-148: Non specialist optometrist compared to general ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for vertical cup-to-disc ratio[55,57]	2	Retrospective observational	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for optic disc haemorrhage[55,57]	2	Retrospective observational	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	

(a) *Both studies were observer masked but both studies tested agreement in the ability to read 48 pairs of stereo photographs rather than clinical examination of patients. One study[56] did not report confidence intervals for the kappa statistic.*

(b) *There is variation between studies noted in number of participating optometrists and ophthalmologists and their experience and training.*

Table 10-149: Non specialist optometrist compared to general ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for vertical cup-to-disc ratio	96	Range from: 0.31 fair (CI95%: 0.31 - 0.41) to 0.46 moderate	Low
Inter-observer agreement for optic disc haemorrhage	96	Range from: 0.42 moderate (CI95%: 0.37 – 0.47) to 0.77 substantial	Low

10.3.1.2 Economic evidence

No studies were identified.

10.3.1.3 Patient views evidence

No studies were identified.

10.3.1.4 Evidence statements - Non specialist optometrist compared to general ophthalmologist

Clinical There is fair to moderate agreement between non specialist optometrists and general ophthalmologists in assessment of vertical cup-to-disc ratio assessment but the evidence is from retrospective examination from stereo photograph pairs. (LOW QUALITY)

There is moderate to substantial agreement between non specialist optometrists and general ophthalmologists in detecting the presence of optic disc haemorrhage but the evidence is from retrospective examination from stereo photograph pairs. (LOW QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared non specialist optometrist to general ophthalmologist.

10.3.2 Non specialist optometrist compared to specialist ophthalmologist

See Evidence Table 22, Appendix D

10.3.2.1 Clinical evidence

Table 10-150: Non specialist optometrist compared to specialist ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for diagnosis decisions[6]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)
Inter-observer agreement for vertical cup-to-disc ratio[148]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)
Inter-observer agreement optic disc haemorrhage[148]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)
Inter-observer agreement for overall health status of optic nerve head[148]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

(a) *One study[6] was observer masked and patients randomly selected from community optometrist referrals but only one consultant ophthalmologist and one trainee general ophthalmologist participated in the study. The other study[148] was not observer masked, patients were not recruited in a random or consecutive fashion and only one consultant ophthalmologist participated in the study*

(b) *In one study[6] the community optometrists participating in the study received in-house training through glaucoma clinic attendance with the consultant ophthalmologist. In the other study[148] the community optometrists participating in the study attended 2 hours of lectures on optic disc examination.*

Table 10-151: Non specialist optometrist compared to specialist ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for diagnosis decisions	100	0.70 substantial (CI95%: 0.54 - 0.87)	Moderate
Inter-observer agreement for vertical cup-to-disc ratio	50	0.84 almost perfect (CI95%: 0.81 - 0.87)	Moderate
Inter-observer agreement optic disc haemorrhage	50	0.67 substantial (CI95%: 0.45 - 0.89)	Moderate
Inter-observer agreement for overall health status of optic nerve head	50	0.62 substantial (CI95%: 0.53 - 0.70)	Moderate

10.3.2.2 Economic evidence

No studies were identified.

10.3.2.3 Patient views evidence

No studies were identified.

10.3.2.4 Evidence statements - Non specialist optometrist compared to specialist ophthalmologist

Clinical There is substantial agreement on the kappa scale between non specialist optometrists with in-house training and specialist ophthalmologists in diagnostic management decisions from all test results. (MODERATE QUALITY)

There is almost perfect agreement on the kappa scale between non specialist optometrists with in-house training and specialist ophthalmologists in assessment of vertical cup-to-disc ratio. (MODERATE QUALITY)

There is substantial agreement on the kappa scale between non specialist optometrists with in-house training and specialist ophthalmologists in detecting the presence of optic disc haemorrhage. (MODERATE QUALITY)

There is substantial agreement on the kappa scale between non specialist optometrists with in-house training and specialist ophthalmologists in assessment of overall health status of the optic nerve head. (MODERATE QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared non specialist optometrists to specialist ophthalmologists.

10.3.3 Specialist ophthalmologist compared to general ophthalmologist

See Evidence Table 22, Appendix D

10.3.3.1 Clinical evidence

Table 10-152: Specialist ophthalmologist compared to general ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for diagnosis decisions[6]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

(a) *The study was observer masked and patients randomly selected from community optometrist referrals but only one consultant ophthalmologist and one trainee general ophthalmologist participated in the study.*

(b) *The community optometrists participating in the study received in-house training through glaucoma clinic attendance with the consultant ophthalmologist.*

Table 10-153: Specialist ophthalmologist compared to general ophthalmologist - Clinical summary of findings

Outcome	*Number of patients*	*Mean kappa statistic*	*Quality*
Inter-observer agreement for diagnosis decisions	100	0.54 moderate (CI95%: 0.35 - 0.73)	Moderate

10.3.3.2 Economic evidence

No studies were identified.

10.3.3.3 Patient views evidence

No studies were identified.

10.3.3.4 Evidence statements - Specialist ophthalmologist compared to general ophthalmologist

Clinical There is moderate agreement on the kappa scale between specialist ophthalmologists and general ophthalmologists in diagnostic management decisions from all test results. (MODERATE QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared specialist ophthalmologists to general ophthalmologists.

10.3.4 General ophthalmologist compared to certified optometrist with a special interest

See Evidence Table 24, Appendix D

10.3.4.1 Clinical evidence

No studies were identified.

10.3.4.2 Economic evidence

We found a cost analysis comparing a referral refinement scheme to normal practice in the UK. Patients in the scheme are referred from a community optometrist to an optometrist with a special interest who decides whether the patient needs to be referred to the Hospital Eye Service. In the comparative normal practice arm, patients are referred directly from the community optometrist to the Hospital Eye Service via a GP. See economic evidence table in Appendix D for details.

Table 10-154: General ophthalmologist compared to certified optometrist with a special interest - Economic study characteristics

Study	*Limitations*	*Applicability*	*Other Comments*
Henson2003[60]	Serious limitations (a)	Partially applicable (b)	

(a) *Not a full economic evaluation. Cost of false negatives was not included.*

(b) *Patients were referred from community optometrists to either an optometrist with special interest or a GP and the Hospital Eye Service. Hence this study does not entirely answer the clinical question.*

Table 10-155: General ophthalmologist compared to certified optometrist with a special interest - Economic summary of findings

Study	*Incremental cost (2001 £) for 3 years of referral scheme*	*Incremental effects*	*ICER*	*Uncertainty*
Henson2003[60]	13,426	NR	NR	If 23 patients per month are referred to the certified optometrist, the scheme saves approximately £16 per patient.

10.3.4.3 Patient views evidence

No studies were identified.

10.3.4.4 Evidence statements - General ophthalmologist compared to certified optometrist with a special interest

Clinical No studies were identified where the statistical agreement between general ophthalmologist and certified optometrist with a specialist interest was either moderate or better.

Economic Referring patients to accredited optometrists could decrease costs compared to a direct referral to ophthalmologists. The evidence has serious limitations and only partial applicability.

10.3.5 Recommendations and link to evidence

Recommendation	**Diagnosis of OHT and suspected COAG and formulation of a management plan should be made by a suitably trained healthcare professional with:** • **a specialist qualification (when not working under the supervision of a consultant ophthalmologist) and** • **relevant experience.**
Relative values of different outcomes	Accurate measurement of visual field, optic nerve, IOP and the anterior chamber drainage angle are all considered as equally important outcomes because COAG is defined by all four. Further studies are needed to show agreement between different types of clinicians in the assessment of these parameters.
Trade off between clinical benefits and harms	Patients may receive their diagnosis sooner if evaluated in a community setting. Diagnosis of OHT and COAG suspects by staff other than consultant ophthalmologists may increase access to consultants' care for patients requiring formal COAG diagnosis. Refer to section 1.8 for assumptions for OHT and COAG suspect.
Economic considerations	Diagnosis by healthcare professionals other than ophthalmologists could be cost-saving even when the cost of referrals to ophthalmologists is taken into account.
Quality of evidence	The clinical evidence was of variable quality due to the following limitations: studies were not carried out in a systematic and controlled way, and there was the potential for selection bias as some patients were volunteers. The economic evidence has serious limitations because the only study identified was not a full economic evaluation, the cost of false negatives were not estimated and the capital cost of necessary equipment for accredited optometrists was not included. The economic evidence has partial applicability as it does not directly answer the clinical question.
Other considerations	Although not addressed as a clinical question the GDG noted that there is not always a high level of agreement between specialist ophthalmologists. However specialist ophthalmologists are considered to be the reference standard in this review. Therefore the reliability of our reference standard could be questionable. Evidence is only available for optometrists, with no studies available for other non-medical healthcare professionals or non-ophthalmologist medical

staff.

The GDG noted that the correct equipment to complete diagnostic assessments in keeping with the reference standards for tonometry, standard automated central thresholding perimetry and biomicroscopic slit lamp examination are required for healthcare professionals to perform diagnosis in a community setting and should be available.

Patient preference for assessment at hospital or in the community should be considered.

10.3.6 Supporting recommendations

Recommendation	**Refer people with suspected optic nerve damage or suspected visual field defect to a consultant ophthalmologist for consideration of a definitive diagnosis of COAG and formulation of a management plan.**
Trade off between clinical benefits and harms	The consequence of either failing to identify COAG or incorrect diagnosis may lead to irreversible blindness and visual disability.
Economic considerations	There are high costs associated with false negative and false positive diagnoses of COAG. It is important to obtain the most accurate diagnosis.
Other considerations	None

Recommendation	**Healthcare professionals involved in the diagnosis of OHT, COAG suspect status and preliminary identification of COAG should be trained in case detection and referral refinement and be able to identify abnormalities based on relevant clinical tests and assessments. They should understand the principles of diagnosis of OHT and COAG and be able to perform and interpret all of the following:** • **medical and ocular history** • **differential diagnosis** • **Goldmann applanation tonometry (slit lamp mounted)** • **standard automated perimetry (central thresholding test)** • **central supra-threshold perimetry** • **stereoscopic slit lamp biomicroscopic examination of anterior segment** • **examination of the posterior segment using a slit lamp binocular indirect ophthalmoscopy** • **gonioscopy** • **Van Herick's peripheral anterior chamber depth assessment test** • **CCT measurement.**
Trade off between clinical benefits and harms	Training is likely to improve quality of care by increasing the healthcare professional's knowledge of discriminatory power (sensitivity and specificity).
Economic considerations	None
Other considerations	The GDG noted that the correct equipment to complete diagnostic assessments in keeping with the reference standards for tonometry, standard automated central thresholding perimetry and biomicroscopic slit lamp examination are required for healthcare professionals to perform diagnosis in a community setting and should be available.

10.4 Effectiveness of monitoring by different healthcare professionals

We searched for any studies comparing the agreement in the monitoring of ocular hypertension or COAG between the different groups healthcare professionals listed in the matrix at the beginning of this chapter. We did not compare agreement within groups.

10.4.1 Non specialist optometrist compared to general ophthalmologist

See Evidence Tables 22 and 24, Appendix D

10.4.1.1 Clinical evidence

Table 10-156: Non specialist optometrist compared to general ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for visual field assessment for right and left eyes[8]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	
Inter-observer agreement for follow up intervals[8]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	
Inter-observer agreement (ICC) for visual field assessment for right and left eyes[52,142]	1	RCT	No serious limitations (a)	No serious inconsistency	No serious indirectness	(c)
Inter-observer agreement (ICC) for vertical cup-to-disc ratio assessment for right and left eyes[52,142]	1	RCT	No serious limitations (a)	No serious inconsistency	No serious indirectness	(c)
Inter-observer agreement (ICC) for IOP measurement for right and left eyes[52,142]	1	RCT	No serious limitations (a)	No serious inconsistency	No serious indirectness	(c)
Inter-observer agreement for vertical cup-to-disc ratio[55,57]	2	Retrospective observational	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	
Inter-observer agreement for optic disc haemorrhage [55,57]	2	Retrospective observational	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	

(a) *One study[8] was observer masked but it was not clear whether the patients were recruited in a randomised or consecutive fashion. Only one general ophthalmologist (research fellow) and one senior optometrist participated in the study and confidence intervals for the kappa statistic were not reported. Both the studies[55,57] were observer masked but tested agreement in the ability to read 48 pairs of stereo photographs rather than clinical examination of patients. One study[56] did not report confidence intervals for the kappa statistic. The RCT study[52,142] did not report confidence intervals for the ICC agreement statistic.*

(b) *For the studies[55,57] there is variation between studies noted in number of participating optometrists and ophthalmologists and their experience and training.*
(c) *For the RCT study[52,142] participating community optometrists received in-house training through lectures and demonstrations. An adjusted Intraclass Correlation Coefficient (ICC) was used in place of the kappa statistic which provides and equivalent scale to measure agreement between the community optometrists and the general ophthalmologists in the Hospital Eye Service setting.*

Table 10-157: Non specialist optometrist compared to general ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for visual field assessment for right and left eyes	54	0.81 almost perfect (right eye) 0.80 substantial (left eye)	Moderate
Inter-observer agreement for follow up intervals	54	0.97 almost perfect	Moderate
Inter-observer agreement (ICC) for visual field assessment for right and left eyes	403	0.55 moderate (right eye) 0.61 substantial (left eye)	High
Inter-observer agreement (ICC) for vertical cup-to-disc ratio assessment for right and left eyes	403	0.50 moderate (right eye) 0.54 moderate (left eye)	High
Inter-observer agreement (ICC) for IOP measurement for right and left eyes	403	0.45 moderate (right eye) 0.40 fair (left eye)	High
Inter-observer agreement for vertical cup-to-disc ratio	96	Range from: 0.31 fair (CI95%: 0.31 - 0.41) to 0.46 moderate	Low
Inter-observer agreement for optic disc haemorrhage	96	Range from: 0.42 moderate (CI95%: 0.37 – 0.47) to 0.77 substantial	Low

10.4.1.2 Economic evidence

We found a UK study where patients with COAG were randomised to either follow-up by the Hospital Eye Service or community optometrists. See economic evidence table in Appendix D for details.

Table 10-158: Non specialist optometrist compared to general ophthalmologist - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Coast1997[23] (a)	Serious limitations (b)	Partially applicable (c)	

(a) *Based on a RCT[52,140]*
(b) *Not a full economic evaluation; cost of false positives and false negatives was not included and optometrists fees were probably underestimated.*
(c) *Optometrists were volunteers from community optometrists. It is a shared care scheme rather than a comparison between two alternative healthcare professionals.*

Table 10-159: Non specialist optometrist compared to general ophthalmologist - Economic summary of findings

Study	Incremental full cost (£) per year per patient	Incremental effects	ICER	Uncertainty
Coast1997[23]	13 (a)	NR	NR	When follow up interval in with optometrist was similar to that with ophthalmologist, monitoring by optometrist costs £14 less per patient.

(a) *Costs include cost of staff, training of optometrists, consumables, referrals from optometrists to ophthalmologist (19% patients), and overheads.*

10.4.1.3 Patient views evidence

No studies were identified.

10.4.1.4 Evidence statements - Non specialist optometrist compared to general ophthalmologist

Clinical There is almost perfect and substantial agreement on the kappa scale between non specialist optometrists and general ophthalmologists in visual field assessment for the right and left eyes respectively. (MODERATE QUALITY)

There is almost perfect agreement on the kappa scale between non specialist optometrists and general ophthalmologists in follow-up intervals. (MODERATE QUALITY)

There is moderate and substantial agreement on the ICC scale between non specialist optometrists with in-house training and general ophthalmologists in visual field assessment for the right and left eyes respectively. (HIGH QUALITY)

There is moderate and substantial agreement on the ICC scale between non specialist optometrists with in-house training and general ophthalmologists in assessment of vertical cup-to-disc ratio for both eyes. (HIGH QUALITY)

There is moderate and fair agreement on the ICC scale between non specialist optometrists with in-house training and general ophthalmologists in IOP measurement for the right and left eyes respectively. (HIGH QUALITY)

There is fair to moderate agreement between non specialist optometrists and general ophthalmologists in assessment of vertical cup-to-disc ratio assessment but the evidence is from retrospective examination from stereo photograph pairs. (LOW QUALITY)

There is moderate to substantial agreement between non specialist optometrists and general ophthalmologists in detecting the presence of optic disc haemorrhage but the evidence is from retrospective examination from stereo photograph pairs. (LOW QUALITY)

Economic Monitoring by non specialist optometrist is more costly than monitoring by general ophthalmologist unless the follow-up intervals are similar. The evidence has serious limitations and partial applicability.

10.4.2 Recommendations and link to evidence

Recommendation	**People with a confirmed diagnosis of OHT or suspected COAG and who have an established management plan may be monitored (but not treated) by a suitably trained healthcare professional with knowledge of OHT and COAG, relevant experience, and ability to detect a change in clinical status. The healthcare professional should be able to perform and interpret all of the following:** • **Goldmann applanation tonometry (slit lamp mounted)** • **standard automated perimetry (central thresholding test)** • **central supra-threshold perimetry (this visual field strategy may be used to monitor people with OHT or COAG suspect status when they have normal visual field)** • **stereoscopic slit lamp biomicroscopic examination of anterior segment** • **Van Herick's peripheral anterior chamber depth assessment test** • **examination of the posterior segment using slit lamp binocular indirect ophthalmoscopy.**
Relative values of different outcomes	The most important aspects of monitoring are: Progression Detection of changes in clinical status Diagnosis, including being alert to ocular and systemic comorbidities Starting treatment Changing treatment Tests at each visit Follow up interval
Trade off between clinical benefits and harms	Factors to be considered during monitoring are: Prevention of sight loss Side effects of treatment Interactions with other medications Incorrect treatment (absent or inadequate) leading to sight loss Incorrect diagnosis leading to sight loss Incorrect diagnosis leading to over treatment
Economic considerations	Monitoring by trained healthcare professionals other than ophthalmologists could be cost-saving even when the cost of referrals is taken into account.
Quality of evidence	The clinical evidence was of variable quality due to the following

limitations: studies were not carried out in a systematic and controlled way, and there was the potential for selection bias as some patients were volunteers.

The economic evidence has serious limitations and partial applicability because the only study identified was not a full economic evaluation, the cost of false positives and false negatives was not included, and there was potential selection bias as some patients were volunteers.

The optometrists in the study were volunteers. The study was a shared care scheme rather than a comparison between the care of two alternative healthcare professionals.

Other considerations

Specialist ophthalmologists are considered to be the reference standard in this review. Although not addressed as a clinical question the GDG noted that there is not always a high level of agreement between specialist ophthalmologists themselves.

Evidence is only available for optometrists, with no studies available for other non-medical healthcare professionals or non-ophthalmologist medical staff.

The GDG noted that the correct equipment to complete diagnostic assessments in keeping with the reference standards for tonometry, standard automated central thresholding perimetry and biomicroscopic slit lamp examination are required for healthcare professionals to perform diagnosis in a community setting and should be available.

Patient preference for assessment at hospital or in the community should be considered.

10.5 Effectiveness of treatment by different healthcare professionals

We searched for any studies comparing the agreement in the decisions to treat patients with ocular hypertension or COAG between the different groups healthcare professionals listed in the matrix at the beginning of this chapter. We did not compare agreement within groups.

10.5.1 Non specialist optometrist compared to general ophthalmologist

See Evidence Table 22, Appendix D

10.5.1.1 Clinical evidence

Table 10-160: Non specialist optometrist compared to general ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for decision to treat[6]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for treatment decisions (start/increase/reduce) for right and left eyes[8]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	

(a) *One study[6] was observer masked and patients randomly selected from community optometrist referrals but only one consultant ophthalmologist and one trainee general ophthalmologist participated in the study. The other study[8] was observer masked but it was not clear whether the patients were recruited in a randomised or consecutive fashion. Only one general ophthalmologist (research fellow) and one senior optometrist participated in the study and confidence intervals for the kappa statistic were not reported.*

Table 10-161: Non specialist optometrist compared to general ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for decision to treat	100	0.62 substantial (CI95%: 0.45 - 0.79)	Moderate
Inter-observer agreement for treatment decisions (start/increase/reduce) for right and left eyes	54	1.00 perfect (right eye) 0.93 almost perfect (left eye)	Moderate

10.5.1.2 Economic evidence

No studies were identified.

10.5.1.3 Patient views evidence

No studies were identified.

10.5.1.4 Evidence statements - Non specialist optometrist compared to general ophthalmologist

Clinical There is substantial agreement on the kappa scale between non specialist optometrists with in-house training and general ophthalmologists in decision to treat. (MODERATE QUALITY)

There is perfect and almost perfect agreement on the kappa scale between non specialist optometrists and general ophthalmologists in treatment decisions (start/increase/reduce) for the right and left eyes respectively. (MODERATE QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared non specialist optometrists to general ophthalmologists.

10.5.2 Non specialist optometrist compared to specialist ophthalmologist

See Evidence Table 22, Appendix D

10.5.2.1 Clinical evidence

Table 10-162: Non specialist optometrist compared to specialist ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for decision to treat[6]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

(a) *The study was observer masked and patients randomly selected from community optometrist referrals but only one consultant ophthalmologist and one trainee general ophthalmologist participated in the study.*
(b) *The community optometrists participating in the study received in-house training through glaucoma clinic attendance with the consultant ophthalmologist.*

Table 10-163: Non specialist optometrist compared to specialist ophthalmologist - Clinical summary of findings

Outcome	*Number of patients*	*Mean kappa statistic*	*Quality*
Inter-observer agreement for decision to treat	100	0.72 substantial (CI95%: 0.57 - 0.86)	Moderate

10.5.2.2 Economic evidence

No studies were identified.

10.5.2.3 Patient views evidence

No studies were identified.

10.5.2.4 Evidence statements - Non specialist optometrist compared to specialist ophthalmologist

Clinical There is substantial agreement on the kappa scale between non specialist optometrists with in-house training and specialist ophthalmologists in decision to treat. (MODERATE QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared non specialist optometrists to specialist ophthalmologists.

10.5.3 Specialist ophthalmologist compared to general ophthalmologist

See Evidence Table 22, Appendix D

10.5.3.1 Clinical evidence

Table 10-164: Specialist ophthalmologist compared to general ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for decision to treat[6]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for treatment decisions (start/increase/reduce)[7]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

(a) *One study[6] was observer masked and patients randomly selected from community optometrist referrals but only one consultant ophthalmologist and one trainee general ophthalmologist participated in the study. The other study[7] was observer masked and patients were recruited sequentially but confidence intervals for the kappa statistic are not reported and kappa statistics are only reported for one specialist ophthalmologist.*

(b) *The community optometrists participating in one study[6] received in-house training through glaucoma clinic attendance with the consultant ophthalmologist. The certified optometrists in the other study[7] also received in-house training through patient assessments with a consultant.*

Table 10-165: Specialist ophthalmologist compared to general ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for decision to treat	100	0.55 moderate (CI95%: 0.37 - 0.73)	Moderate
Inter-observer agreement for treatment decisions (start/increase/reduce)	350	0.52 moderate	Moderate

10.5.3.2 Economic evidence

No studies were identified.

10.5.3.3 Patient views evidence

No studies were identified.

10.5.3.4 Evidence statements - Specialist ophthalmologist compared to general ophthalmologist

Clinical There is moderate agreement on the kappa scale between specialist ophthalmologists and general ophthalmologists in decision to treat. (MODERATE QUALITY)

There is moderate agreement on the kappa scale between specialist ophthalmologists and general ophthalmologists in treatment decisions (start/increase/reduce). (MODERATE QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared specialist ophthalmologists to general ophthalmologists.

10.5.4 Specialist ophthalmologist compared to certified optometrist with a special interest

See Evidence Table 22, Appendix D

10.5.4.1 Clinical evidence

Table 10-166: Specialist ophthalmologist compared to certified optometrist with a special interest - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for treatment decisions (start/increase/reduce)[7]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

(a) *The study was observer masked and patients were recruited sequentially but confidence intervals for the kappa statistic are not reported and kappa statistics are only reported for one specialist ophthalmologist.*

(b) *The certified optometrists participating in the study received in-house training through patient assessments with a consultant.*

Table 10-167: Specialist ophthalmologist compared to certified optometrist with a special interest - Clinical summary of findings

Outcome	*Number of patients*	*Mean kappa statistic*	*Quality*
Inter-observer agreement for treatment decisions (start/increase/reduce)	350	0.67 substantial	Moderate

10.5.4.2 Economic evidence

No studies were identified.

10.5.4.3 Patient views evidence

No studies were identified.

10.5.4.4 Evidence statements - Specialist ophthalmologist compared to certified optometrist with a special interest

Clinical There is substantial agreement on the kappa scale between specialist ophthalmologists and certified optometrists with a specialist interest in treatment decisions (start/increase/reduce). (MODERATE QUALITY)

Economic No studies meeting the inclusion criteria were identified which compared specialist ophthalmologists to certified optometrists with a special interest.

10.5.5 Recommendations and link to evidence

Recommendations marked by an asterisk (*) are first presented separately due to the difference in supporting evidence. Later these recommendations have been merged into a single recommendation in section 10.6 (Summary of all recommendations on service provision) to reflect the importance of considering them together when managing OHT and COAG.

Recommendation	*** People with diagnoses of OHT, suspected COAG and COAG should be monitored and treated by a trained healthcare professional who has all of the following:** • **a specialist qualification (when not working under the supervision of a consultant ophthalmologist)** • **relevant experience** • **ability to detect a change in clinical status.**
Relative values of different outcomes	Treatment decisions are dependent upon: Diagnosis, including being alert to ocular and systemic comorbidities Severity of COAG or level of conversion risk Effectiveness, contra-indications, precautions and interactions of existing anti-COAG medications Tolerance of current anti-COAG medications Systemic conditions and medications
Trade off between clinical benefits and harms	Treatment by non-medical healthcare professionals or non-ophthalmologists will increase the number of healthcare professionals available from which care may be accessed.
Economic considerations	None
Quality of evidence	The clinical evidence was of moderate quality. Studies were not carried out in a systematic and controlled way and there was the potential for selection bias as some patients were volunteers.
Other considerations	There are not enough ophthalmologists at present to do all the work required so the work needs to be shared. Currently hospital lists are full and this results in delayed appointments. Evidence is only available for optometrists, with no studies available for other non-medical healthcare professionals or non-ophthalmologist medical staff.

10.5.6 Supporting recommendations

Recommendation	**Healthcare professionals involved in the monitoring and treatment of people with OHT, suspected COAG and established COAG should be trained to make management decisions on all of the following:** • **risk factors for conversion to COAG** • **coexisting pathology** • **risk of vision loss** • **monitoring and clinical status change detection (for example, visual field changes, stereoscopic slit lamp biomicroscopic examination of anterior segment and posterior segment)** • **pharmacology of IOP-lowering medications** • **treatment changes for COAG, COAG suspect status and OHT (with consideration given to relevant contraindications and interactions).**
Trade off between clinical benefits and harms	All clinical tests need to be performed correctly so as to properly inform decisions based upon results. A clear understanding of the nature of the test and how to interpret results is necessary. Decision-making should be based upon clinical circumstances and current examination.
Economic considerations	Training is costly but essential to ensure quality care.
Other considerations	Training healthcare professionals takes time.

Recommendation	**Healthcare professionals who diagnose, treat or monitor people independently of consultant ophthalmologist supervision should take full responsibility for the care they provide.**
Trade off between clinical benefits and harms	Clinical governance applies to all NHS services. Although a consultant ophthalmologist may be responsible for the care of a patient they may delegate the task diagnosis, treatment and monitoring to another suitably trained healthcare professional under their supervision. When healthcare professionals provide care independently of consultant supervision they should practice within the limits of their competence. Patients should clearly understand who is responsible for their care.
Economic considerations	None
Other considerations	None

10.6 Summary of all recommendations on service provision

➢ Diagnosis of OHT and suspected COAG and formulation of a management plan should be made by a suitably trained healthcare professional with:

- a specialist qualification (when not working under the supervision of a consultant ophthalmologist) and
- relevant experience.

➢ Refer people with suspected optic nerve damage or suspected visual field defect to a consultant ophthalmologist for consideration of a definitive diagnosis of COAG and formulation of a management plan.

➢ Healthcare professionals involved in the diagnosis of OHT, COAG suspect status and preliminary identification of COAG should be trained in case detection and referral refinement and be able to identify abnormalities based on relevant clinical tests and assessments. They should understand the principles of diagnosis of OHT and COAG and be able to perform and interpret all of the following:

- medical and ocular history
- differential diagnosis
- Goldmann applanation tonometry (slit lamp mounted)
- standard automated perimetry (central thresholding test)
- central supra-threshold perimetry
- stereoscopic slit lamp biomicroscopic examination of anterior segment
- examination of the posterior segment using a slit lamp binocular indirect ophthalmoscopy
- gonioscopy
- Van Herick's peripheral anterior chamber depth assessment test
- CCT measurement.

➢ People with diagnoses of OHT, suspected COAG and COAG should be monitored and treated by a trained healthcare professional who has all of the following:

- a specialist qualification (when not working under the supervision of a consultant ophthalmologist)
- relevant experience
- ability to detect a change in clinical status.

➢ Healthcare professionals involved in the monitoring and treatment of people with OHT, suspected COAG and established COAG should be trained to make management decisions on all of the following:

- risk factors for conversion to COAG
- coexisting pathology
- risk of vision loss
- monitoring and clinical status change detection (for example, visual field changes, stereoscopic slit lamp biomicroscopic examination of anterior segment and posterior segment)
- pharmacology of IOP-lowering medications
- treatment changes for COAG, COAG suspect status and OHT (with consideration given to relevant contraindications and interactions).

➢ People with a confirmed diagnosis of OHT or suspected COAG and who have an established management plan may be monitored (but not treated) by a suitably trained healthcare professional with knowledge of OHT and COAG, relevant experience, and ability to detect a change in clinical status. The healthcare professional should be able to perform and interpret all of the following:

- Goldmann applanation tonometry (slit lamp mounted)
- standard automated perimetry (central thresholding test)
- central supra-threshold perimetry (this visual field strategy may be used to monitor people with OHT or COAG suspect status when they have normal visual field)
- stereoscopic slit lamp biomicroscopic examination of anterior segment
- Van Herick's peripheral anterior chamber depth assessment test
- examination of the posterior segment using slit lamp binocular indirect ophthalmoscopy.

➢ Healthcare professionals who diagnose, treat or monitor people independently of consultant ophthalmologist supervision should take full responsibility for the care they provide.

10.7 Research recommendation on service provision

See APPENDIX G

The GDG recommended the following research question:

➢ In people identified on primary examination as exhibiting possible COAG, OHT or suspected COAG, what is the comparative effectiveness of diagnosis by different healthcare professions?

Why this is important

The answer to this question has the potential to improve access to care by increasing the number of available healthcare professionals and locations. The current available evidence is weak. There is one RCT, but it is of limited general use because of its design. There has not been any large-scale research on service provision in this area in the past 10 years. However, the Department of Health did pilot alternative COAG care pathways, which shows that central government is interested in this area. Primary research and several RCTs would be needed to answer the questions in this research recommendation..

11 Provision of information for patients

11.1 Introduction

The way patients are provided with information could affect the outcome of their treatment. Improved patient understanding of OHT and COAG and involvement in its management could reduce stress and uncertainty for patients and potentially improve adherence with medical treatment. This in turn could help prolong sighted lifetime.

11.1.1 Comparison of methods of giving information to patients

We searched for studies comparing the effectiveness of different ways of providing information to COAG patients in improving the outcome for patients e.g. a greater reduction in intraocular pressure, a difference in visual field progression, better adherence with medications.

11.1.1.1 Clinical evidence

No studies were identified

11.1.1.2 Economic evidence

No studies were identified

11.1.1.3 Patient views evidence

No studies were identified

11.1.2 Supporting recommendation

Recommendation	**Offer people the opportunity to discuss their diagnosis, prognosis and treatment; and provide them with relevant information in an accessible format at initial and subsequent visits. This may include information on the following:** • **their specific condition (OHT, suspected COAG and COAG), its life-long implications and their prognosis for retention of sight** • **that once lost, sight cannot be recovered** • **that glaucoma can run in families and that family members may wish to be tested for the disease** • **that COAG in the early stages and OHT and suspected COAG are symptomless** • **that most people treated for COAG will not lose their sight** • **the importance of the person's role in their own treatment – for example, the ongoing regular application of eye drops to preserve sight** • **the different types of treatment options, including mode of action, frequency and severity of side effects, and risks and benefits of treatment, so that people are able to be active in the decision making process** • **how to apply eye drops, including technique (punctal occulsion and devices) and hygiene (storage)** • **the need for regular monitoring as specified by the healthcare professional** • **methods of investigations during assessment** • **the length of time and the possible need for assistance to attend each appointment** • **support groups** • **compliance aids (such as dispensers) available from their GP or community pharmacist** • **Letter of Vision Impairment (LVI), Referral of Vision Impaired Patient (RVI) and Certificate of Visual Impairment (CVI) registration** • **Driver and Vehicle Licensing Agency (DVLA) regulations.**
Trade off between clinical benefits and harms	The GDG considered it important that patients are fully aware of their condition and its management. Information is important in allowing patients to become fully aware of their condition and its management. Opportunities for raising concerns must also be given. There is potential for harm if this is not provided, for example resulting in low adherence with treatment or monitoring appointments. Improved understanding has the potential to reduce anxiety, with the potential of impacting on the patient's

	quality of life.
Economic considerations	There is potentially a significant increase in cost effectiveness by improving COAG management. For example, if drops are instilled correctly the drug is likely to be more effective with no change in its cost.
Other considerations	None

11.2 Summary of recommendations on provision of information for patients

➢ Offer people the opportunity to discuss their diagnosis, prognosis and treatment; and provide them with relevant information in an accessible format at initial and subsequent visits. This may include information on the following:

- their specific condition (OHT, suspected COAG and COAG), its life-long implications and their prognosis for retention of sight
- that once lost, sight cannot be recovered
- that glaucoma can run in families and that family members may wish to be tested for the disease
- that COAG in the early stages and OHT and suspected COAG are symptomless
- that most people treated for COAG will not lose their sight
- the importance of the person's role in their own treatment – for example, the ongoing regular application of eye drops to preserve sight
- the different types of treatment options, including mode of action, frequency and severity of side effects, and risks and benefits of treatment, so that people are able to be active in the decision making process
- how to apply eye drops, including technique (punctal occulsion and devices) and hygiene (storage)
- the need for regular monitoring as specified by the healthcare professional
- methods of investigations during assessment
- the length of time and the possible need for assistance to attend each appointment
- support groups
- compliance aids (such as dispensers) available from their GP or community pharmacist
- Letter of Vision Impairment (LVI), Referral of Vision Impaired Patient (RVI) and Certificate of Visual Impairment (CVI) registration
- Driver and Vehicle Licensing Agency (DVLA) regulations.

11.3 Research recommendation on provision of information for patients

See APPENDIX G

The GDG recommended the following research question:

➢ What is the clinical effectiveness and cost effectiveness of providing people with COAG with a 'glaucoma card' or individual record of care compared with standard treatment?

Why this is important

The answer to this question would provide evidence of better care in terms of treatment outcome and the experience that people with COAG have. Involving them and helping them understand how to manage their COAG could reduce stress and uncertainty and potentially improve adherence to medical treatment, allowing them to remain sighted for longer. No RCTs or systematic reviews on the subject were identified. The study design for the proposed research should be an RCT. A qualitative research component would be needed to develop an appropriate intervention and patient-focused outcome measure to assess the experience of people with COAG. A standard visual function (field of vision) test would be appropriate for evaluating visual outcome. A large sample size and long study period – probably at least 5 years – would be needed to determine visual outcome, with the associated cost implications.

Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension

Appendices A – G

2nd DRAFT 12th January 2009

APPENDICES

Produced by the National Collaborating Centre for Acute Care

Contents

Appendix A

SCOPE

1 Guideline title

Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension

1.1 Short title

Glaucoma

2 Background

a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Acute Care to develop a clinical guideline on the diagnosis and management of chronic open angle glaucoma and ocular hypertension for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see section 6). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) Approximately 10% of UK blindness registrations are ascribed to glaucoma. It is estimated that in the UK about 2% of people older than 40 have chronic open angle glaucoma, and this rises to almost 10% in people older than 75. With changes in population demographics the number of people affected by glaucoma is expected to rise.

b) Chronic open-angle glaucoma tends to be asymptomatic and therefore many people will not notice any symptoms until severe visual damage has occurred. Population-based screening programmes are being considered and the Department of Health's National Screening Committee is undertaking a review of screening programmes due to be published in 2007.

c) Recent national guidelines on glaucoma include 'Guidelines for the management of open angle glaucoma and ocular hypertension' (Royal College of Ophthalmologists, 2004). The Department of Health Do Once And Share project has also developed a glaucoma pathway and dataset (2006).

d) There is a clinical need for a guideline on diagnosis and management of chronic open angle glaucoma because this is a common and potentially blinding condition associated with uncertainty and variation in clinical practice in a number of areas. These include:

- an agreed case definition for ocular hypertension and chronic open angle glaucoma
- an agreed terminology incorporating the influence of raised intraocular pressure (that is, primary open angle glaucoma compared with normal tension glaucoma)
- agreement on when to treat chronic open angle glaucoma and how aggressively to do so
- agreement on whether to treat (simple) ocular hypertension
- which tests should be standard or optional for purposes of diagnosis and chronic disease monitoring
- how frequently patients should be followed up for chronic disease monitoring purposes and whether this interval should vary with perceived disease 'severity'
- who should monitor glaucoma, where this should be undertaken and whether different care providers should be used depending on perceived disease 'severity'

4 The guideline

a) The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see appendix).

c) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults (18 and older) with a diagnosis of chronic open angle glaucoma or ocular hypertension. That is, individuals who, in the presence of open or narrow (but not occludable or closed) anterior chamber angles have one or more of the following features:

- glaucomatous visual field loss
- glaucomatous optic neuropathy
- raised intraocular pressure.

b) People with chronic open angle glaucoma or ocular hypertension associated with pseudoexfoliation or pigment dispersion.

c) People who have higher prevalence of glaucoma and may have worse clinical outcomes including:

- people with a family history of glaucoma,
- younger people (<50 years)
- people who are of black African or black Caribbean descent

4.1.2 Groups that will not be covered

a) People younger than 18 years.

b) People with secondary glaucoma (for example neovascular or uveitic) except for those described in 4.1.1 b.

c) People with, or at risk of, primary or secondary angle closure glaucoma.

d) Adults with primary congenital, infantile or childhood glaucoma.

4.2 Healthcare setting

a) Community, primary care, secondary care outpatient and day treatment services, and tertiary care specialist services

4.3 Clinical management

a) The diagnosis of chronic open angle glaucoma and ocular hypertension in patients presenting at community optometrists and those referred to hospital eye services using one or more of the tests below:

- measurement of intraocular pressure
- visual field test
- optic nerve head assessment
- anterior chamber angle assessment.

b) The appropriate use of pharmacological interventions, for example effectiveness, cost effectiveness, initiation and duration of treatment. Pharmacological treatments considered will include:

- eye drops
  - beta blockers
  - prostaglandin related drugs
  - sympathomimetics
  - carbonic anhydrase inhibitors
  - miotics
- systemic medications
  - carbonic anhydrase inhibitors

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.

c) The effectiveness of penetrating and nonpenetrating surgical drainage procedures with and without pharmacological augmentation or drainage devices.

d) The effectiveness of postsurgical drain manipulation with and without the use of pharmacological augmentation.

e) The effectiveness of laser procedures to facilitate aqueous outflow or reduce aqueous production.

f) The information, education and support needs of patients to achieve treatment concordance will be considered.

g) The most appropriate service models, where evidence of clinical and cost effectiveness is available.

h) The guideline development group will consider making recommendations on the principal complementary and alternative interventions or approaches to care relevant to the guideline topic.

i) The guideline development group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

j) Population based screening programmes for glaucoma are not within the remit of this guideline.

4.4 Status

4.4.1 Scope

This is the final scope.

4.4.2 Guideline

The development of the guideline recommendations will begin in June 2007.

Associated NICE Guidance Medicines Concordance (in development) for publication December 2008.

5 Further information

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'The guidelines manual'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

6 Referral from the Department of Health

The Department of Health asked the Institute:

'To prepare a clinical guideline on the diagnosis and management of chronic open angle glaucoma and ocular hypertension (raised intraocular pressure). The guideline should include recommendations on the most appropriate service models where evidence of effectiveness is available.'

Appendix B

1 Declarations of interests

1.1 Introduction

All members of the GDG and all members of the NCC-AC staff were required to make formal declarations of interest at the outset, and these were updated at every subsequent meeting throughout the development process. No interests were declared that required actions.

1.2 Declarations of interests of the GDG members

1.2.1 Ms Cecilia Fenerty

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She declared a personal pecuniary interest: she is a glaucoma speciality ophthalmic consultant working for the NHS with a subspecialty interest in glaucoma. She declared two non-personal pecuniary interests: her place of work, Manchester Royal Eye Hospital, received an award from Allergan in 2006 for £2500. She also received a Pfizer grant for research into persistence with glaucoma therapy (this research was not product specific). She declared no personal family interests or personal non-pecuniary interests.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	The declarations above plus: She declared a non-personal pecuniary interest: she received a donation of drop aids from Alcon for a study into compliance. This device is product specific as it can only be used with Travatan/Duotrav. The trial itself was not funded by Alcon.
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.2 Ms Wendy Franks

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She declared a personal pecuniary interest: she is a glaucoma specialist employed by Moorfields Eye Hospital NHS Trust and undertakes work in private practice. She declared a non-personal pecuniary interest: she received sponsorship for studies from Alcon, Allergan and Pfizer in her capacity as Director of Glaucoma contract research, a post she relinquished upon joining the GDG. She declared a personal non-pecuniary interest: she has published papers about her views of effectiveness of medical treatments. She declared no personal family interests.
Second GDG Meeting **(25th June 2007)**	She did not attend this meeting.
Third GDG Meeting **(26th July 2007)**	The declarations above plus: She declared a non-personal pecuniary interest: her department has received grants from the pharmaceutical industry.
Fourth GDG Meeting **(11th September 2007)**	She did not attend this meeting.
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	She did not attend this meeting.
Seventh GDG Meeting **(29th January 2008)**	The declarations above plus: She declared a personal pecuniary interest: she received an honorarium of €2000 covering travel/subsistence expenses to speak at the Rotterdam Glaucoma Club in January 2008. The lectures were not related to any company products. The meeting had sponsorship from Alcon.
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.3 Ms Mary Freeman

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She did not attend this meeting.
Second GDG Meeting **(25th June 2007)**	She declared a personal pecuniary interest: she received an honorarium from Novartis for speaking at an annual nurse symposium on age related macular degeneration in 2006 and 2007. Novartis also supported the attendance of an annual international conference in September '06 on "Advances in Wet AMD" by providing reasonable accommodation and travel expenses. Alcon supported the attendance of a meeting for specialist nurses on glaucoma by providing reasonable mileage cost and overnight accommodation in Hemel Hempstead. She sees NHS glaucoma patients. She declared no personal family interest, non-personal pecuniary interest, or personal non-pecuniary interest.
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	The declarations above plus: She declared a non-personal pecuniary interest: she is a study co-ordinator for a phase 3 trial using Macugen for diabetic maculopathy supported by Pfizer.
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	The declarations above plus: She declared a personal pecuniary interest: She was invited to speak at the annual Nurse symposium 2008 sponsored by Novartis on AMD. She accepted reasonable hospitality (overnight accommodation and transport). She declined an honorarium which was instead made payable to a hospital charitable fund. Post meeting she declared a personal non-pecuniary interest: She has had an article accepted for publication in Eye News on the glaucoma referral scheme in Sheffield. Due for publication Oct/Nov 08. She declared two personal pecuniary interests: She has also been invited to chair and speak at an educational meeting on glaucoma for nurses in Doncaster in November 08 sponsored by Allergan. She declined an honorarium and her speaker fees will be paid to the Trust. She has also invited to speak at the Royal College of Nursing (RCN) conference on the glaucoma referral scheme in Sheffield in September 08 for which she accepted reasonable overnight accommodation and transport cost reimbursement.

1.2.4 Mr Dennis Keight

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared a personal pecuniary interest: he owns shares in Astrazeneca and his pension is paid by Astrazeneca. Astrazeneca do not manufacture any drugs within this guideline. He declared a personal family interest: his wife is employed by Western Cheshire PCT as an IT project manager. His wife also acts as a consultant for Informing Healthcare (Wales) as a Health Data Consultant. He declared a personal non-pecuniary interest: he is a member of the International Glaucoma Association. He declared no non-personal pecuniary interest.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	He did not attend this meeting.
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	He amended his personal family interest: His wife is no longer employed directly by Western Cheshire PCT but occasionally undertakes consultancy work for them.
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.5 Ms Susana Ramirez-Florez

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She declared two non-personal pecuniary interests: She is an NHS Consultant Ophthalmologist and also undertakes work in private practice. Additionally the Department of Health, through the modernisation agency awarded Peterborough District Hospital, where she is employed, a grant of £422000 for the Glaucoma Community Optometrist Project. She declared no personal family interests or personal non-pecuniary interests.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	The declarations above plus: She declared a non-personal pecuniary interest: she took part in a visual field workshop for ophthalmic doctors in Peterborough which were sponsored by Allergan.
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	The declarations above plus: She declared two non-personal pecuniary interests: Peterborough & Stamford NHS Foundation Trust, her employer, distributed 60 posters designed by the Glaucoma Alliance Group lead by the RNIB to GP practices which were printed by Allergan, Alcon and Pfizer. After prior approval from NICE she was nominated for an award from Allergan, and was given travel expenses and accommodation to the venue after the Annual Ophthalmological Congress in Liverpool.
Ninth GDG Meeting **(25th April 2008)**	The declarations above plus: She declared a non-personal pecuniary interest: Her place of work is a pilot site for the Sibling Awareness Project led by the RNIB.
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	The declarations above plus: She declared a personal non-pecuniary interest: she was invited to a Merck Sharp and Dohme glaucoma meeting on 2 November 2008.
Twelfth GDG Meeting **(9th July 2008)**	The declarations above plus: She declared a non-personal pecuniary interest: Peterborough & Stamford NHS Foundation Trust was awarded 3rd place in the recent Allergan glaucoma awards and the prize of £3,000 will be spent on equipment for glaucoma care.
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.6 Ms Safina Rashid

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She did not attend this meeting.
Second GDG Meeting **(25th June 2007)**	She declared a personal pecuniary interest: she is an NHS employee. She declared no personal family interest, non-personal pecuniary interest, or personal non-pecuniary interest.
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	She did not attend this meeting.
Fifth GDG Meeting **(24th October 2007)**	The declarations above plus: She declared a personal pecuniary interest: she is the NHS Chair for BIOS (British and Irish Orthoptic Society).
Sixth GDG Meeting **(5th December 2007)**	She did not attend this meeting.
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	The declarations above plus: She declared a non-personal pecuniary interest: she led a teaching programme for nurses and optometrists which was sponsored by Pfizer via a £400 donation to the departmental research fund.
Eleventh GDG Meeting **(3rd June 2008)**	She did not attend this meeting.
Twelfth GDG Meeting **(9th July 2008)**	She did not attend this meeting.
Thirteenth GDG Meeting **(31st July 2008)**	She did not attend this meeting

1.2.7 Mr John Sparrow

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared a personal pecuniary interest: he is an NHS employee caring for glaucoma patients. He is a member of a limited liability partnership, the Consultant Eye Surgeons Partnership which delivers both NHS and private work although he does not undertake work in private practice. He declared two non-personal pecuniary interests: he was previously a primary investigator in the UK Glaucoma Treatment Study (UKGTS), a RCT of treatment for early glaucoma vs placebo. Funding for this study came through Moorfields Eye Hospital R&D department but originally was a grant from a drug company. In May 2007, he resigned as a PI at the study steering group meeting. Additionally he was previously a member of a research group investigating opacification of a particular lens implant (Hydroview H60M) used for cataract surgery. A grant from the lens manufacturer (Bausch & Lomb) now supports work looking into the extent and nature of this problem with recall of the patients who received this lens implant in Bristol. In May 2007, he resigned as an investigator on this study. He declared no personal family interests or personal non-pecuniary interests.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	He did not attend this meeting.
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.8 Mr Paul Spry

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared the following personal pecuniary interests: he owns shares in Healthcare Locums. He is also Editor-in-chief of the Optometric Glaucoma Society E-Journal, the production of which is sponsored by Pfizer. He is Chair of the College of Optometrists Glaucoma Panel. He declared a personal family interest: his wife works for Somerset PCT as a pharmacist medicines manager. He declared a non-personal pecuniary interest: he is a member of the steering committee for the United Kingdom Glaucoma treatment study. This study is funded by Pfizer. He declared no personal non-pecuniary interests.
Second GDG Meeting **(25th June 2007)**	He did not attend this meeting.
Third GDG Meeting **(26th July 2007)**	He did not attend this meeting.
Fourth GDG Meeting **(11th September 2007)**	He did not attend this meeting.
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	The declarations above plus: He declared two personal pecuniary interests: he works for New Medica which is an extended contractor for glaucoma care to NHS. He also received expenses for accommodation and transport costs to a conference on shared care from Allergan. His honorarium was donated to the Bristol Eye Hospital charitable trust.
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.9 Mr Chris Steele

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared a personal pecuniary interest: he is an NHS employee caring for glaucoma patients. He declared no personal family interest, non-personal pecuniary interest or personal non-pecuniary interest.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	He did not attend this meeting.
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	He did not attend this meeting.

1.2.10 Ms Sheila Urquhart

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She declared a personal pecuniary interest: she was employed by Peterborough PCT as Clinical Governance Optometry Lead. She declared no personal family interest, non-personal pecuniary interest or personal non-pecuniary interest.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	She did not attend this meeting.
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	She declared that her personal pecuniary interest had expired: she is no longer Clinical Governance Optometry Lead for Peterborough PCT and so did not receive PCT funding after 30th April 2008
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.11 Mr Richard Wormald

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared a personal pecuniary interest: he is an NHS employee caring for glaucoma patients. He also undertakes work in private practice. He declared a non-personal non-pecuniary interest: he is on the steering committee for the UK Glaucoma Treatment Trial which is a study sponsored by Pfizer.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	The declarations above plus: He declared a personal non-pecuniary interest: he has been asked to speak at the Closed Meeting of the European Glaucoma Society on the deliberations of the NICE GDG
Fourth GDG Meeting **(11th September 2007)**	The declarations above plus: He declared a personal pecuniary interest: he received a fee from Merck Sharp and Dohme for £400 for running Saturday workshop on research methods for residents. He declared two non-personal pecuniary interests: He is investigator for the UK Glaucoma Treatment Trial and co-investigator for a compliance study at St Georges both of which are funded by Pfizer. He declared a personal non-pecuniary interest: he was invited to join the UK Glaucoma Alliance.
Fifth GDG Meeting **(24th October 2007)**	The declarations above plus: He declared a personal pecuniary interest: he received accommodation and travel expenses for a meeting in Durham on glaucoma funded by Alcon.
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	The declarations above plus: He declared a personal pecuniary interest: he spoke at a Merck Sharp and Dohme funded meeting and donated his fees to glaucoma department at Moorfields Eye Hospital.
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	He declared a personal pecuniary interest, expenses and honorarium for visit to University of Ottawa a visiting professor.
Eleventh GDG Meeting **(3rd June 2008)**	He did not attend this meeting.
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	The declarations above plus: He declared a personal pecuniary interest: he is chairing a clinical trials workshop in September 2008 which is sponsored by ACCO who in turn is funded by Allergan, his travel and accommodation expenses will be paid for.

1.2.12 Mr David Wright

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared two personal pecuniary interests: as well as being a salaried employee of the International Glaucoma Association he is paid honoraria from Allergan, Pfizer, Alcon and Merck Sharp and Dohme, on an occasional basis for giving independent patients' perspective presentations. He declared a non-personal pecuniary interest: the International Glaucoma Association, his employer, receives funding for publications from Allergan, Alcon and Pfizer. Allergan has part funded a nurse employed by the IGA. He declared a personal non-pecuniary interest: he is a member of the UK Glaucoma Alliance, World Patient Association Eye Health programme. He declared no personal family interests.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	He did not attend this meeting.
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	The declarations above plus: He declared a non-personal pecuniary interest: he received an honorarium worth £1500 from Pfizer for the All Eyes on Glaucoma Programme.
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	He did not attend this meeting.
Eight GDG Meeting **(13th March 2008)**	He did not attend this meeting.
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.3 Declarations of interests of the NCC-AC members

GDG meeting	Declaration of Interests of the NCC-AC members
First GDG meeting **(4th June 2007)**	None
Second GDG Meeting **(25th June 2007)**	None
Third GDG Meeting **(26th July 2007)**	None
Fourth GDG Meeting **(11th September 2007)**	None
Fifth GDG Meeting **(24th October 2007)**	None
Sixth GDG Meeting **(5th December 2007)**	None
Seventh GDG Meeting **(29th January 2008)**	None
Eight GDG Meeting **(13th March 2008)**	None
Ninth GDG Meeting **(25th April 2008)**	None
Tenth GDG Meeting **(19th May 2008)**	None
Eleventh GDG Meeting **(3rd June 2008)**	None
Twelfth GDG Meeting **(9th July 2008)**	None
Thirteenth GDG Meeting **(31st July 2008)**	None

Appendix C

Search Strategies

Overview of Search Strategies

Searches were constructed by using the groups of terms listed below. These groups are expanded in full in the section on **Search Terms** following this.

Clinical searches were conducted in the following databases: Medline and Embase for all searches; The Cochrane Library (Central Register of Controlled Trials) for all searches excluding adverse events, risk factors and progression searches; Cinahl excluding laser and surgical treatments, additionally we did not have access to Cinahl when we ran the gonioscopy search; PsychINFO for patient education and information for patients; AMED (Allied and Complementary Medicine Database) for the complementary and alternative interventions; The Cochrane Database of Systematic Reviews and the Health Technology Assessment Database were searched for anything relating to glaucoma.

Economic searches were conducted in Medline, Embase, NHS EED (NHS Economic Evaluation Database) and HEED (Health Economic Evaluations Database). The HTA (Health Technology Assessment) database was also searched.

Adverse events – medications

Glaucoma/OHT terms
AND
Drugs intervention terms
AND
Adverse event terms
NOT
Animal/Publications filter

Complementary therapy

Simplified glaucoma/OHT terms
AND
Complementary therapy terms
AND
RCT filter or systematic review filter
NOT
Animal/Publications filter

Diagnosis searches

Glaucoma/OHT terms
AND
Diagnostic test terms
NOT
Animal/Publications filter

Economic searches

Glaucoma/OHT terms

AND
Intervention terms (Drugs/Surgery/Laser)
AND
Economic filter
NOT
Animal/Publications filter

Gonioscopy

Gonioscopy complete search provided below

Intervention searches

Glaucoma/OHT terms
AND
Intervention terms (Drugs/Surgery/Laser)
AND
RCT filter or systematic review filter
NOT
Animal/Publications filter

Monitoring

Simplified glaucoma/OHT terms
AND
Monitoring terms
NOT
Animal/Publications filter

Patient education

Glaucoma/OHT terms
AND
Patient education terms
NOT
Animal/Publications filter

Patient views

Glaucoma/OHT terms
AND
Patient view terms

Pigmentary dispersion syndrome

Pigmentary dispersion syndrome terms
AND
RCT filter
NOT
Animal/Publications filter

Progression searches

1.IOP-Glaucoma association complete search provided below
2. Progression from OHT to glaucoma complete search provided below

Quality of life

Glaucoma/OHT terms
AND
Quality of life terms
NOT
Animal/Publications filter

Risk factors

Risk factors complete search provided below

Service provision

Simplified glaucoma/OHT terms
AND
Service provision terms
NOT
Animal/Publications filter

Search terms

Adverse event terms

Adverse event terms Medline (OVID platform)

1 (ae or co or po or to or de).fs.

2 (safe or safety or side effect$ or undesirable effect$ or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.

3 risk$.mp. or exp cohort studies/ or between group:.tw.

4 1 or 2 or 3

Adverse event terms Embase (OVID platform)

1 (ae or co or po or to or de).fs.

2 (safe or safety or side effect$ or undesirable effect$ or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.

3 risk$.mp. or exp cohort studies/ or between group:.tw.

4 1 or 2 or 3

Adverse events complete search Cinahl (Dialog/Datastar interface)

1 nonexperimental-studies#.de.

2 (confidence adj intervals).sh. or (funding adj source).sh.

3 1 or 2

Animal/Publication filter

Animal/publication Medline (OVID platform)

1 (Case-Reports NOT Randomized-Controlled-Trial OR Letter OR Historical-Article OR Review-Of-Reported-Cases).PT. OR (exp Animals/ NOT Humans/)

Animal/publication filter Embase (OVID platform)

1 Case-Study/ or Abstract-Report/ or Letter/ or (case adj report).tw. or ((exp Animal/ or Nonhuman/ or exp Animal-Experiment/) not exp Human/)

Complementary therapy terms

Complementary therapy terms Medline (OVID platform)

1 exp Complementary Therapies/ or (herbal remed$ or homeopath$).tw.

2 Ginkgo biloba/ or ginkgo biloba.tw.

3 exp vitamins/ or (vitamin$ or multivitamin$ or megavitamin$ or mega-vitamin or multi-vitamin).tw.

4 (therapeutic touch or (touch adj5 (therap$ or heal$ or treat$)) or ((energy based or energy-based) and (therap$ or heal$ or treat$)) or energy healing or Reiki).tw.

5 exercise therapy/ or exercise.tw.

6 diet therapy/ or special diet.tw.

7 Osteopathic medicine/ or exp Musculoskeletal manipulation/ or spinal manipulation.tw.

8 (meditation or relaxation).tw.

9 cannabis/ or cannabinoids/ or (cannabis or marijuana).tw.

10 neuroprotective agents/ or memantine/ or (neuroprotective agent$ or neuroprotection or memantine).tw.

11 exp acupuncture therapy/ or acupuncture.tw.

12 or/1-11

Complementary therapy terms Embase (OVID platform)

1 exp alternative medicine/ or (herbal remed$ or homeopath$).tw.

2 ginkgo biloba/ or ginkgo biloba.tw.

3 exp vitamin/ or (vitamin$ or multivitamin$ or megavitamin$ or multi-vitamin$ or mega-vitamin$).tw.

4 (therapeutic touch or (touch adj5 (therap$ or heal$ or treat$)) or ((energy based or energy-based) and (therap$ or heal$ or treat$)) or energy healing or Reiki).tw.

5 exercise therapy/ or exercise.tw.

6 diet therapy/ or special diet.tw.

7 Osteopathic medicine/ or Manipulative medicine/ or spinal manipulation.tw.

8 (meditation or relaxation).tw.

9 Cannabis/ or cannabinoids/ or (cannabis or marijuana).tw.

10 Neuroprotection/ or memantine/ or (neuroprotective agent$ or neuroprotection or memantine).tw.

11 Acupuncture/ or acupuncture.tw.

12 or/1-11

Complementary therapy terms The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Complementary Therapies explode all trees

2 herbal remed* or homeopath*

3 MeSH descriptor Ginkgo biloba, this term only

4 ginkgo biloba

5 MeSH descriptor Vitamins explode all trees

6 vitamin* or multivitamin* or megavitamin* or mega-vitamin or multi-vitamin

7 (therapeutic touch or (touch near (therap* or heal* or treat*)) or ((energy based or energy-based) and (therap* or heal* or treat*)) or energy healing or Reiki)

8 MeSH descriptor Exercise Therapy explode all trees

9 exercise

10 MeSH descriptor Diet Therapy, this term only

11 special diet

12 spinal manipulation

13 meditation or relaxation

14 MeSH descriptor Cannabis, this term only

15 MeSH descriptor Cannabinoids, this term only

16 cannabis or marijuana

17 MeSH descriptor Neuroprotective Agents explode all trees

18 MeSH descriptor Memantine, this term only

19 neuroprotective agent* or neuroprotection or memantine

20 MeSH descriptor Acupuncture, this term only

21 acupuncture

22 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

Complementary therapy terms Cinahl (NLH Search 2.0 interface)

1 ALTERNATIVE THERAPIES/ OR (herbal remed* OR homeopath*)

2 GINKGO BILOBA/ OR ginkgo biloba

3 exp VITAMINS/ OR vitamin* OR multivitamin* OR megavitamin* OR mega-vitamin OR multi-vitamin

4 (therapeutic AND touch OR (touch AND (therap* OR heal* OR treat*)) OR ((energy based OR energy-based) AND (therap* OR heal* OR treat*)) OR energy AND healing OR Reiki).af

5 EXERCISE/ OR THERAPEUTIC EXERCISE/ OR exercise

6 DIET THERAPY/ OR SPECIAL DIET/ OR special diet

7 OSTEOPATHIC MEDICINE/ OR exp MUSCULOSKELETAL MANIPULATION/ OR spinal manipulation

8 (meditation OR relaxation).af

9 CANNABIS/ OR CANNABINOIDS/ OR cannabis OR marijuana

10 NEUROPROTECTIVE AGENTS/ OR MEMANTINE/ OR neuroprotective agent* OR neuroprotection OR memantine

11 exp ACUPUNCTURE THERAPY/ OR acupuncture

12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

Complementary therapy terms Amed (NLH Search 2.0 interface)

1 COMPLEMENTARY MEDICINE/ OR COMPLEMENTARY THERAPIES/ OR (herbal remed* OR homeopath*)

2 GINKGO BILOBA/ OR ginkgo biloba

3 exp VITAMINS/ OR vitamin* OR multivitamin* OR megavitamin* OR mega-vitamin OR multi-vitamin

4 (therapeutic AND touch OR (touch AND (therap* OR heal* OR treat*)) OR ((energy AND based OR energy-based) AND (therap* OR heal* OR treat*)) OR energy AND healing OR Reiki).af

5 EXERCISE/ OR exercise

6 (special AND diet).ti,ab

7 OSTEOPATHY/ OR spinal manipulation

8 MEDITATION/ OR RELAXATION/ OR (meditation OR relaxation).af

9 CANNABIS/ OR CANNABINOIDS/ OR cannabis OR marijuana

10 neuroprotective agent* OR neuroprotection OR memantine

11 ACUPUNCTURE/ OR acupuncture

12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

Diagnostic test terms

Diagnostic test terms Medline (OVID platform)

1 exp Perimetry/

2 (Visual field exam$ or visual field test or SITA or Humphrey or Swedish interactive testing algorithm or Henson or ((threshold or supra threshold or supra-threshold) adj3 perimetry)).tw.

3 exp Tonometry, Ocular/

4 (Tonomet$ or applanation or tonopen or pneumotonometry or Perkins or Goldmann or pulse air).tw.

5 exp tomography, optical coherence/ or exp tomography, optical/ or exp ophthalmoscopy/

6 (((stereo or digital or optic nerve head) adj3 photograph$) or Heidelberg or ((scanning or laser) adj3 ophthalmoscop$) or optical coherence tomography or polarimetry or nerve fiber analys$ or nerve fibre analys$ or Octopus or frequency doubling technology or Armaly).tw.

7 or/1-6

Diagnostic test terms Embase (OVID platform)

1 Perimetry/

2 (Visual field exam$ or visual field test or SITA or Humphrey or Swedish interactive testing algorithm or Henson or ((threshold or supra threshold or supra-threshold) adj3 perimetry)).tw.

3 Tonometry, Ocular/

4 (Tonomet$ or applanation or tonopen or pneumotonometry or Perkins or Goldmann or pulse air).tw.

5 exp tomography, exp optical coherence/ or tomography, optical/ or ophthalmoscopy/ or scanning laser ophthalmoscopy/

6 (((stereo or digital or optic nerve head) adj3 photograph$) or Heidelberg or ((scanning or laser) adj3 ophthalmoscop$) or optical coherence tomography or polarimetry or nerve fiber analys$ or nerve fibre analys$ or Octopus or frequency doubling technology or Armaly).tw.

7 or/1-6

Diagnostic test terms The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Perimetry explode all trees

2 (Visual field exam* or visual field test or SITA or Humphrey or Swedish interactive testing algorithm or Henson or ((threshold or supra threshold or supra-threshold) near perimetry))

3 MeSH descriptor Tonometry, Ocular explode all trees

4 (Tonomet* or applanation or tonopen or pneumotonometry or Perkins or Goldmann or pulse air)

5 MeSH descriptor Tomography, Optical explode all trees

6 MeSH descriptor Tomography, Optical Coherence explode all trees

7 MeSH descriptor Ophthalmoscopy explode all trees

8 (((stereo or digital or optic nerve head) near photograph*) or Heidelberg or ((scanning or laser) near ophthalmoscop*) or optical coherence tomography or polarimetry or nerve fiber analys* or nerve fibre analys* or Octopus or frequency doubling technology or Armaly)

9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

Diagnostic test terms Cinahl (NLH Search 2.0 interface)

1 exp PERIMETRY/

2 (Visual AND field AND exam* OR visual AND field AND test OR SITA OR Humphrey OR Swedish AND interactive AND testing AND algorithm OR Henson OR ((threshold OR supra threshold OR supra-threshold) AND perimetry)).ti,ab

3 exp TONOMETRY/

4 (Tonomet* OR applanation OR tonopen OR pneumotonometry OR Perkins OR Goldmann OR pulse AND air).ti,ab

5 exp OPHTHALMOSCOPY/

6 (((stereo OR digital OR optic nerve head) AND photograph*) OR Heidelberg OR ((scanning OR laser) AND ophthalmoscop*) OR optical AND coherence AND tomography OR polarimetry OR nerve AND fiber AND analys* OR nerve AND fibre AND analys* OR Octopus OR frequency AND doubling AND technology OR Armaly).ti,ab

7 1 or 2 or 3 or 4 or 5 or 6

Economic filter

Economic filter (including quality of life terms) Medline (OVID platform)

1 exp "Costs and Cost Analysis"/

2 Economics/

3 exp Economics, Nursing/ or exp Economics, Medical/ or Economics/ or exp Economics, Hospital/ or exp Economics, Pharmaceutical/

4 exp "Fees and Charges"/

5 exp Budgets/

6 budget$.tw.

7 cost$.tw.

8 (economic$ or pharmacoeconomic$ or pharmaco-economic$).tw.

9 (price$ or pricing$).tw.

10 (financial or finance or finances or financed).tw.

11 (fee or fees).tw.

12 (value adj2 (money or monetary)).tw.

13 ec.fs.

14 exp Resource Allocation/

15 resourc$ allocat$.tw.

16 expenditure$.tw.

17 (fund or funds or funding or fundings or funded).tw.

18 (ration or rations or rationing or rationings or rationed).tw.

19 (saving or savings).tw.

20 or/1-19

21 exp "Quality of Life"/

22 quality of life.tw.

23 life quality.tw.

24 Value of Life/

25 quality adjusted life.tw.

26 (qaly$ or qald$ or qale$ or qtime$).tw.

27 disability adjusted life.tw.

28 daly$.tw.

29 exp Health Status Indicators/

30 health status.tw.

31 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

32 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

33 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

34 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

35 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

36 (euroqol or euro qol or eq5d or eq 5d).tw.

37 (hql or hqol or h qol or hrqol or hr qol).tw.

38 (hye or hyes).tw.

39 health$ equivalent$ year$.tw.

40 (hui or hui1 or hui2 or hui3).tw.

41 utilit$.tw.

42 disutilit$.tw.

43 rosser.tw.

44 quality of wellbeing.tw.

45 qwb.tw.

46 willingness to pay.tw.

47 standard gamble$.tw.

48 time trade off.tw.

49 time tradeoff.tw.

50 tto.tw.

51 factor analy$.tw.

52 preference based.tw.

53 (state adj2 valu$).tw.

54 Life Expectancy/

55 life expectancy$.tw.

56 ((duration or length or period of time or lasting or last or lasted) adj4 symptom$).tw.

57 or/21-56

58 exp models, economic/

59 models, theoretical/ or models, organizational/

60 markov chains/

61 markov$.tw.

62 Monte Carlo Method/

63 monte carlo.tw.

64 exp Decision Theory/

65 (decision$ adj2 (tree$ or analy$ or model$)).tw.

66 exp models, statistical/

67 model$.tw.

68 or/58-67

69 20 or 57 or 68

Economic filter (including quality of life terms) Embase (OVID platform)

1 exp economic aspect/

2 cost$.tw.

3 (price$ or pricing$).tw.

4 (fee or fees).tw.

5 (financial or finance or finances or financed).tw.

6 (value adj2 (money or monetary)).tw.

7 resourc$ allocat$.tw.

8 expenditure$.tw.

9 (fund or funds or funding or fundings or funded).tw.

10 (ration or rations or rationing or rationings or rationed).tw.

11 (saving or savings).tw.

12 or/1-11

13 Quality of Life/

14 quality of life.tw.

15 life quality.tw.

16 quality adjusted life.tw.

17 (qaly$ or qald$ or qale$ or qtime$).tw.

18 disability adjusted life.tw.

19 daly$.tw.

20 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

21 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

22 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

23 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

24 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

25 (euroqol or euro qol or eq5d or eq 5d).tw.

26 (hql or hqol or h qol or hrqol or hr qol).tw.

27 (hye or hyes).tw.
28 health$ equivalent$ year$.tw.
29 (hui or hui1 or hui2 or hui3).tw.
30 health utilit$.tw.
31 disutilit$.tw.
32 rosser.tw.
33 (quality of wellbeing or quality of well being).tw.
34 qwb.tw.
35 willingness to pay.tw.
36 standard gamble$.tw.
37 time trade off.tw.
38 time tradeoff.tw.
39 tto.tw.
40 factor analy$.tw.
41 preference based.tw.
42 (state adj2 valu$).tw.
43 Life Expectancy/
44 life expectancy$.tw.
45 ((duration or length or period of time or lasting or last or lasted) adj4 symptom$).tw.
46 or/13-46
47 exp model/
48 exp Mathematical Model/
49 markov$.tw.
50 Monte Carlo Method/
51 monte carlo.tw.
52 exp Decision Theory/
53 (decision$ adj2 (tree$ or anlay$ or model$)).tw.
54 model$.tw.
55 or/47-55
56 12 or 46 or 55

COAG/OHT terms

COAG/OHT terms Medline (OVID platform)

1 Ocular Hypertension/
2 ((increas$ or elevat$ or high$) adj3 (ocular or intraocular or intra-ocular) adj3 pressure).tw.
3 ocular hypertension.tw.
4 exp Glaucoma, Open-Angle/
5 (open adj5 angle adj5 glaucom$).tw.

6 ((low or normal or sine) adj5 (tension or pressure) adj5 glaucom$).tw.

7 (poag or oht or ntg or npg).tw.

8 ((primary or chronic or exfoliat$ or pseudo-exfoliat$ or pseudo exfoliat$ or pseudoexfoliat$ or pigment$) adj5 glaucom$).tw.

9 or/1-8

COAG/OHT terms Embase (OVID platform)

1 Intraocular Hypertension/

2 ((increas$ or elevat$ or high$ or raise$) adj3 (ocular or intraocular or intra-ocular) adj3 pressure).tw.

3 ocular hypertension.tw.

4 Open Angle Glaucoma/

5 Low Tension Glaucoma/

6 (open adj5 angle adj5 glaucom$).tw.

7 ((low or normal or sine) adj5 (tension or pressure) adj5 glaucom$).tw.

8 (poag or oht or ntg or npg).tw.

9 ((primary or chronic or exfoliat$ or pseudo-exfoliat$ or pseudo exfoliat$ or pseudoexfoliat$ or pigment$) adj5 glaucom$).tw.

10 or/1-9

COAG/OHT terms The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Ocular Hypertension, this term only

2 ((increas* or elevat* or high* or raise*) near (ocular or intraocular or intra-ocular) near pressure)

3 ocular hypertension

4 MeSH descriptor Glaucoma, Open-Angle

5 (open near angle near glaucom*)

6 ((low or normal or sine) near (tension or pressure) near glaucom*)

7 (poag or oht or ntg or npg)

8 ((primary or chronic or exfoliat* or pseudo-exfoliat* or pseudo exfoliat* or pseudoexfoliat* or pigment*) near glaucom*)

9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

COAG/OHT terms Cinahl (NLH Search 2.0 interface)

1 OCULAR HYPERTENSION/

2 (ocular AND hypertension).ti,ab

3 GLAUCOMA/

4 1 or 2 or 3

COAG/OHT terms PsycINFO (NLH Search 2.0 interface)

1 GLAUCOMA/
2 glaucoma.ti,ab
3 (intraocular AND pressure OR intraocular AND tension).ti,ab
4 1 or 2 or 3

Gonioscopy complete search

Gonioscopy complete search Medline (OVID platform)

1 Glaucoma/
2 exp Glaucoma, Open-Angle/
3 glaucoma$.tw.
4 Ocular Hypertension/
5 ((increas$ or elevat$ or high$ or raise$) adj3 (ocular or intraocular or intra-ocular) adj3 pressure).tw.
6 ocular hypertension.tw.
7 (poag or oht or ntg or npg).tw.
8 or/1-7
9 Gonioscopy/
10 gonioscop$.tw.
11 or/9-10
12 animal/ not human/
13 (comment or letter or editorial or case reports).pt.
14 12 or 13
15 (8 and 11) not 14

Gonioscopy complete search Embase (OVID platform)

1 Glaucoma/
2 Open Angle Glaucoma/
3 Low Tension Glaucoma/
4 glaucoma$.tw.
5 Intraocular Hypertension/
6 ((increas$ or elevat$ or high$ or raise$) adj3 (ocular or intraocular or intra-ocular) adj3 pressure).tw.
7 ocular hypertension.tw.
8 (poag or oht or ntg or npg).tw.
9 or/1-8
10 Gonioscopy/
11 gonioscop$.tw.
12 or/10-11
13 (exp Animal/ or Nonhuman/ or exp Animal-Experiment/) not exp Human/

14 Case-Study/ or Abstract-Report/ or Letter/ or (case adj report).tw.

15 13 or 14

16 (9 and 12) not 15

Gonioscopy complete search The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Gonioscopy, this term only

2 gonioscop*

3 #1 or #2

Medication intervention terms

Medication intervention terms Medline (OVID platform)

1 exp Drug Therapy/

2 exp Antihypertensive Agents/

3 exp adrenergic beta-antagonists/

4 (beta-blocker$ or betablocker$ or timolol or carteolol or betaxolol or levobunolol or befunolol or metipranolol or teoptic or betagan or optipranolol).mp.

5 (prostaglandin$ or bimatoprost or latanoprost or travoprost or unoprostone or lumigan or xalatan or travatan).mp.

6 (carbonic anhydrase inhibitor$ or dorzolamid$ or brinzolamid$ or acetazolamide or azopt or trusopt or diamox).mp.

7 (sympathomimetic$ or brimonidin$ or apraclonidin$ or clonidin$ or dipivefrin$).mp.

8 (miotic$ or pilocarpin$).mp.

9 or/1-8

Medication intervention terms Embase (OVID platform)

1 exp Drug Therapy/

2 exp Antihypertensive Agents/

3 exp Antiglaucoma Agent/

4 exp Beta Adrenergic Receptor Blocking Agent/

5 (beta-blocker$ or betablocker$ or timolol or carteolol or betaxolol or levobunolol or befunolol or metipranolol or teoptic or betagan or optipranolol).mp.

6 (prostaglandin$ or bimatoprost or latanoprost or travoprost or unoprostone or lumigan or xalatan or travatan).mp.

7 (carbonic anhydrase inhibitor$ or dorzolamid$ or brinzolamid$ or acetazolamide or azopt or trusopt or diamox).mp.

8 (sympathomimetic$ or brimonidin$ or apraclonidin$ or clonidin$ or dipivefrin$).mp.

9 (miotic$ or pilocarpin$).mp.

10 or/1-9

Medication intervention terms The Cochrane Library (Wiley Interscience

interface)

1 MeSH descriptor Drug Therapy explode all trees

2 MeSH descriptor Antihypertensive Agents explode all trees

3 MeSH descriptor Adrenergic beta-Antagonists explode all trees

4 beta-blocker* or betablocker* or timolol or carteolol or betaxolol or levobunolol or befunolol or metipranolol or teoptic or betagan or optipranolol

5 prostaglandin* or bimatoprost or latanoprost or travoprost or unoprostone or lumigan or xalatan or travatan

6 carbonic anhydrase inhibitor* or dorzolamid* or brinzolamid* or acetazolamide or azopt or trusopt or diamox

7 sympathomimetic* or brimonidin* or apraclonidin* or clonidin* or dipivefrin*

8 miotic* or pilocarpin*

9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

Medication intervention terms Cinahl (NLH Search 2.0 interface)

1 exp DRUG THERAPY/

2 exp ANTIHYPERTENSIVE AGENTS/

3 (beta-blocker* OR betablocker* OR timolol OR carteolol OR betaxolol OR levobunolol OR befunolol OR metipranolol OR teoptic OR betagan OR optipranolol).af

4 (prostaglandin* OR bimatoprost OR latanoprost OR travoprost OR unoprostone OR lumigan OR xalatan OR travatan).af

5 (carbonic AND anhydrase AND inhibitor* OR dorzolamid* OR brinzolamid* OR acetazolamide OR azopt OR trusopt OR diamox).af

6 (sympathomimetic* OR brimonidin* OR apraclonidin* OR clonidin* OR dipivefrin*).af

7 (miotic* OR pilocarpin*).af

8 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7

Monitoring terms

Monitoring terms Medline/Embase (Ovid interface)

1 (review$ adj (interval$ or visit$ or inspect$ or examin$ or attend$ or check-up$ or recall$)).tw.

2 (routine$ adj (interval$ or visit$ or inspect$ or examin$ or attend$ or check-up$ or recall$)).tw.

3 (periodic$ adj (interval$ or visit$ or inspect$ or examin$ or attend$ or check-up$ or recall$)).tw.

4 (regular adj (visit$ or inspect$ or examin$ or attend$ or check-up$)).tw.

5 (recall$ adj interval$).tw.

6 (visit$ adj5 clinic$).tw.

7 or/1-6

Monitoring terms The Cochrane Library (Wiley Interscience interface)

1 (review* next (interval* or visit* or inspect* or examin* or attend* or check-up* or recall*))

2 (routine* next (interval* or visit* or inspect* or examin* or attend* or check-up* or recall*))

3 (periodic* next (interval* or visit* or inspect* or examin* or attend* or check-up* or recall*))

4 (regular next (visit* or inspect* or examin* or attend* or check-up*))

5 (recall* next interval*)

6 (visit* near clinic*).tw.

7 #1 or #2 or #3 or #4 or #5 or #6

Patient education terms

Patient education terms Medline (OVID platform)

1 Patients/ or Inpatients/ or Outpatients/

2 Caregivers/ or exp Family/ or exp Parents/ or exp Legal-Guardians/

3 (patients or carer$ or famil$).tw.

4 or/1-3

5 Popular-Works-Publication-Type/ or exp Information-Services/ or Publications/ or Books/ or Pamphlets/ or Counseling/ or Directive-Counseling/

6 4 and 5

7 ((patient or patients) adj3 (education or educate or educating or information or literature or leaflet$ or booklet$ or pamphlet$)).ti,ab.

8 Patient-Education/ or Patient-Education-Handout-Publication-Type/

9 or/6-8

Patient education terms Embase (OVID platform)

1 Patient/ or Hospital patient/ or Outpatient/

2 Caregiver/ or exp Family/ or exp Parent/

3 (patients or carer$ or famil$).tw.

4 or/1-3

5 Information Service/ or Information center/ or Publication/ or Book/ or Counseling/ or Directive counseling/

6 4 and 5

7 ((patient or patients) adj3 (education or educate or educating or information or literature or leaflet$ or booklet$ or pamphlet$)).ti,ab.

8 Patient information/ or Patient education/

9 or/6-8

Patient education terms Cinahl (NLH Search 2.0 interface)

1 PATIENTS/

2 INPATIENTS/

3 CAREGIVERS/

4 exp FAMILY/

5 exp PARENTS/

6 exp GUARDIANSHIP, LEGAL/

7 (patients OR carer* OR famil*).ti,ab

8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 exp INFORMATION SERVICES/

10 BOOKS/

11 PAMPHLETS/

12 COUNSELING/

13 9 or 10 or 11 or 12

14 8 and 13

15 ((patient OR patients) AND (education OR educate OR educating OR information OR literature OR leaflet* OR booklet* OR pamphlet*)).ti,ab

16 PATIENT EDUCATION/

17 14 or 15 or 16

Patient education terms PsycINFO (NLH Search 2.0 interface)

1 PATIENTS/ OR MEDICAL PATIENTS/

2 OUTPATIENTS/

3 CAREGIVERS/

4 exp FAMILY/

5 exp PARENTS/

6 GUARDIANSHIP/

7 (patients OR carer* OR famil*).ti,ab

8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 exp INFORMATION SERVICES/

10 BOOKS/

11 COUNSELING/

12 9 or 10 or 11

13 8 and 13

14 ((patient OR patients) AND (education OR educate OR educating OR information OR literature OR leaflet* OR booklet* OR pamphlet*)).ti,ab

15 CLIENT EDUCATION/

16 HEALTH EDUCATION/

17 14 or 15 or 16

Patient view terms

Patient view terms Medline (OVID platform)

1 exp Consumer-Satisfaction/ or Personal-Satisfaction/ or exp Patient-Acceptance-Of-Health-Care/ or exp Consumer-Participation/ or exp Patient-Rights/ or Health Care Surveys/ or Questionnaires/ or Interview/ or Focus groups/

2 (patient$ adj3 (view$ or opinion$ or awareness or persistenc$ or attitude$ or compliance or satisfaction or concern$ or belief$ or feeling$ or position or idea$ or preference$ or choice$)).tw.

3 (Discomfort or comfort or inconvenience or bother or trouble or fear$ or anxiety or anxious).tw.

4 or/1-3

Patient view terms Embase (OVID platform)

1 Consumer attitude/ or patient satisfaction/ or patient compliance/ or patient right/ or health survey/ or questionnaire/ or interview/

2 (patient$ adj3 (view$ or opinion$ or awareness or persistenc$ or attitude$ or compliance or satisfaction or concern$ or belief$ or feeling$ or position or idea$ or preference$ or choice$)).tw.

3 (Discomfort or comfort or inconvenience or bother or trouble or fear$ or anxiety or anxious).tw.

4 or/1-3

Patient view terms Cinahl (NLH Search 2.0 interface)

1 PATIENT SATISFACTION/

2 CONSUMER SATISFACTION/ OR CONSUMER ATTITUDES/

3 PATIENT RIGHTS/

4 SURVEYS/

5 QUESTIONNAIRES/

6 FOCUS GROUPS/

7 INTERVIEWS/

8 ((patient* AND (view* OR opinion* OR awareness OR persistenc* OR attitude* OR compliance OR satisfaction OR concern* OR belief* OR feeling* OR position OR idea* OR preference* OR choice*))).ti,ab

9 (Discomfort OR comfort OR inconvenience OR bother OR trouble OR fear* OR anxiety OR anxious).ti,ab

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

Patient view terms PsycINFO (NLH Search 2.0 interface)

1 CONSUMER ATTITUDES/ OR CONSUMER SATISFACTION/ OR CONSUMER SURVEYS/

2 SURVEYS/

3 QUESTIONNAIRES/

4 INTERVIEWS/

5 ((patient* AND (view* OR opinion* OR awareness OR persistenc* OR attitude* OR compliance OR satisfaction OR concern* OR belief* OR feeling* OR position OR idea* OR preference* OR choice*))).ti,ab

6 (Discomfort OR comfort OR inconvenience OR bother OR trouble OR fear* OR anxiety OR anxious).ti,ab

7 1 or 2 or 3 or 4 or 5 or 6

Pigmentary dispersion syndrome terms

Pigmentary dispersion syndrome Medline/Embase (OVID platform)

1 pigment$ dispers$ syndrome.tw.

Pigmentary dispersion syndrome The Cochrane Library (Wiley Interscience interface)

1 pigment* dispers* syndrome

Progression terms

1. IOP-Glaucoma association complete search

Progression Medline (IOP-glaucoma association) (OVID platform)

1 Glaucoma/

2 Glaucoma, Open-Angle/

3 (open adj5 angle adj5 glaucom$).tw.

4 ((low or normal or sine) adj5 (tension or pressure) adj5 glaucom$).tw.

5 or/1-4

6 (visual field$ or optic disc$ or optic nerve$ or optic neuropathy$).mp.

7 ((intraocular or intra-ocular or ocular) adj pressure).mp.

8 exp regression analysis/

9 regression.tw.

10 disease progression/

11 progression.tw.

12 prognosis/

13 or/8-12

14 5 and 6 and 7 and 13

Progression Embase (IOP-glaucoma association) (OVID platform)

1 Glaucoma/

2 Open Angle Glaucoma/

3 Low Tension Glaucoma/

4 (open adj5 angle adj5 glaucom$).tw.

5 ((low or normal or sine) adj5 (tension or pressure) adj5 glaucom$).tw.

6 or/1-5

7 ((intraocular or intra-ocular or ocular) adj pressure).mp.

8 (visual field$ or optic disc$ or optic nerve$ or optic neuropathy$).mp.
9 exp regression analysis/
10 regression.tw.
11 disease course/
12 progression.tw.
13 prognosis/
14 or 9-13
15 6 and 7 and 8 and 14

2. Progression from OHT to glaucoma complete search

Progression 2 Medline (progression OHT to glaucoma) (OVID platform)

1 Glaucoma/
2 Glaucoma, Open-Angle/
3 glaucom$.tw.
4 or/1-3
5 Ocular Hypertension/
6 ((intraocular or ocular) adj hypertension).mp.
7 5 or 6
8 disease progression/
9 progression.tw.
10 conversion.tw.
11 prognosis/
12 or/8-11
13 4 and 7 and 12

Progression 2 Embase (progression OHT to glaucoma) (OVID platform)

1 Glaucoma/
2 Open Angle Glaucoma/
3 Low Tension Glaucoma/
4 glaucoma$.tw.
5 or/1-4
6 Intraocular Hypertension/
7 ((intraocular or ocular) adj hypertension).mp.
8 6 or 7
9 disease course/
10 progression.tw.
11 conversion.tw.
12 prognosis/
13 or/9-12

14 5 and 8 and 13

Quality of life terms

Quality of life terms Medline (OVID platform)

1 exp "Quality of Life"/

2 quality of life.tw.

3 life quality.tw.

4 Value of Life/

5 quality adjusted life.tw.

6 (qaly$ or qald$ or qale$ or qtime$).tw.

7 disability adjusted life.tw.

8 daly$.tw.

9 exp Health Status Indicators/

10 health status.tw.

11 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

12 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

13 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

14 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

15 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

16 (euroqol or euro qol or eq5d or eq 5d).tw.

17 (hql or hqol or h qol or hrqol or hr qol).tw.

18 (hye or hyes).tw.

19 health$ equivalent$ year$.tw.

20 (hui or hui1 or hui2 or hui3).tw.

21 utilit$.tw.

22 disutilit$.tw.

23 rosser.tw.

24 quality of wellbeing.tw.

25 qwb.tw.

26 willingness to pay.tw.

27 standard gamble$.tw.

28 time trade off.tw.

29 time tradeoff.tw.

30 tto.tw.

31 factor analy$.tw.

32 preference based.tw.

33 (state adj2 valu$).tw.

34 Life Expectancy/

35 life expectancy$.tw.

36 ((duration or length or period of time or lasting or last or lasted) adj4 symptom$).tw.

37 or/1-36

Quality of life terms Embase (OVID platform)

1 Quality of Life/

2 quality of life.tw.

3 life quality.tw.

4 quality adjusted life.tw.

5 (qaly$ or qald$ or qale$ or qtime$).tw.

6 disability adjusted life.tw.

7 daly$.tw.

8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

9 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

13 (euroqol or euro qol or eq5d or eq 5d).tw.

14 (hql or hqol or h qol or hrqol or hr qol).tw.

15 (hye or hyes).tw.

16 health$ equivalent$ year$.tw.

17 (hui or hui1 or hui2 or hui3).tw.

18 health utilit$.tw.

19 disutilit$.tw.

20 rosser.tw.

21 (quality of wellbeing or quality of well being).tw.

22 qwb.tw.

23 willingness to pay.tw.

24 standard gamble$.tw.

25 time trade off.tw.

26 time tradeoff.tw.

27 tto.tw.

28 factor analy$.tw.

29 preference based.tw.

30 (state adj2 valu$).tw.

31 Life Expectancy/

32 life expectancy$.tw.

33 ((duration or length or period of time or lasting or last or lasted) adj4 symptom$).tw.

34 or/1-33

Randomised controlled trial (RCT) filter

RCT filter Medline (OVID platform)

1 Randomized-Controlled-Trials/ or Random-Allocation/ or Double-Blind-Method/ or Single-Blind-Method/ or exp Clinical-Trials as topic/ or Cross-Over-Studies/ or Prospective-Studies/ or Placebos/

2 (Randomized-Controlled-Trial or Clinical-Trial or Controlled-Clinical-Trial).pt.

3 ((((((((((clinical or control or controlled) adj (study or trial)) or (single or double or triple)) adj (blind$3 or mask$3)) or randomised or randomized or random$) adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or crossover) adj (design or study or trial)) or placebo or placebos).ti,ab.

4 or/1-3

RCT filter Embase (OVID platform)

1 Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/

2 ((((((((((clinical or control or controlled) adj (study or trial)) or (single or double or triple)) adj (blind$3 or mask$3)) or randomised or randomized or random$) adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or crossover) adj (design or study or trial)) or placebo or placebos).ti,ab.

3 1 or 2

Risk factors complete search

Risk factors complete search Medline (OVID platform)

1 ocular hypertension/

2 ((ocular or intraocular) adj1 hypertension).tw.

3 1 or 2

4 exp Glaucoma, Open-Angle/ or Glaucoma/

5 (glaucoma or poag).tw.

6 4 or 5

7 3 and 6

8 prevalence/

9 incidence/

10 epidemiology/

11 Longitudinal Studies/

12 ((incidence or prevalence or epidemiol$) adj3 (glaucom$ or poag or vision or visual or blind$)).tw.

13 or/8-12

14 7 and 13

15 age factors/

16 aged/

17 middle aged/

18 elderly.tw.

19 exp population groups/

20 (race or racial).tw.

21 ethnic$.tw.

22 family history.tw.

23 (inherited or familial).tw.

24 myopia/

25 (myopia or myopic).tw.

26 ((short or near) adj2 sight$).tw.

27 (shortsight$ or nearsight$).tw.

28 exp Diabetes Mellitus, Type 2/

29 diabetes.tw.

30 ((exfoliat$ or pseudo-exfoliat$ or pseudo exfoliat$ or pseudoexfoliat$ or pigment$) adj5 (glaucom$ or syndrome or disorder)).tw.

31 pigment$ dispers$ syndrome.tw.

32 central corneal thickness.tw.

33 ((ocular or intraocular or intra-ocular) adj pressure).tw.

34 (cup adj2 disc adj1 ratio).tw.

35 (disc adj1 (haemorrhag$ or hemorrhag$ or bleed$)).tw.

36 or/15-35

37 7 and 36

38 exp risk/

39 causality/

40 Precipitating Factors/

41 prognosis/

42 (risk adj3 (stratif$ or assess$ or factor?)).tw.

43 (risk adj1 relative).tw.

44 (predict$ or prognosis or prognostic).tw.

45 cohort studies/

46 or/38-45

47 37 and 46

48 14 or 47

Risk factors complete search Embase (OVID platform)

1 Intraocular Hypertension/
2 ((ocular or intraocular) adj1 hypertension).tw.
3 1 or 2
4 exp OPEN ANGLE GLAUCOMA/ or GLAUCOMA/
5 (glaucoma or poag).tw.
6 4 or 5
7 3 and 6
8 PREVALENCE/
9 INCIDENCE/
10 EPIDEMIOLOGY/
11 LONGITUDINAL STUDY/
12 ((incidence or prevalence or epidemiol$) adj3 (glaucom$ or poag or vision or visual or blind$)).tw.
13 or/8-12
14 7 and 13
15 Middle Aged/
16 elderly.tw.
17 Ethnic and Racial Groups/
18 exp RACE/
19 (race or racial).tw.
20 ethnic$.tw.
21 Familial Incidence/
22 family history.tw.
23 (inherited or familial).tw.
24 MYOPIA/
25 (myopia or myopic).tw.
26 ((short or near) adj2 sight$).tw.
27 (shortsight$ or nearsight$).tw.
28 exp Diabetes Mellitus, Type 2/
29 diabetes.tw.
30 ((exfoliat$ or pseudo-exfoliat$ or pseudo exfoliat$ or pseudoexfoliat$ or pigment$) adj5 (glaucom$ or syndrome or disorder)).tw.
31 pigment$ dispers$ syndrome.tw.
32 central corneal thickness.tw.
33 ((ocular or intraocular or intra-ocular) adj pressure).tw.
34 intraocular pressure abnormality/
35 (cup adj2 disc adj1 ratio).tw.
36 (disc adj1 (haemorrhag$ or hemorrhag$ or bleed$)).tw.
37 or/15-36
38 7 and 37

39 exp RISK/

40 PROGNOSIS/

41 PREDICTION/

42 (risk adj3 (stratif$ or assess$ or factor?)).tw.

43 (risk adj1 relative).tw.

44 (predict$ or prognosis or prognostic).tw.

45 cohort analysis/

46 or/39-45

47 38 and 46

48 14 or 47

Service provision terms

Service provision terms Medline (OVID platform)

1 optometrist$.tw.

2 ophthalmologist$.tw.

3 orthoptist$.tw.

4 Nursing/ or Community Health Nursing/ or Nursing, Team/ or Nursing Staff/ or Nursing Care/ or Nursing Assessment/ or Nursing Staff, Hospital/

5 nurse$.tw.

6 or/1-5

Service provision terms Embase (OVID platform)

1 optometrist$.mp.

2 ophthalmologist$.mp.

3 orthoptist$.mp.

4 nurse$.mp.

5 or/1-4

Service provision terms The Cochrane Library (Wiley Interscience interface)

1 optometrist*

2 ophthalmologist*

3 orthoptist*

4 MeSH descriptor Nursing, this term only

5 MeSH descriptor Community Health Nursing, this term only

6 MeSH descriptor Nursing, Team explode all trees

7 MeSH descriptor Nursing Staff, this term only

8 MeSH descriptor Nursing Care, this term only

9 MeSH descriptor Nursing Assessment, this term only

10 MeSH descriptor Nursing Staff, Hospital, this term only

11 nurse*

12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

Simplified glaucoma/OHT terms

Simplified glaucoma/OHT terms Medline (OVID platform)

1 ocular hypertension/ or exp glaucoma/

2 (ocular hypertension or glaucoma).tw.

3 1 or 2

Simplified glaucoma/OHT terms Embase (OVID platform)

1 Intraocular Hypertension/ or exp glaucoma/

2 (ocular hypertension or glaucoma).tw.

3 1 or 2

Simplified glaucoma/OHT terms The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Ocular Hypertension explode all trees

2 MeSH descriptor Glaucoma, this term only

3 ocular hypertension

4 glaucoma

5 #1 OR #2 OR #3 OR #4

Surgical/laser intervention terms

Surgical/laser intervention terms Medline (OVID platform)

1 exp Ophthalmologic Surgical Procedures/

2 su.fs.

3 (surgical or surgery).tw.

4 (preoperativ$ or perioperativ$ or postoperativ$).tw.

5 (trabeculectom$ or sclerectom$ or viscocanalostom$ or iridotom$).mp.

6 (cyclo-destruction or cyclodestruction or cyclo-modulation or cyclomodulation).mp.

7 krukenberg spindle$.tw.

8 trabeculoplast$.mp.

9 laser$.mp.

10 or/1-9

Surgical/laser intervention terms Embase (OVID platform)

1 Eye surgery/

2 exp Glaucoma surgery/
3 su.fs.
4 (surgical or surgery).tw.
5 (preoperativ$ or perioperativ$ or postoperativ$).tw.
6 (trabeculectom$ or sclerectom$ or viscocanalostom$ or iridotom$).mp.
7 (cyclo-destruction or cyclodestruction or cyclo-modulation or cyclomodulation).mp.
8 krukenberg spindle$.tw.
9 trabeculoplast$.mp.
10 laser$.mp.
11 or/1-10

Surgical/laser intervention terms The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Ophthalmologic Surgical Procedures explode all trees
2 su.fs
3 surgical or surgery
4 preoperativ* or perioperativ or postoperativ*
5 trabeculectom* or sclerectom* or viscocanalostom* or iridotom*
6 cyclo-destruction or cyclodestruction or cyclo-modulation or cyclomodulation
7 krukenberg spindle*
8 trabeculoplast*
9 laser*
10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

Systematic review filter

Systematic review filter Medline (OVID platform)

1 meta-analysis/
2 (metaanalys$ or meta-analys$ or meta analys$).tw.
3 exp "review literature"/
4 (systematic$ adj3 (review$ or overview$)).tw.
5 (selection criteria or data extraction).ab. and review.pt.
6 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
7 (reference list$ or bibliograph$ or hand search$ or hand-search$ or manual search$ or relevant journals).ab.
8 or/1-7

Systematic review filter Embase (OVID platform)

1 meta analysis/
2 (metaanalys$ or meta-analys$ or meta analys$).tw.

3 systematic review/

4 (systematic$ adj3 (review$ or overview$)).tw.

5 (selection criteria or data extraction).ab. and Review.pt.

6 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.

7 (reference list$ or bibliograph$ or hand search$ or manual search$ or relevant journals).ab.

8 or/1-7

Appendix D

Evidence tables

Evidence Table 1 Diagnostic accuracy of non-contact tonometry vs. Goldmann contact tonometry

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Atkinson et al, 1992[5] **Study design:** Diagnostic **Evidence level:** II	**Patient group:** Patients from general ophthalmology outpatients departments and glaucoma clinics across 3 UK centres. (type of glaucoma not specified) **Exclusion criteria:** Uncooperative patients or those with scarred corneas **All patients** **N:** 403 eyes **Age (median):** NR **M/F:** NR **Drop outs:** NR	**Assessment tool under investigation:** Pulse air non-contact tonometry* measured before Goldmann tonometry. Three different machines: • Machines A and B (same hospital) used at least 3 readings until 3 readings lay within 5mmHg of each other • Machine C (different centre) used 4 successive readings. If any reading >30mmHg a further set was taken with machine set to 30+ mode. **Gold standard:** Goldmann applanation tonometry (GAT) (calibrated Haag-Streit AG Goldmann tonometer. • Measured within 3 minutes of pulse air reading. Patients did not move from position between measurement and instillation of oxybuprocaine 0.4% & fluorescein.	**Machine A (64 eyes) †** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test odds Post-Test Odds (Probability) +ve result Post-Test Probability -ve result **Machine B (223 eyes) †** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test odds Post-Test Odds (Probability) +ve result Post-Test Probability -ve result **Machine C (116 eyes) †** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test odds Post-Test Odds (Probability) +ve result Post-Test Probability -ve result	 81% 93% 85% 93% 31% 12.47 0.16 0.45 5.67 (85%) 5.28 (84%) 40% 95% 84% 71% 40% 8.1 0.63 0.65 5.29 (84%) 1.34 (57%) 48% 94% 63% 89% 18% 7.54 0.56 0.22 1.67 (63%) 1.12 (53%)	**Funding:** Not reported **Limitations:** Number of eyes were recruited was reported but not the number of patients. Does not report the proportion of patients with glaucoma or ocular hypertension. **Also reported:** mean (SD) IOP , and correlation coefficient (r) and linear regression equation (between two; mean (SD) differences in IOP between type of tonometer; **Additional Notes:** † (ability to detect a Goldmann IOP >21mmHg) Observer masked * Study presented as 3 studies, 3 machines used in two centres

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, Sig=statistically significant at 5%, N=total number of patients randomised, CI95%= 95% Confidence Interval

Evidence Table 2 Diagnostic accuracy of non-gonioscopic methods vs. gonioscopy

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Baskaran et al., 2007[9] **Study design:** Diagnostic **Evidence level:** III	**Patient group:** Phakic subjects with narrow angles and normal subjects with closed angles attending glaucoma or general ophthalmology clinics in the Singapore National Eye Centre. **Exclusion criteria:** Subjects with corneal disorders and uveitis excluded **<u>All patients</u>** **N:** 120 (120 eyes) **Age (mean ± SD):** 62.1 ± 11.3 **M/F:** 52/68 73% Chinese 7% Malay 20% Indian **Drop outs:** 0 **Diagnosis:** 44% PACG 56% POAG	**Reference standard:** Gonioscopy: static and indentation with 2 or 4 mirror prisms. For gonioscopy: narrow angle defined as the presence of a Schaffer grade of up to 1 (10° iridotrabecular angle) for at least 180° of the angle on gonioscopy with or without peripheral anterior synchae **Assessment tool under investigation:** Scanning peripheral Anterior Chamber Depth analyzer (SPAC) and modified Van Herick's grade Van Herick's test. Peripheral anterior chamber depth of ≤25% of the corneal thickness as angle closed and ≥40% angle open as optimal cut-off using standard photos For SPAC: 3 categorical grades for risk of angle closure S=suspect ≥4 points exceeding 95% CI; P=potential ≥4 points exceeding 72% CI; N=normal. Optimal cut-off is S or P as closed and N as open angle	**Detection of angle-closure by eye using Van Herick's test at cut off ≤25%** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result	85% (45/53) 90% (60/67) 87% (45/52) 88% (60/68) 44% (53/120) 8.13 0.17 0.44 87% (CI95% 76 – 93%) 12% (CI95% 7 – 20%)	**Funding:** National Medical research Council, Singapore **Limitations:** Asian population (73% Chinese) where PACG is more prevalent. It was not clear whether Van Herick's test was performed independently and in a masked fashion to gonioscopy. **Additional Outcomes:** **Notes:** SPAC assessment observer was masked to results of gonioscopy and Van Herick's test
			Detection of angle-closure by eye using Van Herick's test at cut off ≤5% to ≥15%	Sensitivity 30% (16/53) Specificity 100% (67/67)	
			Detection of angle-closure by eye using Van Herick's test at cut off ≤15% to ≥25%	Sensitivity 60% (32/53) Specificity 100% (67/67)	
			Detection of angle-closure by eye using Van Herick's test at cut off ≤40% to ≥75%	Sensitivity 96% (51/53) Specificity 76% (51/67)	
			Detection of angle-closure by eye using SPAC at cut off S,P =closed angle (N=open) Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result	85% (45/53) 73% (49/67) 71% (45/63) 868% (49/57) 44% (53/120) 3.16 0.21 0.44 71% (CI95% 62 – 79%) 14% (CI95% 8 – 24%)	

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
			Detection of angle-closure by eye using SPAC at cut off S =closed angle (P, N=open)	Sensitivity 60% (32/53) Specificity 85% (57/67)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, Sig=statistically significant at 5%, N=total number of patients randomised, CI95%= 95% Confidence Interval

Non-gonioscopic methods vs. gonioscopy (continued)

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Nolan et al., 2007[112] **Study design:** Diagnostic test **Evidence level:** II	**Patient group:** Patients with suspected or confirmed primary angle closure (PACG). Patients with POAG, OHT and cataracts were also included. All patients were from glaucoma clinics at the University Hospital of Singapore. **Inclusion criteria:** ≥40 years **Exclusion criteria:** Patients with pseudophakia or previous glaucoma surgery **All patients** **N:** 203 (342 eyes) **Age (median):** 62.5 (range, 40-86) **M/F:** 80/123 **Drop outs:** 3* **Diagnosis:** 17% Normal 33% Suspected/confirmed narrow angles 37% PACG 7% POAG 6% Other	**Reference standard:** Gonioscopy using Goldmann 2 mirror lens & Sussmann 4-mirror lens. Angle closure defined by gonioscopy as a Spaeth grade of 0° ≥1 Quadrant (posterior trabecular meshwork not visible) **Assessment tool under investigation:** Non-contact anterior segment optical coherence tomography (AS-OCT) (Carl Zeiss Meditec) **AS-OCT**: angle closure defined by as contact between the peripheral iris and angle wall anterior to scleral spur. Individuals classified as angle closure if ≥1 quadrants of the angle closed in either eye	**Detection of angle-closure by individual (one or both eyes)** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result **Detection of angle-closure by eye** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result	 98% (97/99) 55% (56/101) 68% (97/142) 97% (56/58) 50% (99/200) 2.20 0.04 0.50 68% (CI95%: 63 – 73%) 4% (CI95%: 1 – 13%) 94% (143/152) 55% (105/190) 63% (143/228) 92% (105/114) 44% (152/342) 2.10 0.11 0.44 63% (CI95%: 59 – 66%) 8% (CI95%: 5 – 14%)	**Funding:** National University of Singapore **Limitations:** Patients in Asian population where PACG is more prevalent. **Additional Outcomes:** **Notes:** *In 3 subjects it was not possible to obtain gonioscopic readings or OCT images Investigators were masked to gonioscopy results

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, Sig=statistically significant at 5%, N=total number of patients randomised, CI95%= 95% Confidence Interval

Non-gonioscopic methods vs. gonioscopy (continued)

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Thomas 1996[149] **Study design:** Diagnostic test **Evidence level:** II	**Patient group:** New patients attending outpatient clinic Christian Medical College, Vellore, India (type of glaucoma not specified) **Exclusion criteria:** Patients with acute conditions (4 patients were excluded: phacolytic glaucoma, phacomorphic glaucoma and corneal ulcer) **<u>All patients</u>** **N:** 96 (96 eyes) **Age (mean):** 45.45 (range 14 to 74, SD 14.90) **M/F:** 50/46 **Drop outs:** 4	**Assessment tool under investigation:** Flashlight test (1/2 and 1/3 shadow) Van Herick's test **Reference standard:** Gonioscopy performed on Haag Streit slit lamp and Goldmann single mirror goniolens followed by Sussmann 4-mirror lens for examination of peripheral anterior synchae suggestive of angle closure by glaucoma specialist. **Flashlight** – crescentic shadow formed from beam directed parallel to the iris was graded according to area between the limbus and pupillary edge. 4 grades used: more than ½ ; ½ to 1/3; minimal and no shadow **Van Herick's test** If peripheral anterior chamber depth (PACD) was ≥ to corneal thickness recorded as grade 4; 50% corneal thickness = grade 3; 25% corneal thickness = grade 2 and < 25% corneal thickness = grade 1. ***Grade 1 taken as narrow***	**Flashlight test (1/2 iris shadow)** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result **Flashlight test (1/3 iris shadow)** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result **Van Herick's test (cut off = grade 1)** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result	 48% (10/21) 83% (62/75) 43% (10/23) 85% (62/73) 22% (21/96) 2.75 0.63 0.22 44% (CI95%: 28 – 60%) 15% (CI95%: 11 – 21%) 86% (18/21) 71% (53/75) 45% (18/40) 95% (53/56) 22% (21/96) 2.92 0.2 0.22 45% (CI95%: 36 – 55%) 5% (CI95%: 2 – 14%) 62% (13/21) 89% (67/75) 62% (13/21) 89% (67/75) 22% (21/96) 5.80 0.43 0.22 62% (CI95%: 44 – 77%) 11% (CI95%: 7 – 17%)	**Funding:** NR **Limitations:** Patients in Indian population where PACG is more prevalent. **Additional Outcomes:** Flashlight Test (one third shadow) OR Van Herick's Test Flashlight Test (one third shadow) AND Van Herick's Test Gonioscopy grading (Goldman single mirror) **Notes:** Diagnostic parameters were recalculated for figures estimated for 2x2 tables using the prevalence 21/96 and reported figures for sensitivity and specificity Gonioscopy was carried out immediately after the other diagnostic test under investigation One eye selected randomly from each patient Glaucoma specialist was masked to the previous test results

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, Sig=statistically significant at 5%, N=total number of patients randomised, CI95%= 95% Confidence Interval

Evidence Table 3 Any treatment vs. no treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kass et al., 2002[72] Ocular Hypertension Treatment Study (OHTS) **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** Median follow-up for African American participants 72 months and 78 months for other participants.	**Patient group:** OHT patients **Inclusion criteria:** Age between 40-80 years, a qualifying IOP between 24 mmHg and 32 mmHg in one eye and between 21 mmHg and 32 mmHg in the other eye, gonioscopically open angles, 2 normal and reliable visual field tests per eye and normal optic discs **Exclusion criteria:** Visual acuity worse than 20/40 in either eye, previous intraocular surgery (other than uncomplicated cataract extraction with posterior chamber lens implantation), and diabetic retinopathy or other diseases capable of causing visual field loss or optic disc deterioration. **Setting**: 22 clinical centres, USA **<u>All patients</u>** **N:** 1636 **<u>Group 1</u>** **N:** 817 **N medication withdrawn**:40 **M/F:** 359/458 **Age categories:** 40 to ≤ 50 years: 291 (35.6%) >50 to ≤ 60 years: 270 (33.0%) >60 to ≤ 70 years: 202 (24.7%) >70 to 80 years: 64 (6.6%) **Previous use of OHT medication**: 35.0% **First-degree family history of glaucoma**: 34.0%	**Group 1** Topical ocular hypotensive medication. Treatment to achieve a target IOP of 24 mm Hg or less and a minimum 20% reduction in IOP from the average of the qualifying IOP and IOP at the baseline randomisation visit. Topical medication was changed and/or added until both of these goals were met or the participant was receiving maximum tolerated topical medical therapy. Medications were added and changed in one-eyed therapeutic trials. Included all topical ocular hypotensive medications commercially available in the US. Follow-up visits every six months. **Group 2** No treatment	**Patients developed POAG** (end points of visual field abnormality or optic disc deterioration)	**Group1:** 36/817 (4.4%) African American: 14/203 Other: 22/614 **Group 2:** 89/819 (10.9%) African American: 26/205 Other: 63/614	**Funding:** Study was supported by grants EY09341 and EY09307 from the National Eye Institute and the National Centre on Minority Health and Health Disparities, National Institutes of Health, Bethesda, Md; Merck Research Laboratories, White House Station, NJ; and by an unrestricted grant from Research to Prevent Blindness, New York, NY. **Limitations:** Patient and clinician were not blinded to randomisation during follow-up. **Additional outcomes:** Cumulative probability of developing a reproducible visual field abnormality or an optic disc deteriorations due to POAG or a variety of other caused was reported. Estimated of the effect of treatment after adjusting.
			Cumulative probability of developing POAG	**Hazard Ratio:** 0.40 (95% CI: 0.27 to 0.59) **p value:** <0.0001	
			Cumulative probability of developing POAG at 60 months:	**Group1:** 4.4% **Group 2:** 9.5%	
			Cumulative probability of developing POAG	**African-American participants:** Hazard ratio: 0.54 (95% CI:0.28-1.03 **Other participants:** Hazard ratio: 0.34 (95% CI:0.21-0.56 P=0.26	
			Change in IOP	**Group 1:** Baseline: 24.9±2.6 Reduction from baseline: -22.4%±9.9 **Group 2:** Baseline: 24.9±2.7 Reduction from baseline: -4.0%±11.6	
			Adverse effects:	**Ocular symptoms:** **Group1:** 57% **Group 2:** 47% **P value:** <0.001 **Symptoms affecting skin, hair or**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Myopia ≥1-diopter spherical equivalent: 34.4% **Oral B-adrenergic antagonist:** 5.4% **Oral calcium channel blocker:** 12.8% **History of migraine:** 10.4% **History of diabetes:** 11.5% **History of hypertension:** 37.5% **History of low blood pressure:** 4.8% **History of cardiovascular disease:** 6.8% **History of stroke:**0.9% **Drop outs:** 115 (28 died) **Group 2** **N:** 819 **N medication initiated:**42 **M/F:** 346/473 **Age categories:** 40 to ≤ 50 years: 287 (35.0%) >50 to ≤ 60 years: 259 (31.6%) >60 to ≤ 70 years: 210 (25.6%) >70 to 80 years: 63 (7.7%) **Previous use of OHT medication:** 39.3% **First-degree family history of glaucoma:** 35.6% **Myopia ≥1-diopter spherical equivalent:** 33.7% **Oral B-adrenergic antagonist:** 4.6% **Oral calcium channel blocker:** 14.0% **History of migraine:** 11.7% **History of diabetes:** 12.1% **History of hypertension:** 38.1% **History of low blood pressure:** 4.0% **History of cardiovascular disease:** 6.5% **History of stroke:** 1.6% **Drop outs:** 113 (29 died)			**nails:** **Group1:** 23% **Group 2:** 18% **P value:** <0.001	Treatment benefit for reproducible visual field abnormality attributed to POAG and for reproducible optic disc deterioration attributed to POAG reported. **Notes:** Randomisation method was adequate and primary outcome assessment was masked. 3328 screened but 1636 entered into study (1692 not eligible for various reasons).
			Difference between groups total hospitalisations	**P=0.56**	
			Difference between groups worsening of pre-existing conditions	**P=0.28**	
			Difference between groups mortality rates	**P=0.70**	
			Other adverse events (≥10%) **Tearing/watering** **Itching** **Blurry or dim vision** **Feels like object in eye** **Poor night vision** **Difficulty Sleeping** **Headache** **Loss of libido** **Numbness/tingling arms**	**Medication (%)** **(%)** **12.6** **11.4** **11.4** **10.1** **12.2** **17.2** **10.7** **11.2** **13.9**	**Observation** **13.2** **11.8** **11.6** **10.6** **11.8** **16.8** **11.8** **12.6** **16.3**

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Any treatment vs. no treatment (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Heijl et al., 2002[59] Early Manifest Glaucoma Trial (EMGT) **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** At least 6 years. Open label design but outcome measurement was masked	**Patient group:** patients with chronic open angle glaucoma **Inclusion criteria:** Men and women with newly diagnosed, previously untreated COAG (POAG, NTG or PEX) with repeatable visual field defects in at least one eye measured using Humphrey 24-2 full programme. Age between 50 and 80 years **Exclusion criteria:** • Advanced visual field defects (MD-16dB or threat to fixation) • Visual acuity < 0.5 • Mean IOP >30 mmHg • Lens opacities exceeding N1, C1 or P1 in Lens Opacities Classification System • Patients with glaucomatous visual field defects in both eyes eligible if MD = -10 dB or better in one eye and -16 dB in other eye. **Setting:** 2 clinical centres (1 reading and 1 co-ordinating), Sweden **<u>All patients</u>** **N:** 255 **<u>Group 1</u>** **N:** 129 **Both eyes eligible:**: 34 (26%) **One eye eligible:** 95 (74%) **Age ± SD:** 68.2 ± 4.8 (range 58-78) **M/F:** 47/82 **Mean Baseline IOP mmHg ± SD:** 20.6 ± 4.1 **Patients with IOP < 21 mmHg:** 69 **Mean Visual Acuity:** ± SD: 0.9 ± 0.1	**Group 1** Betaxolol 5 mg/ml 2/day and argon laser trabeculoplasty (ALT) 360 degrees performed 1 week after inclusion. If eligible eye achieved 25 mmHg in 2 consecutive visits or other eye was 35 mmHg in 1 visit then latanoprost 50 µm/day. **Group 2** No treatment **Examination methods:** Patients were followed up at 3 month intervals for visual acuity, Goldmann tonometry, Humphrey 30-2 Full threshold visual field testing, ophthalmoscopy, slit lamp examination and optic disc photographs every 6 months. *Visual field progression defined as worsening of 3 consecutive points in the Glaucoma Change Probability map, confirmed by 3 consecutive visual fields.	**Glaucoma progression (visual or optic disc changed*) after follow up of 48 months** Data from Rolim et al., 2007[124]	**Group 1:** 39/129 (30%) **Group 2:** 62/126 (49%) **p value:** 0.002 (calculated by NCC-AC Chi-squared test)	**Funding:** Study was supported by grants U10EY10260 and U10EY10261 from the National Eye Institute, Bethseda, USA and K2002-74X-10426-10A from the Swedish Research Council, Stockholm **Limitations:** **Additional outcomes:** Health-related quality of life scores **Notes:** Randomised using computer generated sequence. Computerised visual field and optic disc photographs read by masked observers. IOP evaluation also masked. An Intention to Treat analysis was used. Patients and clinicians were not masked to treatment allocation
			Glaucoma progression (visual field and optic disc) after 6 years (range 51-102 months	**Group 1:** 58/129 (45%) **Group 2:** 78/126 (62%) **p value:** 0.07	
			Visual field progression alone after 6 years (range 51-102 months	**Group 1:** 57/129 (44%) **Group 2:** 78/126 (62%) **p value:** 0.005 (calculated by NCC-AC Chi-squared test)	
			Ocular side effects (reduction in visual acuity, floaters or conjunctivitis)	**Group 1:** 21/129 (16%) **Group 2:** 16/126 (13%) **p value:** 0.43 (calculated by NCC-AC Chi-squared test)	
			Systemic side effects (asthma, bradycardia, depression)	**Group 1:** 6/129 (4.6%) **Group 2:** 1/126 (0.8%) **p value:** 0.12 (calculated by NCC-AC Fishers exact test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Mean deviation ± SD: -5.0 ± 3.7 dB **Number of optic disc abnormalities (cupping, notching, haemorrhage):** 147 **Myopia ≤1-diopter spherical equivalent**: 19(12%) **Exfoliation Syndrome**: 9 (6%) Disease History: **Family history of glaucoma**: 26 (20%) 34.4% **Cardiovascular disease**: 19 (15%) **Stoke/low blood pressure**: 12 (9%) **General artheriosclerosis**: 4 (3%) **Peripheral vasospasms and migraine**: 21 (16%) **Pulmonary disease**: 3 (2%) **Diabetes**: 3 (2%) Medication use: **Antihypertensives**: 31 (24%) **Corticosteroids**: 0 **Insulin or oestrogen**: 57 (44%) **Drop outs:** 24 (3 lost to follow up, 15 died, 6 received ALT but discontinued medications) **<u>Group 2</u>** **N:** 126 **Both eyes eligible**: 27 (21%) **One eye eligible**: 99 (79%) **Age ± SD:** 68.0 ± 5.0 (range 50-79) **M/F:** 39/87 **Mean Baseline IOP mmHg ± SD**: 20.9 ± 4.1 **Patients with IOP < 21 mmHg**: 63 **Mean Visual Acuity**: ± SD: 1.0 ± 0.1 **Mean deviation ± SD**: -4.4 ± 3.3 dB **Number of optic disc abnormalities (cupping, notching, haemorrhage):** 138 **Myopia ≤1-diopter spherical equivalent**: 23(15%) **Exfoliation Syndrome**: 16 (10%) Disease History: **Family history of glaucoma**: 24 (19%)	*Optic disc progression detected from baseline line and follow up photographs by a masked reader using flicker chronoscopy and			

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	34.4% **Cardiovascular disease:** 14 (11%) **Stoke/low blood pressure:** 5 (4%) **General artheriosclerosis:** 5 (4%) **Peripheral vasospasms and migraine:** 26 (21%) **Pulmonary disease:** 0 **Diabetes:** 6 (5%) Medication use: **Antihypertensives:** 31 (25%) **Corticosteroids:** 4 (3%) **Insulin or oestrogen:** 55 (44%) **Drop outs:** 10 (3 lost to follow up, 7 died)				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Any treatment vs. no treatment (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Collaborative Normal-Tension Glaucoma Study Group, 1998[24] Collaborative Normal-Tension Glaucoma Study (CNTGS) **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 5 years.	**Patient Group:** Normal tension glaucoma **Inclusion criteria:** Unilateral or bilateral normal tension glaucoma with optic disc abnormalities and visual field defects and IOP ≤ 24 mmHg in either eye. Age 20 to 90 years. After 4 week washout patients required to have a median of 10 IOP readings of ≤ 20 mmHg and 3 good baseline visual fields. **Exclusion criteria:** • Patients on systemic beta-blockers or clonidine. • Patients unable to perform visual field test • Eyes with previous laser treatment, ocular surgery • Eyes with traumatic VF defects • Narrow angles • Best correct visual acuity of < 20/30 • Baseline visual fields too damaged to record further progression **Setting**: 24 clinical centres, international **<u>All patients</u>** **N:** 145 **<u>Group 1</u>** **N:** 79 **Age ± SD:** 65.5 ± 9.6 **M/F:** 30/49 **Mean IOP at randomisation mmHg ± SD**: 16.1 ± 2.3	**Group 1** Achieved 30% change in IOP using medical or surgical interventions except for beta-blockers or adrenergic agonists. **Group 2** No treatment **Examination methods:** Patients were followed up at 3 month intervals for first year and every 6 months thereafter. Tests performed for visual acuity, visual field using Humphrey and appearance of optic disc and optic disc photographs every year. Visual field progression was defined by deepening of existing scotoma, expansion of an existing scotoma or new or expanded threat to fixation (cluster of 3 points) or fresh scotoma in previously normal part of visual field. *Visual field progression was confirmed by 4/5 consecutive follow up visits showed progression relative to baseline.	**Glaucoma progression (optic disc or visual field progression*)** Data from Sycha et al., 2003[146]	**Group 1**: 22/61 (31%) **Group 2**: 31/79 (39%) **p value**: 0.7 (calculated by NCC-AC Chi-squared test)	**Funding:** Glaucoma research Foundation with grants from Oxnard Foundation and Edward J Daly Foundation, San Francisco, USA **Limitations:** Allocation concealment and masking of outcome assessment was not clearly reported **Additional outcomes:** **Notes:** Randomisation using block randomisation scheme occurred after selected eye had a visual field defect that threatened fixation. Intention to treat analysis was performed The study was carried out before the introduction of topical carbonic anhydrase inhibitors and prostaglandin analogues.
			Visual Field Progression*	**Group 1**: 11/61 (18%) **Group 2**: 24/79 (30%) **p value**: 0.09 (calculated by NCC-AC Chi-squared test)	
			Cataract Formation	**Group 1**: 23/61 (38%) **Group 2**: 11/79 (14%) **p value**: 0.011 (calculated by NCC-AC Chi-squared test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Visual Acuity: 0.89 ± 2.86 **Mean deviation at randomisation ± SD:** -7.54 ± 4.31 dB **Refraction:** -0.66 ± 2.86 Ethnicity **Asian:** 9 **Black:** 2 **Hispanic:** 2 **White:** 65 **Drop outs:** 5 **Group 2** **N:** 61 **Age ± SD:** 66.3 ± 10.3 **M/F:** 17/44 **Mean IOP at randomisation mmHg ± SD:** 16.9 ± 2.1 **Visual Acuity:** 0.89 ± 0.15 **Mean deviation at randomisation ± SD:** -8.38 ± 5.26 dB **Refraction:** -1.09 ± 3.3 Ethnicity **Asian:** 3 **Black:** 5 **Hispanic:** 1 **White:** 51 **Drop outs:**	Optic disc damage was independently assesses by masked observers using stereo photographs and agreed.			

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 4 Beta-blockers vs. no treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Vass et al., 2007[155] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum treatment 12 months (range 12 months to 10 years).	**Patient group:** All people with Ocular Hypertension (POAG patients included but all the studies in this category were in OHT patients). **Inclusion criteria**: Minimum treatment duration 1 year. People with a mean IOP above 21 mm Hg. **Exclusion criteria:** Patients with Normal Tension Glaucoma. Trials excluded on methodology if graded inadequate on allocation concealment. **<u>All patients</u>** **N:** 4979 from 26 trials **Age (mean):** NR **M/F:** NR **Drop outs:** NR Caucasian: 2907 African: 562 Hispanic: 59 Asian: 15 Race NR: 16 trials Sample range: 18-1636	**Group 1** Beta-blocker **Group 2** Placebo or no treatment.	**Incidence of visual field defect progression: (OHT patients)** **Sensitivity analysis** **Drop outs due to drug related adverse events:** **Long-term studies concerning incidence of visual field progression (follow-up of at least 3 years):**	**Group1 (beta-blocker):** 45/469 (9.6%) **Group 2 (placebo/untreated):** 64/466 (13.7%) **Peto OR:** 0.67 (95% CI: 0.45, 1.00); 8 studies Heterogeneity: Chi^2=4.00, df=6 (P=0.68), I^2=0% **Group 1:** 18/253 **Group 2:** 26/246 **OR:** 0.64 (95% CI: 0.34, 1.19); 4studies Heterogeneity: Chi^2=0.17, df=2 (P=0.92), I^2=0% **Group1:** 17/255 **Group 2:** 14/248 **Peto OR:** 1.24 (95% CI: 0.59, 2.58); 4 studies Heterogeneity: Chi^2=2.05, df=2 (P=0.36), I^2=2.4% **Group1:** 44/444 **Group 2:** 62/438 **Peto OR:** 0.67 (95% CI: 0.45, 1.01); 6 studies Heterogeneity: Chi^2=3.91, df=5 (P=0.56), I^2=0%	**Funding:** Department of Ophthalmology and Clinical Pharmacology, University of Vienna **Limitations:** IOP change from baseline not reported as an outcome Quality assessment not reported in detail for each trial **Additional outcomes:** Interclass comparisons. Sensitivity analysis also conducted to determine the effect of excluding trials falling below a quality threshold with either exclusion of trials scoring C (inadequate) on any aspect of methodological trial quality or exclusion of trials which had assumed that eyes within an individual were independent (fellow eye used as a control group). **Notes:** Studies included in Vass 2007 that do not meet guideline inclusion criteria because eyes were randomised Wishart & Batterbury, 1992 and Kass et al., 1989

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

RCTs included in VASS 2007 that meet guideline inclusion criteria

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Quality Check	Notes
Epstein et al., 1989[42] [USA]	Timolol 0.5% 2/day v No treatment	5 years	Glaucoma Clinical Centre & MSD	OHT	107	60	BB: 24.0 ± 1.3 NT: 23.9 ± 1.6	10 / 62	Randomisation Method: NR Allocation concealment: N Masked outcome assessment: Y Incomplete outcome data: N ***Moderate risk of bias***	No IOP figures, estimate from graph. **Open label** No previous treatment. VF defects using Goldmann or Octopus perimeters
Heijl & Bengtsson, 2000[58] [Sweden]	Timolol 0.5% 2/day v Placebo	10 years	MSD, Järnhardt Foundation & Malmö Hospital	OHT (30% PEX or PG)	90	63	BB: 27.1 ± NR NT: 26.2 ± NR	NR / 38	Randomisation method: Y Allocation concealment: Y Masked outcome assessment: Y Incomplete outcome data: N ***Low risk of bias***	Eyes with previous antiglaucoma therapy were permitted with a wash-out of 2 weeks.
Kamal et al., 2003[69] [UK]	Betaxolol 0.5% 2/day v Placebo	5 years	Guide Dogs for the Blind, Blue Light Fund & Alcon	OHT	356	66 (>35)	BB: 26.3 ± 2.3 NT: 25.6 ± 2.2	NR / NR	Randomisation method: Y Allocation concealment: Y Masked outcome assessment: Y Incomplete outcome data: N ***Low risk of bias***	No previous treatment. Conversion to glaucoma defined by AGIS criteria
Kitazwa, 1990[76] [Japan]	Timolol 0.5% 2/day v Placebo	2 years	NR	OHT	20	NR	NR	NR / NR	Randomisation method: NR Allocation concealment: NR Masked outcome assessment: NR Incomplete outcome data: N ***High risk of bias***	No IOP data. Study does not report whether treatment was 1st option VF defects using Humphrey perimeter
Schulzer et al., 1991[131] [Canada]	Timolol 0.25% - 0.5% 2/day v No Treatment	6 years	MSD & Canadian MRC	OHT	137	60 (>45)	BB: 26.3 ± 3.5 NT: 26.1 ± 3.2	NR / 31	Randomisation method: NR Allocation concealment: NR Masked outcome assessment: Y Incomplete outcome data: N ***Moderate risk of bias***	**Open label** No previous treatment. VF defects using Goldmann or Octopus perimeters

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Quality Check	Notes
Schwartz et al., 1995[134] [USA]	Timolol 0.5% 2/day v Placebo	1 to 2 years	MSD	OHT (43% PEX or PG)	37	60	BB: 23.1 ± 2.5 NT: 23.7 ± 3.6	8 / 22	Randomisation method: Y Allocation concealment: NR Masked outcome assessment: Y Incomplete outcome data: N ***Low risk of bias***	Results by presented by eye No previous treatment. VF defects using Goldmann perimeter

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 5 Timolol 0.5% vs. timolol 0.25%

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Mills1983[101] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** patients with chronic open angle glaucoma **Setting:** Manchester, UK **Inclusion criteria** Patients with optic nerve head and visual field changes of open angle glaucoma, either controlled on topical glaucoma medication or presenting as new patients. **Exclusion criteria:** Patients with a history of cardiovascular disease or bronchospasm or who were receiving concomitant medication for a cardiovascular disease. **<u>All patients</u>** **N:** 30 **Age (mean ± SD):** 70 ± 8.8 **M/F:** 16/14 **Mean IOP:** NR **Drop outs:** 9 **<u>Group 1</u>** **N:** 15 **Age (mean):** 71 **M/F:** 9/6 **Mean IOP:** 26.9 ± 5.1 (RE), 26.8 ± 5.5 (LE) **Drop outs:** 4 in total. 3 required additional treatment as pressure not adequately controlled by Timolol alone) and 1 had elevated IOP immediately after instillation of treatment which was therefore discontinued) **<u>Group 2</u>**	**Group 1** Timolol 0.25% twice daily **Group 2** Timolol 0.5% twice daily **All** 7 day wash-out period for patients on topical glaucoma therapy Each patient had a day curve of IOP at 0900, 1200, 1600 and 2000) measured by Goldmann applanation tonometry and Haag-Streit slit lamp. A mean of the day curve pressures was calculated. Patients were reviewed at 1, 3, 6, 9 and 12 months.	**Mean ± SD diurnal IOP at baseline (mm Hg)**	**Group 1:** 26.9± 5.1(RE), 26.8± 5.5 (LE) **Group 2:** 24.2 ± 3.75 (RE), 25.4 ± 4.1 (LE) **95% CI:** NR **p value:** NR	**Funding:** NR **Limitations:** 8 patients (3 group 1 and 5 group 2) required further treatment to control their IOP and were given pilocarpine. These patients weren't included in the final analysis. **Additional outcomes:** Side effects were few. 1 patient complained of occasional hallucinations and 2 of tinnitus which was temporary **Notes:**
			Mean ± SD diurnal IOP at 6 months (mm Hg)	**Group 1:** 20.5 ± 4.3 (RE), 20.1 ± 3.2 (LE) **Group 2:** 20.1 ± 4.2 (RE), 21.2 ± 3.9 (LE) **95% CI:** NR **p value:** 0.8 (RE); 0.4 (LE)	
			Mean ± SD diurnal change in IOP from baseline at 6 months (mm Hg)	**Group1:** 6.4 ± 4.3 (RE), 6.7 ± 3.2 (LE) **Group 2:** 4.1 ± 4.2 (RE), 4.2 ±3.9 (LE) **95% CI:** NR **p value:** 0.14 (RE); 0.04 (LE)	
			Mean ± SD diurnal IOP at 9 months (mm Hg)	**Group 1:** 18.4 ± 4.4 (RE), 18.6 ± 2.9 (LE) **Group 2:** 17.5 ± 3.8 (RE), 19.1± 4.3 (LE) **95% CI:** NR **p value:** 0.55 (RE); 0.71 (LE)	
			Mean ± SD diurnal change in IOP from baseline at 9 months (mm Hg)	**Group1:** 8.5 ± 4.4(RE), 8.2 ± 2.9(LE) **Group 2:** 6.7 ± 3.8 (RE), 6.3 ±4.3 (LE) **95% CI:** NR **p value:** 0.22 (RE); 0.16 (LE)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 15 **Age (mean):** 69 **M/F:** 6/9 **Mean IOP:** 24.2 ± 3.75 (RE), 25.4 ± 4.1 (LE) **Drop outs:** 5 (additional treatment was needed as pressure not adequately controlled by Timolol alone)		**Mean ± SD diurnal IOP at 12 months (mm Hg)**	**Group 1:** 20.0 ± 2.5 (RE), 20.8 ± 2.1 (LE) **Group 2:** 19.4 ± 2.3 (RE), 20.2 ± 3.6 (LE) **95% CI:** NR **p value:** 0.49 (RE); 0.58 (LE)	
			Mean ± SD diurnal change in IOP from baseline at 12 months (mm Hg)	**Group1:** 6.9 ± 2.5 (RE), 6.0 ± 2.1 (LE) **Group 2:** 4.8 ± 2.3 (RE), 5.1 ± 3.6 (LE) **95% CI:** NR **p value:** 0.02 (RE); 0.40 (LE)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 6 Prostaglandin analogues vs. beta-blockers

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Alm & Stjernschantz, 1995[4] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG & OHT **Setting:** multi-centre across 13 Scandinavian eye clinics **Inclusion criteria:** • Age ≥ 40 years old • Unilateral or bilateral POAG or pigmentary glaucoma or exfoliation glaucoma or OHT ≥ 22 mmHg. • Completion of adequate washout period for sympathomimetics, CAI and miotics. **Exclusion criteria:** • Patients on topical beta blockers within 6 months of study • Angle closure glaucoma history • Ocular trauma • Previous filtration or laser surgery for glaucoma within 6 months of study • Dry eye syndrome • Ocular inflammation or infection within 3 months of study • Contact lens wearers • Those with contraindications for beta blockers • Patients who would not benefit from monotherapy	**Group 1** Latanoprost 0.005% in morning followed by placebo in evening for first 3 months then regimen reversed for next 3 months **Group 2** Latanoprost 0.005% in evening preceded by placebo in morning for first 3 months then regimen reversed for next 3 months **Group 3** Timolol 0.5% 2/day for 6 months **Examination methods:** IOP measured by Goldmann Applanation Tonometry - 3 readings taken in each eye (8 am, 12 noon and 4 pm) and mean used for statistical analysis. (Average of 2 eyes used for bilateral patients) Visual acuity readings, slit lamp examination and blood and urine samples taken throughout study. Photographs of iris taken and classified by independent evaluator Visual fields examined using	**Mean ± SD* baseline diurnal IOP mmHg**	**Group1:** 24.8 ± 3.77 **Group 2:** 25.5 ± 2.91 **Group 3:** 24.6 ± 2.75	**Funding:** Supported by Pharmacia (now Pfizer), Sweden which manufactures latanoprost. **Limitations:** Allocation concealment was not reported. Not known if the statistical calculations are done on an ITT basis. Number of patients remaining at the end of the study does not add up to figures in table listing reasons for withdrawal **Additional outcomes:** Detailed analysis of conjunctival hyperaemia **Notes:** *SD = SE*√n **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from
			Mean ± SD* end point diurnal IOP (6 mths) mmHg	**Group1:** 16.2 ± 2.83 **Group 2:** 17.7 ± 2.91 **Group 3:** 17.9 ± 2.75	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)	**Group1:** 8.6 ± 4.06** **Group 2:** 7.8 ± 3.51** **Group 3:** 6.7 ± 2.99**	
			Change in IOP in Group 1 versus Group 3 at 6 mths	**Group1:** 8.6 ± 4.06** **Group 3:** 6.7 ± 2.99** **p value:** <0.001 (using ANCOVA)	
			% patients at 6 mths reaching acceptable IOP ≤ 17 mmHg	**Group1:** 58/84 (69%) **Group 2:** 27/79 (34%) **p value:** <0.001 (Chi-squared test)	
			Apparent deterioration or visual field	**Groups 1 + 2:** 0 **Group 3:** 1	
			Disc Haemorrhage	**Groups 1 + 2:** 3 **Group 3:** 3	
			Total number of local ocular side effects by group	**Groups 1 + 2:** 86 **Group 3:** 41 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Increase in iris pigmentation	**Groups 1 + 2:** 7 **Group 3:** 0	
			Total number of cardiovascular systemic side effects by group	**Groups 1 + 2:** 20 **Group 3:** 18 Includes upper respiratory tract infection, angina, thrombophlebitis	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	<u>All patients</u> **N:** 267 **Age (mean):** 67 (40-85) **M/F:** 116/151 **Drop outs:** 15 **Race:** NR **<u>Group 1</u>** **N:** 89 **Age (mean):** 67 (40-84) **M/F:** 39/50 **Drop outs:** 5 **OHT:** 43 **COAG:** 46 **<u>Group 2</u>** **N:** 94 **Age (mean):** 67 (44-85) **M/F:** 43/51 **Drop outs:** 9 **OHT:** 44 **COAG:** 50 **<u>Group 3</u>** **N:** 84 **Age (mean):** 66 (42-84) **M/F:** 34/50 **Drop outs:** 5 **OHT:** 36 **COAG:** 48	Humphrey 24:2 or Octopus	**Reasons for withdrawals (dropouts)**	**Groups1 & 2:** • Inadequate IOP control = 1 • Repeated corneal erosions = 1 • Retinal arterial embolus = 1 • Retinal vein thrombosis = 1 • Increase in iris pigmentation = 1 • Information about iris changes = 2 • Decrease in visual acuity due to diabetes = 1 • Burning sensation on tongue = 1 • Cancer metastasis = 1 • Unknown reason for exit = 4 **Group 2:** • Inadequate IOP control = 1 • Information about iris changes = 3 • Headaches = 1	correlation coefficients calculated from Martin 2007[93] (bimatoprost) Computer generated randomisation sequence.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Camras, 1996[17] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG & OHT **Setting:** multi-centre 17 centres across the USA **Inclusion criteria:** • Age ≥ 40 years old • Unilateral or bilateral POAG or pigmentary glaucoma or exfoliation glaucoma or OHT ≥ 22 mmHg with no more than 1 current topical medication • Expectation that patients' IOP would be controlled for 6 months without VF degeneration • Completion of adequate washout period for sympathomimetics, CAI and miotics. **Exclusion criteria:** • Use of any ocular medications other than for glaucoma • Patients with advanced glaucoma that would be at risk during washout period • Angle closure glaucoma history • Ocular trauma • Previous filtration or laser surgery for glaucoma within 6 months of study • Allergies to trial medications • Ocular inflammation or infection within 3 months of study • Contact lens wearers • Those with contraindications for beta blockers • Pregnant women, women of	**Group 1** Latanoprost 0.005% in evening preceded by placebo in morning for 6 months **Group 2** Timolol 0.5% 2/day for 6 months **Examination methods:** IOP measured using Goldmann tonometer taking 3 replicate measurements on same calibrated machine per patient for each visit at 8am, 12 noon and 4 pm VF measured on Humphrey or Octopus 4 weeks before start of study at 6 month stage.	**Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)**	**Group 1:** 6.7 ± 3.4 **Group 2:** 4.9 ± 2.9 **p value:** <0.001 (using 2 tailed unpaired t-test)	**Funding:** Supported by Pharmacia (now Pfizer), Sweden which manufactures latanoprost **Limitations:** Allocation concealment with sealed envelopes was not reported. Lack of reliable ITT data in original study. Assumption that later study figures are reliable **Additional outcomes:** Study reports in detail on conjunctival hyperaemia **Notes:** For patients with 2 eyes eligible – mean IOP value was used for all calculations Computer generated randomisation sequence. Patients and examiners were kept masked to treatment allocation.
			Apparent deterioration or visual field	**Group 1:** 1 **Group 2:** 1	
			Number of patients with local ocular side effects	**Group1:** 71 **Group 2:** 101 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Increase in iris pigmentation	**Group 1:** 1 **Group 2:** 0	
			Number of patients with cardiovascular systemic side effects	**Group1:** 26 **Group 2:** 33 Includes upper respiratory tract infection, palpitations, shortness of breath, syncope	
			Reasons for withdrawals (dropouts)	**Group1:** • Local side effects = 2 (including allergic blepharoconjunctivitis • Systemic effects = 4 (including palpitations, peptic ulcer symptoms and 2 patients with maculopapular rash) • Non medical reasons = 4 (including left area, lost to follow-up, time constraints) **Group 2:** • Inadequate IOP control = 4 • Local side effects = 2 (including swelling of eyelids and allergic conjunctivitis) • Systemic effects = 4 (including	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	child bearing potential & nursing mothers • History of non-compliance **<u>All patients</u>** **N:** 268 **M/F:** 114/154 **Drop outs:** 20 **OHT:** 44 **COAG:** 50 **Black:** 65 **Non-black:** 203 **<u>Group 1</u>** **N:** 128 **Age (mean):** 61 ± 12 (30-89) **M/F:** 58/70 **Drop outs:** 10 **OHT:** 80 **COAG:** 48 **Black:** 27 **Non-black:** 101 **<u>Group 2</u>** **N:** 140 **Age (mean):** 63 ± 11 (33-90) **M/F:** 56/84 **Drop outs:** 10 **OHT:** 90 **COAG:** 50 **Black:** 38 **Non-black:** 102			palpitations, shortness of breath followed by bypass surgery, post mastectomy) • Non medical reasons = 1 patient left study without explanation	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Fellman et al., 2002[44] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG & OHT **Setting:** Multi-centre (44 sites) USA **Inclusion criteria:** • Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Age ≥ 21 • IOP 24-36 mmHg in same eye on 2 separate eligibility visits • Women post menopausal or surgically sterilised **Exclusion criteria:** • Contact lens wearers • Women of childbearing potential • IOP >36mmHg • Visual acuity worse than 0.60 log MAR • Cup/disc ratio > 0.80 • Chronic or recurrent inflammatory eye disease • Ocular trauma in last 6 months • Recent ocular infection or inflammation • Ocular pathology preventing beta blockers or PGAs • Recent ocular surgery • Contraindications for beta blockers – respiratory, cardiovascular, hepatic, renal • Patients on adjunctive IOP lowering therapies, glucocorticoids or NSAIDS • Patients with hypersensitivities to the medications	**Group 1** Travoprost 0.004% evening, placebo in morning **Group 2** Timolol 0.5% 2/day **Examination methods:** 2 different individuals performed IOP measurements on a Goldmann Tonometer. Hyperaemia was made by same observer throughout study looking at photographs depicting ocular hyperaemia. Photographs were taken to record iris pigmentation or eyelash characteristics. VF evaluation using Humphrey or Octopus	**Mean baseline diurnal IOP ± SD**	**Group 1:** 25.9 ± NR **Group 2:** 26.2 ± NR	**Funding:** Alcon Research Ltd which manufactures Travoprost. Dr Fellman has no proprietary interest in any of the medications **Limitations:** **Additional outcomes:** Detailed analysis of conjunctival hyperaemia **Notes:** *withdrawals due to adverse effect of treatment includes non-starters randomised to treatment 3rd arm of travoprost 0.001% not reported here ** Standard Deviations (SD) calculated as pooled variances from known SDs for Camras 1996[17], Martin 2007[93]and
			Mean change in IOP from baseline at 6 months	**Group 1:** 7.1 (8am), 6.6 (10am), 6.5 (4pm) **Group 2:** 6.8 (8am), 6.3 (10am), 5.2 (4pm)	
			Mean change in IOP from baseline mmHg at 6 months (end point – baseline	**Group 1:** 6.73 ± 6.87** **Group 2:** 6.1 ± 4.83** (IOP calculated as mean across 3 times)	
			% patients achieving acceptable target of >25% reduction in IOP over all visits (ITT) *>25% reduction from baseline is equivalent to mean IOP of ≤ 20 mmHg averaged over 3 time points*	**Group 1:** 113/197 (57%) **Group 2:** 79/199 (40%) Patient numbers rounded up.	
			Changes in visual field (baseline visit compared to exit visit)	Study reports no significant differences between treatment groups – actual data NR	
			Number of patients with local ocular adverse events	**Group 1:** 152 **Group 2:** 58 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Increase in iris pigmentation & Eyelash changes	**Group 1:** = 104 **Group 2:** = 4	
			Number of patients with cardiovascular systemic side effects	**Group 1:** = NR **Group 2:** = NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients **N:** 396 (excludes non starters – those that did not attend treatment visits and travoprost 0.00015% not given at this concentration) **Group 1** **N:** 197 **Age (mean ±SD):** 64.4 ± 10.2 **M/F:** 94/103 **OHT:** 61 **COAG:** 136 **Black:** 17 **Non-Black:** 180 **Drop outs:** 9/201 (4.48%)* see notes **Group 3** **N:** 199 **Age (mean ±SD):** 63.9 ± 11.2 **M/F:** 64/105 **OHT:** 71 **COAG:** 128 **Black:** 23 **Non-Black:** 176 **Drop outs:** 2/202 (0.99%)* see notes		**Reasons for withdrawals (dropouts)**	**Group 1** • 9 includes local ocular effects and systemic effects including arrhythmia and **Group 2** • 1 dizziness, asthaenia & ocular discomfort • 1 bradycardia, hypotension and dizziness	Mastropasqua 1999[95] Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Goldberg et al., 2001[47] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 9 months	**Patient group:** COAG & OHT **Setting:** multi-centre 64 sites. Europe + Australia **Inclusion criteria:** • Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Age ≥ 21 • IOP 24-36 mmHg in same eye on 2 separate eligibility visits • Women post menopausal or surgically sterilised **Exclusion criteria:** • Women of childbearing potential • Visual acuity worse than 0.60 log MAR • Cup/disc ratio > 0.80 • Abnormalities preventing applanation tonometry • Severe central field loss: sensitivity <10dB • Chronic or recurrent inflammatory eye disease • Ocular trauma in last 6 months • Recent ocular infection or inflammation • Ocular pathology preventing beta blockers or PGAs • Recent ocular surgery within 3 mths • Contraindications for beta blockers – respiratory, cardiovascular, hepatic, renal	**Group 1** Travoprost 0.004% 1/day evening, placebo in morning **Group 2** Timolol 0.5% 2/day **Examination methods:** IOP measurements made at 9am. 11 am and 4 pm using Goldmann applanation tonometry. Photographs were taken to record iris pigmentation or eyelash characteristics and assessed by 2 independent analysts, with a third to resolve differences. VF evaluation using Humphrey or Octopus Hyperaemia assessed by visual inspection using scale. Aqueous flare and inflammatory cells assessed using slit lamp	**Mean IOP at baseline** (data requested from author)	**Group 1:** 27.4 ± 2.85 (9am), 26.4 ± 3.04 (11am), 25.5 ± 3.18 (4pm) **Group 2:** 27.1 ± 2.88 (9am), 26.2 ± 2.91 (11am), 25.1 ± 2.67 (4pm)	**Funding:** Alcon Research Ltd which manufactures Travoprost **Limitations:** Reasons for dropouts NR **Additional outcomes:** **Notes:** **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost) Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation
			Mean IOP at baseline (using 11 am reading)	**Group 1:** 26.4 ± 3.04 **Group 2:** 26.2 ± 2.91 (calculated as mean across 3 times)	
			Mean IOP at end point (9 months) (data requested from author)	**Group 1:** 18.9 ± 3.59 (9am), 18.0 ± 3.30 (11am), 17.6 ± 3.05 (4pm) **Group 2:** 19.4 ± 3.56 (9am), 18.8 ± 3.42 (11am), 18.7 ± 3.67 (4pm)	
			Mean IOP at end point (9 months) (using 11 am reading)	**Group 1:** 18.0 ± 3.30 **Group 2:** 18.8 ± 3.42 (calculated as mean across 3 times)	
			Mean change in IOP from baseline at 9 months	**Group 1:** 8.5 (9am), 8.4 (11am), 8.0 (4pm) **Group 2:** 7.6 (9am), 7.4 (11am), 6.4 (4pm) **p value** using least-square mean is <0.0001 at all time points	
			Mean change in IOP from baseline mmHg at 9 months (end point –baseline) (using 11 am reading)	**Group 1:** 8.4 ± 3.84** **Group 2:** 7.4 ± 3.46**	
			% patients achieving acceptable target IOP ≤ 20mmHg (not ITT data) *Figures estimated from graph and averaged over 3 time points*	**Group 1:** 161/176 **Group 2:** 133/163	
			Number of patients with local ocular adverse events reported at incidence of >1%	**Group 1:** 107 **Group 2:** 22 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema,	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	• Patients on adjunctive IOP lowering therapies, glucocorticoids • Patients with hypersensitivities to the medications • Patients that could not be safely discontinued from current ocular hypertensive medications **All patients** **N:** 382 **Group 1** **N:** 197 **Age (mean ± SD):** 63.0 ± 10.3 **M/F:** 96/101 **OHT**: 74 **COAG**: 123 **Black:** 2 **Non-Black:** 195 **Drop outs:** 9 **Group 2** **N:** 185 **Age (mean ±SD):** 62.5 ± 10.6 **M/F:** 96/89 **OHT**: 73 **COAG**: 112 **Black:** 2 **Non-Black:** 183 **Drop outs:** 3			dry eye and conjunctival hyperaemia	
			Increase in iris pigmentation & Eyelash changes	**Group 1:** = 10 **Group 2:** = 0	
			Number of patients with cardiovascular systemic side effects	**Group 1:** = NR **Group 2:** = NR	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Higginbotham et al., 2002[61] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months (double masked RCT part of study) Study continued for a further 6 months as an open-label study with everyone receiving the fixed combination treatment.	**Patient group:** COAG or OHT **Setting:** multi-centre (38 eye clinics) USA **Inclusion criteria:** • Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Aged 18 or older • Best corrected visual acuity measuring 20/200 • Pre-study IOP ≥30mmHg without IOP reducing medication OR ≥25mmHg with prior treatment • Previous latanoprost or timolol therapy permitted **Exclusion criteria:** • History of acute angle-closure or occludable angles • Use of contact lenses • Ocular surgery, argon laser trabeculoplasty or ocular inflammation or infection within 3 months of the pre-study visit • Hypersensitivity to benzalkonium chloride • Any other abnormal ocular condition or symptom that investigator determined precluded study enrolment • Presence of concomitant diseases that contraindicate adrenergic antagonist • Nursing mothers, pregnant women and women who were of	**Group 1** Fixed combination of Latanoprost 0.005% & timolol 0.5% 8am AND placebo 8pm **Group 2** Latanoprost 0.005% 8am AND placebo 8pm **Group 3** Timolol 0.5% 8am AND 8pm **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer. Each measurement taken in triplicate in each eye. Measurements taken at 8am, 10am and 4pm at baseline and weeks 2, 13, 26 and 52. Automated visual field examination performed at baseline and weeks 13, 26 and 52.	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 23.1 ± 3.8 **Group 2:** 22.9 ± 4.1 **Group 3:** 23.7 ± 4.1	**Funding:** Pharmacia & Upjohn Inc.; Research to Prevent Blindness Inc. **Limitations:** Run in period 2 – 4 weeks with timolol 0.5 % 2/day prior to starting study Adverse events reported by area of eye they occur making it difficult to assess total no. of patients with a particular event. **Notes:** *Differences estimated (least square mean difference) using a repeated measures analysis of covariance with baseline IOP as a covariate; patient, treatment, visit and centre as main factors; and treatment group-by-visit and treatment group-by-centre interaction factors. **§** values not reported for group 2 to group 3 Intention to treat analysis for the first 6 months included all patients who received at least one drop of medication. For IOP measurements the last
			Mean ± SD diurnal IOP at 6 mths mmHg	**Group1:** 19.9 ± 3.4 **Group 2:** 20.8 ± 4.6 **Group 3:** 23.4 ± 5.4	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths §	**Group1 to Group 3:** -2.9 (95% CI: -3.5 to -2.3, p<0.001)* **Group 1 to Group 2:** -1.0 (95% CI: -1.7 to -0.3, p=0.005)*	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths	**Group 2:** 2.1 ± 5.27** **Group 3:** 0.3 ± 5.27**	
			Percent of patients reaching IOP <15mmHg at of 6 mths §	**Group1:** 6 /130 **Group 2:** 4/128 **Group 3:** 1/129 **P value (group 1 to 3):** 0.06 **P value (group 1 to 2):** 0.56	
			Percent of patients reaching IOP acceptable IOP <18mmHg at of 6 mths § *figures used in meta-analysis*	**Group1:** 28/130 **Group 2:** 30/128 **Group 3:** 8/129 **P value (group 1 to 3)** =0. 01 **P value (group 1 to 2)** =0. 65	
			Percent of patients reaching IOP <21mmHg at of 6 mths §	**Group1:** 68/130 **Group 2:** 63/128 **Group 3:** 39/129 **P value (group 1 to 3)** <0.001 **P value (group 1 to 2)** =0.36	
			Number of ocular side effects †	**Group1:** 86 **Group 2:** 86 **Group 3:** 59 † side effects include belphartis,	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	childbearing potential not using adequate contraception for at least the previous 3 months • Patients who could not adhere to treatment or the visit plan • Patients who had participated in another clinical study within 1 month of previous visit **<u>All patients</u>** **N:** 418 **Age (mean):** NR **M/F:** 215/203 **Drop outs:** 73 **Ethnicity:** white 276, black 110, Hispanic 27, other 5 **Diagnosis:** POAG 278, pseudoexfoliative glaucoma 9, pigmentary glaucoma 13, OHT 109, mixed (different diagnosis in the two eyes) 8, none listed 1 **IOP reducing medication in last 3 months:** 351/418 **<u>Group 1</u>** **N:** 138 **Age (mean):** 61 ±12 **M/F:** 67/71 **Drop outs:** 13 **Ethnicity:** white 90, black 38, Hispanic 7, other 3 **Diagnosis:** POAG 94, pseudoexfoliative glaucoma 2, pigmentary glaucoma 4, OHT 36, mixed 2, none listed 0 **IOP reducing medication in last 3 months:** 117/138	Visual acuity assessed and eye-lid slit lamp biomicroscopy performed at each visit. Ophthalmoscopy performed at pre-study visit and weeks 26 and 52.		hypertrichosis, irritation, melbomianitis, seborrhea, eye hyperaemia, chemosis, conjunctival discolouration, corneal disorder, keratitis, keratopathy, cataract, optic atrophy, errors of refraction, increased IOP, vision decreased, visual field defect, conjunctivitis, epiphora, eye pain, photophobia, vision blurred	available IOP measurement was carried forward. **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost) Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation
			Visual field defects	**Group1:** 7/130 **Group 3:** 4/128	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 140 **Age (mean):** 63 ±13 **M/F:** 80/60 **Drop outs:** 36 **Ethnicity:** white 90, black 35, Hispanic 14, other 1 **Diagnosis:** POAG 95, pseudoexfoliative glaucoma 4, pigmentary glaucoma 5, OHT 33, mixed 3, none listed 0 **IOP reducing medication in last 3 months:** 117/140 **Group 3** **N:** 140 **Age (mean):** 63 ±12 **M/F:** 68/72 **Drop outs:** 24 **Ethnicity:** white 96, black 37, hispanic 6, other 1 **Diagnosis:** POAG 89, exfoliative glaucoma 3, pigmentary glaucoma 4, OHT 40, mixed 3, none listed 1 **IOP reducing medication in last 3 months:** 117/140				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Martin et al., 2007[93] **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG & OHT **Setting:** single centre, Spain **Inclusion criteria:** • Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT in at least one eye • Age > 18 • IOP ≥ 22 mmHg at enrolment and between 24-34 mmHg after washout. • Visual acuity ≥ 0.1 in study eye • Completion of adequate washout period for Sympathomimetics, CAI and miotics. **Exclusion criteria:** • Infection or inflammation of the eye • Any anomaly impeding tonometry • History of contraindications for any treatments • Macular or retinal pathologies • Diabetes • Women of childbearing potential not using contraception • Requirement for other chronic eye medication during the study • Eye surgery 6 mths previously • Laser treatment 3 mths previously **<u>All patients</u>** **N:** 60 **Age (mean):** NR **M/F:** NR **Drop outs:** 0	**Group 1** Bimatoprost 0.03% 1/day at 9pm **Group 2** Timolol 0.5% 2/day **Examination methods:** Applanation tonometry Macular tomography using OCT 3000 Anterior flare determination using laser flare meter	**Mean ± SD baseline diurnal IOP mmHg**	**Group 1:** 24.1 ± 3.2 **Group 2:** 24.1 ± 1.7	**Funding:** Partly financed by the Instituto de Salud Carlos III. Authors declare no commercial interests. **Limitations:** Author reports that the study was not sponsored so allocation concealment was not possible and masking of patients not possible. This may effect self-reporting of adverse events but outcome assessment was performed by an ophthalmologist masked to treatment allocation. Baseline data not reported **Additional outcomes:** Inter or intra group differences in macular thickness not significant Inter or intra group differences in anterior chamber flare not significant **Notes:** No patients discontinued study due to adverse events
			Mean ± SD end point diurnal IOP (6 mths) mmHg	**Group 1:** 13.5 ± 3.1 **Group 2:** 16.6 ± 2.4 **p value** compares difference in end point IOP between groups, p is 0.003 using ANOVA for repeated measures	
			Mean ± SE reduction in diurnal IOP mmHg at 6 mths (baseline – end point)	**Group1:** 10.7 ± 3.8 **Group 2:** 7.6 ± 2.3	
			Proportion of patients reaching acceptable target IOP of ≤18mmHg *Figures estimated from graph*	**Group 1:** 17/30 **Group 2:** 28/30	
			Conjunctival hyperaemia	**Group 1:** 4 **Group 2:** 0	
			Increase in iris pigmentation & Eyelash changes	**Group 1:** 3 **Group 2:** 0	
			Number of patients with cardiovascular systemic side effects	**Group 1:** = NR **Group 2:** = NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 30 **Age (mean):** NR **M/F:** NR **Drop outs:** 0 **Group 2** **N:** 30 **Age (mean):** NR **M/F:** Nr **Drop outs:** 0				Computer generated randomisation sequence. Outcome assessment was masked.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Mastropasqua et al., 1999[95] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** Pigmentary Glaucoma **Setting:** single centre, Italy **Inclusion criteria:** • Untreated IOP > 21 mmHg • Evidence of optic nerve head change and VF changes • Best corrected visual acuity ≥ 15/20 – no media opacities • Refractive errors not exceeding -8 or +6D • MD Humphrey not exceeding -12.0dB • Discontinuation of previous glaucoma treatments of 4 weeks **Exclusion criteria:** • History of ocular, rhinologic, neurologic or systemic disorders accounting for optic nerve head damage • History of haemodynamic crisis • Previous surgery or laser treatment in either eye **<u>All patients</u>** **N:** 36 **Age (mean):** NR **M/F:** 21/15 **Drop outs:** 2 **Race:** NR **Family history:** 9 **<u>Group 1</u>**	**Group 1** Latanoprost 0.005% 1/day 8 pm with placebo am **Group 2** Timolol 0.5% 2/day **Examination methods:** Goldmann applanation tonometer used to measure IOP. Average of 3 readings taken at each time interval: 8am, 12 noon, 4pm, 8pm. Outflow facility measured with a Scholtz electronic tonometer at baseline and at end point of study.	**Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)**	**Group1:** 6.0 ± 4.5 **Group 2:** 4.8 ± 3.0	**Funding:** Funding details not clear but study conducted at Institute of Ophthalmology, University "G D'Annunzio", Chieti, Italy **Limitations:** Small study. **Additional outcomes:** Aqueous outflow facility (C) measured at baseline and after 1 year. µl/min/mmHg Detailed analysis of conjunctival hyperaemia **Notes:** Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation.
			Mean ± SD reduction in diurnal IOP mmHg at 12 months (baseline – end point)	**Group1:** 5.9 ± 4.6 **Group 2:** 4.6 ± 3.1	
			Total number of ocular side effects experienced at least once in 1 year*	**Group1:** 24 **Group 2:** 35 Includes itching, stinging, conjunctival hyperaemia & dry eye	
			Increase in iris pigmentation	**Group1:** 3 **Group 2:** 0	
			Reasons for withdrawals (dropouts)	**Group1:** moved away = 1 **Group 2:** inadequate IOP control = 1	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 18 **Age (mean ± SD):** 46.1 ± 9.9 **M/F:** 10/8 **Family history:** 4 **Drop outs:** 1 **<u>Group 2</u>** **N:** 18 **Age (mean ± SD):** 45.8 ± 10.5 **M/F:** 11/7 **Family history:** 5 **Drop outs:** 1				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Netland et al., 2001[110] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** COAG & OHT **Setting:** Multi-centre USA **Inclusion criteria:** • Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • IOP 24 - 36mmHg in same eye on 2 separate eligibility visits • Women post menopausal or surgically sterilised **Exclusion criteria:** • Contact lens wearers • Women of childbearing potential • IOP >36mmHg • Visual acuity worse than 0.60 log MAR • Chronic or recurrent inflammatory eye disease • Ocular trauma in last 6 months • Recent ocular infection or inflammation • Ocular pathology preventing beta blockers or PGAs • Cup/Disc ratio >0.80 • Recent ocular surgery • Contraindications for beta blockers – respiratory, cardiovascular, hepatic, renal • Patients on adjunctive IOP lowering therapies **<u>All patients</u>** **N:** 585	**Group 1** Travoprost 0.004% evening, placebo in morning **Group 2** Timolol 0.5% 2/day **Group 3** Latanoprost 0.005% evening, placebo in morning **Examination methods:** 2 different individuals performed IOP measurements on a Goldmann Tonometer. Hyperaemia was made by same observer throughout study looking at photographs depicting ocular hyperaemia. Photographs were taken to record iris pigmentation or eyelash characteristics. VF evaluation using Humphrey	**Mean baseline diurnal IOP ± SD**	**Group 1:** 25.5 ± NR **Group 2:** 25.7 ± NR **Group 3:** 25.7 ± NR	**Funding:** Alcon Research Ltd which manufactures Travoprost. **Limitations:** Study provides detailed baseline data on 585 patients but excludes those that were randomised but never started trial. However adverse events % includes patients who never started trial **Additional outcomes:** Detailed analysis of conjunctival hyperaemia **Notes:** *No discontinuations due to adverse events were reported but dropout numbers refer to those that were randomised into the trial but failed to start treatment.
			Mean change in IOP from baseline at 12 mths	**Group 1:** 5.8 (8am), 7.3 (10am), 7.6 (4pm) **Group 2:** 5.0 (8am), 5.8 (10am), 5.8 (4pm) **Group 3:** 6.3 (8am), 7.6 (10am), 7.1 (4pm)	
			Mean change in IOP from baseline mmHg at 12 months (end point – baseline	**Group 1:** 6.9 ± 6.87** **Group 2:** 5.53 ± 4.83** **Group 3:** 7.0 ± 6.87** (calculated as mean across 3 times)	
			Mean diurnal change in IOP from baseline mmHg (expressed as a range)	**Group 1:** 6.6 – 8.1 **Group 2:** 4.7 – 7.1 **Group 3:** 6.2 – 8.1 **p value** compares difference between travoprost 0.004% and Timolol using ANOVA for repeated measures. p is <0.01 at all time points	
			Proportion of patients reaching acceptable target IOP of >30% reduction from baseline or ≤17 mmHg *Patient numbers unclear so numbers randomised used for denominator*	**Group 1:** 108/197 **Group 2:** 75/193 **Group 3:** 97/195	
			Total number of patients with local ocular adverse events reported at incidence of >3%	**Group 1:** 219 **Group 2:** 93 **Group 3:** 121 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 197 **Age (mean ±SD):** 64 ± 13.3 **M/F:** 100/97 **OHT:** 67 **COAG:** 130 **Black:** 49 **Non-Black:** 148 **Drop outs:** 3 *see notes **Group 2** **N:** 195 **Age (mean ±SD):** 64.8 ± 11.6 **M/F:** 107/88 **OHT:** 55 **COAG:** 140 **Black:** 40 **Non-Black:** 155 **Drop outs:** 5 *see notes **Group 3** **N:** 193 **Age (mean ±SD):** 64.5 ± 11.6 **M/F:** 89/104 **OHT:** 59 **COAG:** 134 **Black:** 43 **Non-Black:** 150 **Drop outs:** 3 * see notes		**Increase in iris pigmentation & Eyelash changes**	**Group 1:** 118 **Group 2:** 6 **Group 3:** 60	** Standard Deviations (SD) calculated as pooled variances from known SDs for Camras 1996[17], Martin 2007[93]and Mastropasqua 1999[95] Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation.
			Number of patients with cardiovascular systemic side effects reported at incidence of >3%	**Group 1:** 13 **Group 2:** 9 **Group 3:** 7 Includes hypertension	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Pfeiffer, 2002[116] European Latanoprost Fixed Combination Study Group **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months Plus a 6 month open-label study with all patients using the fixed combination of latanoprost and timolol	**Patient group:** COAG or OHT **Setting:** multicentre - 37 centres, Germany **Inclusion criteria:** • Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Aged 18 or older • IOP ≥25mmHg with prior therapy • IOP ≥30mmHg without prior therapy **Exclusion criteria:** • History of angle-closure glaucoma • Previous ocular surgery, argon laser trabeculoplasty or ocular inflammation or infection 3 months prior to pre-study visit • Patients with a known hypersensitivity or contraindication to any component of study drugs **All patients** **N:** 436 **Age (mean):** NR **M/F:** 196/240 **Drop outs:** 72 **Ethnicity:** NR **Diagnosis: :** POAG 336, pseudoexfoliative glaucoma 22, pigmentary glaucoma 8, ocular hypertension 64, mixed (different	**Group 1** Fixed combination of latanoprost 0.005% & timolol 0.5% am, placebo pm **Group 2** Latanoprost 0.005% 1/day am, placebo pm **Group 3** Timolol 0.5% 2/day **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer at pre-study visit. Method of measurement for other visits not stated. Each measurement taken three times in each eye. Measurements for each visit taken at 8am, 10am and 4pm. Also determined at	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 21.6 ± 3.8 **Group 2:** 22.5 ± 4.0 **Group 3:** 22.5 ± 4.1	**Funding:** Pharmacia Inc **Limitations:** Adverse events poorly reported. Randomisation method and allocation concealment were not reported. Although patients were masked it is not clear whether examiners were masked. **Additional outcomes:** Also reported mean diurnal IOP at week 2 and 13; no. of patients switching to open-label trial on fixed combination. **Notes:** † Reported ocular adverse events: eye irritation, visual field change (suspected), hypertrichosis, hyperaemia, vision decreased, increased iris pigmentation, corneal disorder, cataract, optic atrophy, conjunctivitis, iritis, change in refraction, blepharitis. Gives number of patients for each adverse event. § Reported non-ocular adverse
			Mean ± SD diurnal IOP at 6 mths mmHg	**Group1:** 19.0 ± 3.5 **Group 2:** 20.4 ± 4.9 **Group 3:** 21.4 ± 5.4 **P values:** not reported	
			Mean ± SD reduction in diurnal IOP at 6 mths	**Group 1:** 1.7 ± 3.36** **Group 2:** 2.1 ± 5.42** **Group 3:** 1.1 ± 5.27**	
			Percent of patients reaching IOP <15mmHg at 6 mths or up to treatment failure	**Group1:** 14/140 **Group 2:** 8/147 **Group 3:** 7/149 **P values:** not significant	
			Percent of patients reaching acceptable IOP <18mmHg at 6 mths or up to treatment failure *Used in met-analysis*	**Group1:** 54/140 **Group 2:** 48/147 **Group 3:** 37/149 **P values:** Group 1 to 3 $p<0.05$	
			Percent of patients reaching IOP <21mmHg at 6 mths or up to treatment failure	**Group1:** 110/140 **Group 2:** 101/147 **Group 3:** 83/149 **P values:** not significant	
			No. of ocular adverse events by group seen in ≥1% of any treatment group (NB not no. of patients) §	**Group1:** 34 **Group 2:** 41 **Group 3:** 21	
			No. of non-ocular adverse events by group seen in ≥1% of any treatment group (NB not no. of patients) §	**Group1:** 22 **Group 2:** 18 **Group 3:** 19	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	diagnosis in the two eyes) 6 **Previous IOP reducing medication**: 401 **Group 1** **N:** 140 **Age (mean):** 64 ±13 **M/F:** 67/73 **Drop outs:** 12 **Ethnicity:** NR **Diagnosis:** POAG 106, pseudoexfoliative glaucoma 2, pigmentary glaucoma 3, ocular hypertension 27, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication**: NR **Group 2** **N:** 147 **Age (mean):** 63 ±12 **M/F:** 77/70 **Drop outs:** 28 **Ethnicity:** NR **Diagnosis:** POAG 112, pseudoexfoliative glaucoma 13, pigmentary glaucoma 4, ocular hypertension 16, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication in last**: NR **Group 3** **N:** 149 **Age (mean):** 64 ±10 **M/F:** 52/97 **Drop outs:** 32 **Ethnicity:** NR **Diagnosis:** POAG 118, pseudoexfoliative glaucoma 7,	each visit: best corrected visual acuity and slit lamp examination. Refraction recorded, ophthalmoscopy performed and Colour Polaroid photographs taken at 6 months.	**No. of patients not completing 6 months in randomised group** * **No. of patients not completing 6 months in randomised group OR in open label trial**	**Group1:** 12/140 **Group 2:** 28/147 **Group 3:** 32/149 **P value group 1 to 2:** =0.006 **P value group 1 to 3:** =0.001 **P value group 2 to 3:** =0.10 **Group1:** 10/140 **Group 2:** 14/147 **Group 3:** 16/149 **P values:** not significant	events: cardiovascular disorder, influenza-like symptoms, metabolic disorders, respiratory disorders, cerebrovascular disorders, vertigo, sleep disorders, headache, liver/biliary disorders Patients switched medications to the fixed combination used in for group 1 if treatment failure occurred. Treatment failure defined as increased IOP ≥10% of the mean IOP from baseline and an IOP of ≥23mmHg on two examinations within 2 weeks. Study reports numbers by group. If treatment still did not work patients were withdrawn. **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	pigmentary glaucoma 1, ocular hypertension 21, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication in last:** NR				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Tomita et al., 2004[150] **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 3 years	**Patient group:** Normal tension glaucoma **Setting:** multi-centre (3 sites) Japan **Inclusion criteria:** • Untreated IOP ≤ 21 mmHg • Evidence of optic nerve head change and VF changes • Best corrected visual acuity ≥ 15/20 – no media opacities • Refractive errors not exceeding -8 or +6D • MD Humphrey not exceeding -12.0dB • Discontinuation of previous glaucoma treatments of 4 weeks **Exclusion criteria:** • History of ocular, rhinologic, neurologic or systemic disorders accounting for optic nerve head damage • History of haemodynamic crisis • Previous surgery or laser treatment in either eye **<u>All patients</u>** **N:** 62 **Age (mean):** NR **M/F:** **Drop outs:** 15 (24%) **<u>Group 1</u>**	**Group 1** Latanoprost 0.005% 1/day **Group 2** Timolol 0.5% 2/day **Examination methods:** Average of 2 IOP measurements adopted for baseline IOP. Goldmann tonometry used. Subsequent IOP measurements were taken every month at 9am before morning dose. Humphrey perimetry used for visual field defects every 6 months. If VF measurement did not meet reliability criteria it was repeated after 1 month. Abnormal VF at least 3 adjacent test points. Stereoscopic optic disc photographs taken every 6 months and analysed using 3D image analysis programme.	**Mean ± SD baseline IOP mmHg**	**Group1:** 15.0 ± 1.6 **Group 2:** 15.9 ± 2.0	**Funding:** Funding NR but study conducted by Dept Ophthalmology, University of Tokyo. Gifu University of Medicine and Yamanashi University School of Medicine. **Limitations:** Open label study **Additional outcomes:** **Notes:** No data on adverse events Randomly assigned to groups using a computer generated list kept in a sealed envelope. Optic disc stereophotographs were analysed by a masked observer. **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost)
			Mean ± SD end point IOP (3 years) mmHg	**Group1:** 12.9 ± 2.2 **Group 2:** 14.0 ± 2.0	
			Mean ± SD reduction in IOP mmHg at 6 mths (baseline – end point)	**Group1:** 2.1 ± 2.35** **Group 2:** 1.9 ± 2.17** **p value** NR not signif at any time point using repeated measure ANOVA	
			% reduction both groups	**13-15%** **p value** NR not signif at any time point using repeated measure ANOVA or t test	
			Mean ± SD baseline Mean deviation for VF dB	**Group1:** -6.0 ± 2.1 **Group 2:** -5.9 ± 2.3	
			Mean ± SD end point Mean deviation for VF dB (3 years)	**Group1:** -6.3 ± 3.2 **Group 2:** -5.6 ± 2.9	
			Estimated rate of change of MD ± SE value/Year	**Group1:** -0.34 ± 0.17 **Group 2:** -0.10 ± 0.18 **p value:** Not signif.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 31 **Age (mean ± SD):** 56 ± 10 **M/F:** 14/17 **Drop outs:** 8 **<u>Group 2</u>** **N:** 31 **Age (mean ± SD):** 54.3 ± 8.5 **M/F:** 15/16 **Drop outs:** 7				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Vetrugno et al., 2004[156] **Study design:** RCT Unmasked **Evidence level:** 1 + **Duration of follow-up:** 6 months	**Patient group:** POAG only **Setting:** single centre, Italy **Inclusion criteria:** • Diagnosis of POAG • Age 40 - 60 • Non smokers • IOP < 16 mmHg after 12 months pre treatment with timolol • Refraction ± 3 D ≥ 0.1 in study eye • > 10% reduction of pulsatile ocular blood flow pOBF after 12 months pre treatment with timolol • Systolic brachial pressure 120 – 140 mmHg • Diastolic brachial pressure 70-90 mmHg • Heart rate 66-80 bpm • BMI normal • Normal blood haemological test results **Exclusion criteria:** • Cardiovascular abnormalities (atherosclerosis, carotid stenosis) • Use of systemic vaso-active therapy (beta-blockers, Ca agonists, nitroglycerin derivatives) • Types of glaucoma other than POAG **<u>All patients</u>** **N:** 38	**Group 1** Bimatoprost 0.3 % 1/day 9pm **Group 2** Timolol 0.5% 2/day **Examination methods:** IOP and pOBF measured at 9am each study visit. pOBF measured on a tonograph but IOP measurement methods not reported	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 17.00 ± 1.69 **Group 2:** 16.75 ± 2.38	**Funding:** Author reports that the study is not funded by industry. **Limitations:** • The study is actually looking at the effect of bimatoprost on patients where their IOP has already been lowered effectively with timolol. • Open label study. Treatments were not masked - may affect reporting of adverse events. Outcome assessment was not masked either but same investigator carried out all the tests. • Small study **Additional outcomes:** pOBF mean ± SD **Notes:** No serious adverse events were noted in either group but adverse events were NR for timolol **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost)
			Mean ± SD end point diurnal IOP (6 mths) mmHg	**Group1:** 13.5 ± 1.31 **Group 2:** 15.75 ± 1.67	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)	**Group1:** 3.5 ± 1.84** **Group 2:** 1.0 ± 2.28** **p value** compares IOP at end point between groups (not reduction) p using unpaired t test is < 0.01	
			Conjunctival hyperaemia + itching	**Group 1:** 5 **Group 2:** 0	
			↑ periorbital pigmentation & Eyelash changes	**Group 1:** 2 **Group 2:** 0	
			Number of patients with cardiovascular systemic side effects	**Group 1:** = NR **Group 2:** = NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean ± SD): 51.7 ± 4.8 **M/F:** 22/16 **Race:** NR **Drop outs:** 0 **<u>Group 1</u>** **N:** 19 **Age (mean ± SD):** 52.1 ± 5.01 **M/F:** 12/7 **Drop outs:** 0 **<u>Group 2</u>** **N:** 19 **Age (mean ± SD):** 51.2 ± 4.12 **M/F:** 10/9 **Drop outs:** 0				Computer generated randomisation sequence.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Watson & Stjernschantz, 1996[158] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG & OHT **Setting:** Multi-centre – 14 centres, UK **Inclusion criteria:** • Age ≥ 40 years old • Unilateral or bilateral POAG or pigmentary glaucoma or exfoliation glaucoma or OHT ≥ 22 mmHg. • Completion of adequate washout period for sympathomimetics, CAI and miotics. **Exclusion criteria:** • Patients on topical beta blockers within 6 months of study • Angle closure glaucoma history • Ocular trauma • Previous filtration or laser surgery for glaucoma within 6 months of study • Dry eye syndrome • Ocular inflammation or infection within 3 months of study • Contact lens wearers • Those with contraindications for beta blockers • Women of child bearing potential & nursing mothers • Patients who would not benefit from monotherapy **<u>All patients</u>** **N:** 294 **Age (mean):** 65 ± 10 **M/F:** 191/103 **Drop outs:** 26 (8.8%) **White:** 285	**Group 1** Latanoprost 0.005% 1/day pm + placebo am for 6 months **Group 2** Timolol 0.5% 2/day morning and evening for 6 months **Examination methods:** IOP measured by Goldmann Applanation Tonometry - 3 readings taken at each visit (9 am, 1 pm, 5 pm) and mean taken for statistical analysis. Blood and urine samples taken at baseline and last visit. Iris photography taken Visual Field analysis	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 25.2 ± 3.4 **Group 2:** 25.4 ± 3.6	**Funding:** Supported by Pharmacia (now Pfizer), Sweden which manufactures latanoprost **Limitations:** It is not clear whether analysis of IOP is calculated on an ITT basis. **Additional outcomes:** Detailed analysis of conjunctival hyperaemia **Notes:** **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost) Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation.
			Mean ± SD end point diurnal IOP (6 mths) mmHg	**Group1:** 16.7 ± 2.6 **Group 2:** 17.1 ± 2.6	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)	**Group1:** 8.5 ± 3.68** **Group 2:** 8.3 ± 3.47** **p value** NR - not signif (using covariate analysis)	
			% reduction in IOP at end point of 6 mths	**Group1:** 33.7 **Group 2:** 32.7	
			Number of patients with local ocular side effects	**Group1:** 215 **Group 2:** 158 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Number of patients with ↑ iris pigmentation	**Group1:** 2 **Group 2:** 0	
			Number of patients with cardiovascular systemic side effects	**Group1:** 32 **Group 2:** 28 Includes respiratory infection, bronchitis, arterial hypotension, angina, shortness of breath	
			Reasons for withdrawals (dropouts)	**Group1:** • Inadequate IOP control = 2 • Local side effects = 2 • Breathing problems = 1 • Bad compliance/lost patient = 6 • Contraindicated prescription = 1 **Group 2:** • Breathing/respiratory problems = 3	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Black: 9 **<u>Group 1</u>** **N:** 149 **Age (mean):** 64.7 ± 9.5 **M/F:** 98/51 **Drop outs:** 12 **White:** 143 **Black**: 6 **OHT only**: 80 **COAG or COAG + OHT**: 69 **<u>Group 2</u>** **N:** 145 **Age (mean):** 65.3 ± 10.5 **M/F:** 93/52 **Drop outs:** 14 **White:** 142 **Black:** 3 **OHT only**: 68 **COAG or COAG + OHT**: 77			• Arterial hypotension/bradycardia = 2 • Headaches = 2 • Local side effects = 5 • Previous timolol = 1 • Self withdrawal = 1	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 7 Prostaglandin analogues vs. sympathomimetics

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Camras et al., 2005[18] **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** POAG and OHT patients **Setting:** Multi-centre 23 centres in the USA **Inclusion criteria:** • ≥ 18 years • Naïve to glaucoma therapy or on topical monotherapy • Best-corrected visual acuity ≥ 20/80 • IOP ≥ 22 mm Hg **Exclusion criteria:** • Closed/barely opened anterior chamber angle or history of acute angle closure • No history of Argon laser trabeculoplasty or any ocular surgery or inflammation/infection within the 3 months prior to pre-study visit **<u>All patients</u>** **N:** 303 **Mean IOP:** **Drop outs:** 57 (19%) **<u>Group 1 (reported as ITT group)</u>** **N:** 151 **Age (mean ± SEM):** 62 ± 1.0 **M/F:** 70/81	**Group 1** Latanoprost 0.005% once daily (8 am) for 6 months **Group 2** Brimonidine 0.2% twice daily 8 am and 8 pm) for 6 months **All** Washout period completed as appropriate <u>6 visits</u>: Screening Baseline Week 2 3 months 6 months Follow up Goldmann applanation tonometer to record IOP reading (8am, 10 am , 12 pm and 4 pm except week 2 visit only 8 am)	**Mean diurnal (8 am, noon and 4 pm) IOP at 6 months (mm Hg)**	**Group1:** 18.8 ± 0.3 (± SEM) **Group 2:** 21.5 ± 0.3 (± SEM) **p value:** p < 0.001 (significantly lower than corresponding baseline values)	**Funding:** Supported in part by Pharmacia corporation, a Pfizer company (New York) which manufactures latanoprost and an unrestricted grant from (University of Nebraska Medical Centre) from Research to Prevent Blindness Inc. (New York). **Limitations:** • Open label • Use of adjusted and unadjusted means very confusing. • High drop out rate >20% in Brimonidine group **Additional outcomes:** Percentage of patients achieving pre-specified IOP levels (e.g. ≥ 40%, ≥ 30%, ≥ 10% etc.) after 6 months of treatment **Notes:** Randomisation using computer generated
			Differences in mean diurnal change in IOP between groups: baseline to 6 months	**Mean:** 2.5 ± 0.3 (± SEM) **95% CI:** 1.9- 3.2 **p value:** p < 0.001 in favour of group 1 (latanoprost)	
			Adjusted mean diurnal change in IOP from baseline to 6 months	**Group1:** 5.7 ± 0.3 (± SEM) **Group 2:** 3.1 ± 0.3 (± SEM) **p value:** p < 0.001	
			Differences in mean diurnal change in IOP between groups: baseline to 6 months (Post hoc analyses including 10 am reading).	**Group 1:** 5.5 ± 0.3 (± SEM) **Group 2 :** 3.6 ± 0.3 (± SEM) **Difference in mean:** 2.0 ± 0.4 **95% CI:** 1.3- 2.6 **p value:** p < 0.001 in favour of group 1 (latanoprost)	
			Mean % reduction on diurnal IOP at month 6	**Group1:** 22.6% **Group 2:** 12.8% **95% CI:** NR **p value:** p < 0.001	
			Adverse events resulting in withdrawal from study	**<u>Any adverse event</u>** **Group 1:** 4/151 (3%) **Group 2:** 23/152 (15%) **p value:** p < 0.001 (Fisher's exact test) **<u>External ocular</u>** **Group 1:** 2/151 (1%) **Group 2:** 15/152 (10%) **p value:** p = 0.06 (Fisher's exact test) **<u>Central nervous system</u>**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Race: Caucasian 104 African American 36 Other 11 **Mean IOP ± SEM:** 24.6 ± 0.3 **Drop outs:** 21 (14% including 4 adverse events, 8 IOP not controlled, 2 lost to follow-up and 2 protocol violations) **<u>Group 2 (reported as ITT group)</u>** **N:** 150 **Age (mean ± SEM):** 64 ± 1.0 **M/F:** 77/73 **Race:** Caucasian 103 African American 39 Other 8 **Mean IOP ± SEM:** 24.8 ± 0.2 **Drop outs:** 36 (24% including 23 adverse events, 10 IOP not controlled, 2 lost to follow up, 1 protocol violation).			**Group 1:** 0 **Group 2:** 5/152 (3%) **p value:** p < 0.001 (Fisher's exact test) **<u>Dry mouth:</u>** **Group 1:** 0 **Group 2:** 1/152 (1%) **<u>Other</u>** (including palpitations, reduced visual acuity, blurred vision, increased lacrimation, diplopia) **Group 1:** 2/151 (2%) **Group 2:** 2/152 (1%)	allocation. Masked outcome assessment. Originally 303 patients (152/151) but 2 excluded and not considered in the ITT analysis (terminated after baseline and before instillation of treatment.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. sympathomimetics (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kampik et al., 2002[70] European latanoprost study group **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** POAG and OHT patients **Setting:** Multi-centre- 30 eye clinics in Germany, UK, Spain and Finland **Inclusion criteria:** • Age ≥ 18 years • Unilateral or bilateral POAG or exfoliation glaucoma or OHT with IOP of ≥ 21mm Hg with current monotherapy or dual therapy **Exclusion criteria:** • Previous treatment with latanoprost or brimonidine or ongoing treatment with α-adrenoceptor agonists • Closed or barely open anterior chamber angle or history of acute angle closure • Argon laser trabeculoplasty, filtering surgery or other ocular surgery within the last 3 months • Current use of contact lenses • Ocular inflammation or infection within the last 3 months • Known hypersensitivity to any of the eye drop components **<u>All patients</u>** **N:** 379 **Age (mean):** **M/F:** 154/225 **Mean IOP:** NR **Drop outs:** 52 (13.3%)	**Group 1** Latanoprost 0.005% once daily (10 pm) for 6 months **Group 2** Brimonidine 0.2% twice daily (8 am and 10 pm) for 6 months. **All** At least 4 weeks washout period 4 visits during 6 month study: Baseline 2 weeks 3 months 6 months 3 IOP measurements in each eye using Goldmann applanation tonometer taken at: - 10 am and 5 pm at baseline, 3 months and 6 months - Only before 12 noon at 2 weeks The mean of the 3 measurements was taken and if both eyes were study eyes the	**Mean ± SD diurnal IOP at baseline (mm Hg)**	**Group1:** 25.1 ± 3.7 **Group 2:** 24.9 ± 3.0	**Funding:** Supported by a research grant from Pharmacia Corporation (Peapack, NJ) manufacturers of latanoprost **Limitations:** • Open label • Randomisation method and allocation concealment was not reported. • Significantly higher number of OHT patients in group 1 compared to group 2 (p = 0.027) • **Additional outcomes:** Percentage of patients achieving prespecified IOP levels (e.g. ≤21, ≤20, ≤15 etc.) after 6 months of treatment **Notes:** Masked outcome assessment. Statistical analysis does not include the 4
			Mean ± SD diurnal IOP at 6 months (mm Hg)	**Group1:** 18.0 ± 2.9 **Group 2:** 19.8 ± 3.1	
			Mean ± SD diurnal change in IOP from baseline at 6 months (mm Hg)	**Group1:** 7.1 ± 3.3 **p value:** p < 0.001 (ANCOVA) **Group 2:** 5.2 ± 3.5 **p value:** p < 0.001 (ANCOVA)	
			% reduction in mean IOP from baseline	**Group1:** 28% **Group 2:** 21% **p value:** p < 0.001 (ANCOVA) favouring latanoprost	
			Mean ± SD IOP at 10 am and 5 pm at 6 months (mm Hg)	**<u>IOP 10 am:</u>** **Group1:** 18.1 ± 2.9 **Group 2:** 19.5 ± 3.2 p < 0.001 (ANCOVA) in favour of latanoprost **<u>IOP 5 pm:</u>** **Group 1 :** 17.8 ± 3.0 **Group 2:** 19.8 ± 3.4 **p value:** p < 0.001 (ANCOVA) in favour of latanoprost	
			Number of patients with systemic adverse events*	**Group1:** 23 (including 4 respiratory) **Group 2:** 56 (including 4 respiratory, 1 serious) **p value:** p < 0.005 Fisher exact test (this is for all systemic side effects as defined in the paper). **95% CI:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 187 **Age (mean):** 64 ± 11 **M/F:** 77/110 **Mean IOP:** 25.1 ± 3.7 This group had significantly (p=0.027) more OHT patients than group 2. **Drop outs:** 5 (including IOP not controlled, ocular irritation, Argon laser trabeculoplasty and corneal oedema) **Group 2** **N:** 192 **Age (mean):** 65 ± 12 **M/F:** 77/115 **Mean IOP:** 24.9 ± 3.0 **Drop outs:** 47 (including 4 before instillation of treatment. Other reasons for withdrawing included 14 ocular allergic reactions, 13 IOP not controlled, withdrawal of consent and Argon laser trabeculoplasty).	mean of the 2 eyes was used.	**Number of patients with ocular adverse events****	**Group1:** 62 **Group 2:** 95 **p value:** NS except for significantly more ocular allergic reactions (p < 0.001 Fisher exact test) in the brimonidine group. **95% CI:** NR	patients randomised to receive brimonidine who withdrew consent. *includes respiratory, dry mouth, headaches, fatigue and infection **includes ocular irritation, ocular allergic reaction, increased iris pigmentation, disturbed vision and conjunctival disorders

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 8 Carbonic anhydrase inhibitors vs. no treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Miglior et al., 2005[99] European Glaucoma Prevention Study (EGPS) Group. **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** Median 55.3 months.	**Patient group:** Consecutive patients from clinic population with ocular hypertension (30 years plus). **Setting:** Patients from 18 centres in 4 European countries. **Inclusion:** IOP (22-29mmHg), two normal and reliable visual fields and normal optic discs, PEX allowed (below 2%), normal optic discs in both eyes, open angle, PEX and PDS allowed. **Exclusion**: Visual acuity below 20/40, previous intraocular surgery, previous laser trabeculoplasty within 3 months, secondary causes of elevated IOP. **All patients** **N:** 1077 **Age (mean):** 57.03 ± 10.3 **Race:** Caucasian: 1075, African European: 1 Asian: 1 **Mean IOP**: 23.6 ± 1.6 **Group 1** **N:** 536 **Age (mean):** 56.42 ± 10.32 **M/F:** 232/304 **Mean IOP**: 23.4 ± 1.53 **Dropouts**: 191 (116 adverse events) **Group 2** **N:** 541 **Age (mean):** 57.63 ± 10.30 **M/F:** 259/282	**Group 1** Dorzolamide 2% (CAI) – three times daily. **Group 2** Placebo – three times daily.	**Development of reproducible visual field defects:**	**Group1:** 26/536 (4.9%) **Group 2:** 38/541 (7.0%) **OR:** 0.68 (95% CI: 0.41-1.12)	**Funding:** Supported by The European Commission (BIOMED II program, contract no.: BMH4-CT-96-1598), and Merck (Whitehouse Station, NJ). **Limitations:** High dropouts (30.1%). A comparative analysis of the mean IOP between patients still in the study and those who voluntarily withdrew revealed a higher IOP level in the group of withdrawn patients. It was not possible to calculate standard deviations for mean change in IOP from baseline at each follow up using Cochrane methods because no p values were reported.. **Additional outcomes:** **Notes:** Randomisation by computer generated allocation sequence and allocation concealment. Patients and examiners were masked to treatment assignment. Initially 1081 enrolled and
			Dropouts due to adverse events:	**Group1:** 116/536 (21.7%) **Group 2:** 51/541 (9.4%) **OR:** 2.54 (95% CI: 1.83-3.53)	
			Development of reproducible VF defect or glaucomatous change of optic disc:	**Group1:** 46/536 **Group 2:** 60/541 **OR:** 0.86 (95% CI: 0.58-1.26) **p value:** 0.45	
			Mean IOP at follow up	**6 months** **Group 1:** 20 ± 2.69 (n=484) **Group 2:** 21.3 ± 2.98 (n=492) **12 months** **Group 1:** 19.7 ± 2.88 (n=453) **Group 2:** 21 ± 3.41 (n=475) **2 years** **Group 1:** 19.1 ± 2.85 (n=391) **Group 2:** 20.4 ± 3.35 (n=447) **5 years** **Group 1:** 18.2 ± 3.45 (n=192) **Group 2:** 19.1 ± 3.71 (n=217)	
			Mean % reduction from baseline in observed cases:	**6Months** **Group1:** 14.5% **Group 2:** 9.3% **5 years:** **Group 1:** 22.1% **Group 2:** 18.7%	
			Mean % reduction IOP from baseline in last	**Group1:** 17.9% (SD 14.1%) **Group 2:** 13.7% (SD 15.9%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Mean IOP: 23.5 ± 1.68 **Drop outs**: 134 (51 adverse events)		**observation carried forward analysis:** (5 years)		randomised but 4 excluded as had glaucoma so not included in intention to treat analysis.
			Safety endpoint (IOP 35mmHg or greater):	**Group 1:** 1/536 (0.2%) **Group 2**: 12/541 (2.2%)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 9 Carbonic anhydrase inhibitors vs. beta-blockers

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
March & Ochsner, 2000[92] The Brinzolamide Long-Term Therapy Study Group **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 18 months	**Patient group:** COAG or OHT **Setting:** multi-centre (18 sites) USA **Inclusion criteria:** • Diagnosis of pseudoexfoliative glaucoma, POAG, pigmentary glaucoma or OHT • ≥21 years old • Post menopausal or sterilised women only • IOP 22 – 36 mmHg after washout period **Exclusion criteria:** • Patients with corrected visual acuity of worse than 20/80 • Pregnant or nursing women • Patients with history of hypersensitivity to test medications • Previous intraocular surgery • Ocular trauma • Recent ocular inflammation or infection • Photophobia or diplopia • Contraindications to beta-blockers, CAI • Use of medications causing dry eye • Concomitant use of systemic CAIs **<u>All patients</u>** **N:** 378	**Group 1** Brinzolamide 1% 2/day (+ placebo for afternoon dose) **Group 2** Brinzolamide 1% 3/day **Group 3** Timolol 0.5% 2/day (+ placebo for afternoon dose) **Examination Methods:** At each visit the IOP was measured before the morning dose using a Goldmann tonometer. Automated perimetry was performed at month 12 and on completion.	**Mean ± SD baseline IOP mmHg** (average of both eyes 8am)	**Group1:** 25.1 ± NR **Group 2:** 26.1 ± NR **Group 3:** 25.4 ± NR	**Funding:** Alcon laboratories. Manufacturer of brinzolamide **Limitations:** • Randomisation method and allocation concealment not reported. • Although study states that it is a double masked design it is not clear whether examiners are masked • SDs missing from IOP outcome data • High dropout rate. • Results presented are per protocol not ITT **Additional outcomes:** Corneal thickness and corneal endothelial cell density **Notes:** Randomisation 2:2:1 Drop out figures due to
			Mean ± SD reduction in IOP mmHg at 18 mths (baseline – end point)	**Group1:** 3.3 ± NR **Group 2:** 3.2 ± NR **Group 3:** 5.3 ± NR P is < 0.002 comparing timolol v brinzolamide 2/day or 3/day	
			Number of patients reporting local ocular side effects	**Group1:** 45 **Group 2:** 47 **Group 3:** 19 Includes itching, stinging, vision disturbance, eyelid discomfort, hyperaemia	
			Number of patients reporting bitter taste	**Group1:** 5 **Group 2:** 12 **Group 3:** 0	
			Number of patients with cardiovascular systemic side effects	**Group1:** NR **Group 2:** NR **Group 3:** NR	
			Reasons for withdrawals (dropouts)	**Group1:** • Inadequate IOP control = 9 • Adverse events = 21 • Other (includes self-withdrawal, lost to follow-up, non-compliance) = 14 **Group 2:** • Inadequate IOP control = 13 • Adverse events = 17 • Other (includes self-withdrawal, lost to follow-up, non-compliance) = 33 **Group 3:** • Inadequate IOP control = 1 • Adverse events = 8	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 150 **Age (mean ± SD):** 63.0 ± 11.6 **M/F:** 68/82 **Black/non-black:** 27/123 **OHT/COAG:** 59/91 **Drop outs:** 44 (29%) **Group 2** **N:** 153 **Age (mean ± SD):** 60.3 ± 12.9 **M/F:** 76/77 **Black/non-black:** 33/120 **OHT/COAG:** 57/96 **Drop outs:** 63 (41%) **Group 3** **N:** 75 **Age (mean ± SD):** 59.9 ± 13.2 **M/F:** 28/47 **Black/non-black:** 14/61 **OHT/COAG:** 25/50 **Drop outs:** 27 (36%)			• Other (includes self-withdrawal, lost to follow-up, non-compliance) = 18	other reasons include proportion of patients withdrawing from study at 12 months. Patients are masked to treatment assignment

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Carbonic anhydrase inhibitors vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Strahlman et al., 1995[145] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** COAG & OHT **Setting:** multi-centre, 34 sites **Inclusion criteria:** • 21 – 85 years old • Sufficient washout period for current medications • Untreated IOP of ≥ 23 mmHg • Contact lens wearing discontinued 3 weeks prior to study **Exclusion criteria:** • Patients whom discontinuation of current treatment would cause glaucomatous damage • Patients with corrected visual acuity of worse than 20/60 • History of poor response to ocular hypotensive agents • History of allergy to agents in trial • Contraindications to beta-blockers • Clinically significant dry eye syndrome • Previous intraocular surgery • Ocular trauma • Recent ocular inflammation or infection • Herpes simplex keratitis or corneal ulcer within 1 year • Photophobia or diplopia • Premenopausal, pregnant and nursing women • Concomitant use of systemic	**Group 1** Dorzolamide 2% 3/day **Group 2** Timolol 0.5% 2/day (+ placebo for afternoon dose) **Group 3** Betaxolol 0.5% 2/day (+ placebo for afternoon dose) **Examination methods:** Within each centre investigators were instructed to use the same Goldman tonometer for all IOP measurements for a given patient. IOP was measured at weeks 2, 4 and months 2,3,6,9 and 12. IOP measured at 9.30am, 12.30pm and 3.30pm Humphrey 24-2 or Octopus perimetry was used for the visual field testing at screening and months 6 and 12	**Mean ± SD baseline IOP mmHg** reading at 12.30 pm	**Group1:** 25.2 ± 4.8 **Group 2:** 25.9 ± 5.3 **Group 3:** 26.1 ± 5.7	**Funding:** Merck & co inc. Manufacturers of dorzolamide and timolol **Limitations:** • Randomisation method and allocation concealment not reported. • Although study states that it is a double masked design it is not clear whether examiners are masked • Some patients received additional therapy (timolol or dorzolamide) if IOP was not lowered effectively on monotherapy. The dropout numbers include all patients. **Additional outcomes:** **Notes:** 3:1:1 randomisation Patients are masked to treatment assignment.
			Mean ± SD end point IOP reading at 12.30 pm **12 mths**	**Group1:** 20.5 ± 5.0 **Group 2:** 19.9 ± 4.0 **Group 3:** 20.9 ± 5.4	
			Mean ± SD reduction in IOP mmHg at 12 mths (baseline – end point) reading at 12.30 pm	**Group1:** 4.7± 4.1 **Group 2:** 6.0 ± 4.2 **Group 3:** 5.2 ± 4.9	
			Number of patients reporting local ocular side effects	**Group1:** 195 **Group 2:** 44 **Group 3:** 47 Includes itching, stinging, vision disturbance, eyelid discomfort, conjunctivitis	
			Number of patients reporting bitter taste	**Group1:** 85 **Group 2:** 7 **Group 3:** 9	
			Number of patients with cardiovascular systemic side effects	**Group1:** 8 **Group 2:** 8 **Group 3:** 9 Includes hypertension, angina, tachycardia	
			Reasons for withdrawals (dropouts)	**Group1:** • Inadequate IOP control = 10 • Adverse events = 37 • Administration = 14 **Group 2:** • Inadequate IOP control = 1 • Adverse events = 6 • Administration = 6 **Group 3:** • Inadequate IOP control = 6	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	beta-blockers or CAIs which may affect IOP **<u>All patients</u>** **N:** 523 **Age (mean):** 64 (range 17-85) **M/F:** 243/280 **Drop outs:** 89 **<u>Group 1</u>** **N:** 313 **Age (mean ± SD):** 62.1 ± 11.6 **M/F:** 136/177 **Black/non-black:** 4/309 **OHT/COAG:** 120/220* **Drop outs:** 61 **<u>Group 2</u>** **N:** 103 **Age (mean ± SD):** 63.8 ± 11.4 **M/F:** 53/50 **Black/non-black:** 2/101 **OHT/COAG:** 44/68* **Drop outs:** 13 **<u>Group 3</u>** **N:** 107 **Age (mean ± SD):** 60.7 ± 12.0 **M/F:** 54/53 **Black/non-black:** 3/104 **OHT/COAG:** 33/83* **Drop outs:** 15 * based on eye rather than patient			• Adverse events = 3 • Administration = 6	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 10 Sympathomimetics vs. beta-blockers

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Le Blanc, 1998[83] and Schuman, 1996[132] **$** **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG & OHT **Setting:** multi-centre, Canada & USA **Inclusion criteria:** • Diagnosis of POAG or OHT and on no more than 2 glaucoma drugs • Best corrected visual acuity of 20/80 or better in each eye • Untreated IOP between 23 and 35 mmHg and both eyes within 5 mmHg each other • Washout of current medications **Exclusion criteria:** • Active ocular disease • Severe dry eye • Corneal abnormalities • Advanced glaucoma (C/D≥ 0.8) • Contact lens wearers • Use of other ocular medications • Surgery or laser surgery within 6 months • Uncontrolled hypertension or diabetes • Women with child bearing potential • Contraindications to	**Group 1** Brimonidine 0.2% 2/day **Group 2** Timolol 0.5% 2/day **Examination methods:** IOP was measured at trough - 12 hours after instillation of evening medication and at peak - 2 hours after morning medication. Study does not report how IOP was measured. Horizontal cup to disc ratios and visual field measured using a Humphrey perimeter (Mean Deviation) at months 6 and 12. Snellen chart used for visual acuity at each visit. Direct and indirect ophthalmoscopy was used to evaluate the fundus and optic nerve head. Schirmer tear test at 6 and 12 months	**Mean & 95% CI reduction in peak IOP mmHg (averaged over all time points to 12 months)**	**Group1:** 6.8 CI (7.2 - 6.4) **Group 2:** 5.9 CI (6.4 - 5.4) Group1 was significantly better at reducing pressure than group2 p value < 0.001 at weeks 1 & 2 and month 12 using paired t-test	**Funding:** Allergan Inc. Manufacturers of Brimonidine **Limitations:** Very high drop out rate for brimonidine group 47% **Additional outcomes:** Mean Heart Rate **Notes:** Randomisation by computer generated allocation sequence and allocation concealment. Patients and examiners were masked to treatment assignment. Uneven randomisation. **3:2** **$** Schuman 1996[132] reports intermediate results of Le Blanc 1998[83] (6 months of data) and Schuman 1997 *Drop out figures include those who were
			Mean & 95% CI reduction in trough IOP mmHg (averaged over all time points to 12 months)	**Group1:** 3.9 CI (4.2 - 3.6) **Group 2:** 6.0 CI (6.4 - 5.6) Group2 was significantly better at reducing pressure than group1 p value < 0.001 at all time points using paired t-test	
			Mean ± SD reduction in diurnal IOP mmHg (averaged over all time points to 12 months)	**Group1:** 5.4 ± NR **Group 2:** 5.9 ± NR	
			Mean ± SD baseline peak IOP mmHg 6 months Data from Schuman1996	**Group1:** 25.06 ± 3.38 **Group 2:** 24.73 ± 3.12	
			Mean ± SD reduction in peak IOP mmHg (baseline – end point) 6 months Data from Schuman1996	**Group1:** 6.44 ± 3.86 **Group 2:** 5.8 ± 3.66	
			Mean ± SD baseline trough IOP mmHg 6 months Data from Schuman1996	**Group1:** 25.96 ± 3.01 **Group 2:** 25.85 ± 2.8	
			Mean ± SD reduction in trough IOP mmHg	**Group1:** 3.79 ± 3.37 **Group 2:** 6.10 ± 3.12	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	betablockers or α adrenergic agonists • Hypersensitivity to treatment medications • Those who have participated in previous trial within 30 days start of study. **<u>All patients</u>** **N:** 463 **Age (mean):** NR **M/F:** 234/229 **<u>Group 1</u>** **N:** 280 **Age (mean):** 63 (28.5 - 86.4) **M/F:** 138/142 **Drop outs:** 137/292* **POAG:** 157 **OHT:** 112 **1 eye OHT/1 eye POAG:** 11 **Black:** 32 **Non-black:** 260 **Dropouts:** 137/292* (47%) **<u>Group 2</u>** **N:** 183 **Age (mean):** 61 (32.8 - 83) **M/F:** 96/87 **Drop outs:** 40/191* **POAG:** 98 **OHT:** 78 **1 eye OHT/1 eye POAG:** 7 **Black:** 15 **Non-black:** 168 **Dropouts:** 40/191 (21%)*		**(baseline – end point) 6 months** Data from Schuman1996		eligible for study but didn't begin protocol.
			Possible worsening of visual field (increase >5dB for Mean Deviation)	**Group1:** 5 **Group 2:** 6 No significant between group differences in VF observed	
			***Reasons for withdrawals (dropouts)**	**Group1:** • Inadequate IOP control = 30 • All adverse events = 76 • Ocular Adverse events =43 • Systemic =16 (includes fatigue or drowsiness, headache, dry mouth) • Other reasons (including cataract surgery = 31 **Group 2:** • Inadequate IOP control = 10 • All adverse events = 9 (3 for fatigue or drowsiness) • Other reasons (including cataract surgery = 21	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Sympathomimetics vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Schuman, 1997[133] and Schuman, 1996[132] **$** **Study design:** RCT **Evidence level:** 1+ Double masked **Duration of follow-up:** 12 months	**Patient group:** POAG & OHT **Setting:** multi-centre, USA **Inclusion criteria:** • Diagnosis of POAG or OHT and on no more than 2 glaucoma drugs • Best corrected visual acuity of 20/80 or better in each eye • Untreated IOP between 23 and 35 mmHg and both eyes within 5 mmHg each other **Exclusion criteria:** • Active ocular disease • Severe dry eye • Corneal abnormalities • Advanced glaucoma (C/D≥ 0.8) • Contact lens wearers • Use of other ocular medications • Surgery or laser surgery within 6 months • Uncontrolled hypertension or diabetes • Women with child bearing potential • Contraindications to beta-blockers or α adrenergic agonists • Hypersensitivity to treatment medications • Those who have participated in	**Group 1** Brimonidine 0.2% 2/day **Group 2** Timolol 0.5% 2/day **Examination methods:** IOP was measured at trough - 12 hours after instillation of evening medication and at peak - 2 hours after morning medication. Study does not report how IOP was measured. Horizontal cup to disc ratios and visual field measured using a Humphrey perimeter (Mean Deviation) at months 6 and 12. Snellen chart used for visual acuity at each visit. Direct and indirect ophthalmoscopy was used to evaluate the fundus and optic nerve head. Schirmer tear test at 6 and 12 months	**Mean ± SD reduction in peak IOP mmHg (averaged over all time points to 12 months)**	**Group1:** 6.5 ± NR **Group 2:** 6.1 ± NR No significant difference between groups	**Funding:** Allergan Inc. Manufacturers of Brimonidine **Limitations:** • Study says it is double blind randomised trial (1:1) but the randomisation method is not stated. • No mention of evaluators being masked in methods. • Study reports that patients are given medication in a masked fashion but no further details are available • *Dropout rates were reported as % some as <1.0% so difficult to calculate numbers. Also reported for all those randomised to study including who received treatment but who didn't meet protocol entry criteria. • In the context of adverse events the study was biased towards timolol as most patients had already been taking timolol and therefore tolerated the treatment much better than brimonidine. **Additional outcomes:** Schirmer tear test - significant
			Mean ± SD reduction in trough IOP mmHg (averaged over all time points to 12 months)	**Group1:** 4.3 ± NR **Group 2:** 6.3 ± NR P is significant	
			Mean ± SD baseline peak IOP mmHg 12 months Data from Schuman1996	**Group1:** 24.75 ± 2.97 **Group 2:** 24.56 ± 3.04	
			Mean ± SD reduction in peak IOP mmHg (baseline – end point) 12 months Data from Schuman1996	**Group1:** 5.92 ± 3.19 **Group 2:** 6.01 ± 3.35	
			Mean ± SD baseline trough IOP mmHg 12 months Data from Schuman1996	**Group1:** 25.80 ± 2.31 **Group 2:** 25.87 ± 2.81	
			Mean ± SD reduction in trough IOP mmHg (baseline – end point) 12 months Data from Schuman1996	**Group1:** 3.67 ± 3.98 **Group 2:** 5.88 ± 3.38	
			Possible worsening of visual field (subset of patients)	**Group1:** 17/77 (22.1%) **Group 2:** 23/111 (20.7%)	
			Number of patients	**Group1:** 325	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	previous trial within 30 days start of study. **<u>All patients</u>** **N:** 374 **Age (mean ± SD):** 63 ± 11 **M/F:** 50:50 **Drop outs:** NR* **<u>Group 1</u>** **N:** 186 **Age (mean):** NR **M/F:** NR **Drop outs:** 35 **<u>Group 2</u>** **N:** 188 **Age (mean):** NR **M/F:** NR **Drop outs:** 4		**reporting local ocular adverse events**	**Group 2:** 238 Including stinging, blurring and allergic reactions, hyperaemia, photophobia, pruritis	changes from baseline for both groupd but no significant differences between groups Cup/Disc ratio – no significant changes from baseline or between group **Notes:** **$** Schuman 1996[132] reports intermediate results of Le Blanc 1998[83] (6 months of data) and Schuman 1997
			Number of patients reporting systemic adverse events	**Group1:** 159 **Group 2:** 125 Includes dry mouth, fatigue/drowsiness and headache	
			***Reasons for withdrawals (dropouts)** Data taken from Vass 2007[155] systematic review which reports drop out rates for study	**Group1:** • Local adverse events = 25 • Systemic adverse events = 10 **Group 2:** • Local adverse events = 2 • Systemic adverse events = 2	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Sympathomimetics vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Tsai, 2005[152] **Study design:** RCT **Evidence level:** 1 + **Duration of follow-up:** 12 months	**Patient group:** POAG **Setting:** single centre, China **Inclusion criteria:** • Diagnosis of bilateral POAG • Best corrected visual acuity of 20/50 or better in each eye • Untreated IOP between 22 and 30 mmHg in each eye • >35 years old **Exclusion criteria:** • History of previous glaucoma drugs in previous 4 weeks • Previous laser or surgical treatments • Co-existing retinal disease or non-glaucomatous optic neuropathy • Corneal abnormalities • Lens opacity worse than NC3/NO3 • VF loss > 20dB • Diabetes mellitus • Pregnancy or childbearing potential • Contraindications or hypersensitivity to either of the drugs in trial **<u>All patients</u>** **N:** 44 **Age (mean):** NR **M/F:** NR	**Group 1** Brimonidine 0.2% 2/day **Group 2** Timolol 0.5% Gel (Timoptic) 1/day 8am **Examination methods:** IOP measured using Perkins applanation tonometry every 2 months. At 12 months VF examined using Humphrey perimetry. RNFL thickness measured using scanning laser polarimetry	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 24.2 ± 1.3 **Group 2:** 23.9 ± 1.1	**Funding:** Conducted at Chang Gung Memorial Hospital, Taiwan, Republic of China **Limitations:** Open label and examiners not masked. change in IOP and visual field progression were not primary outcomes **Additional outcomes:** RNFL thickness significantly decreased from baseline for timolol compared to brimonidine **Notes:**
			Mean ± SD end point diurnal IOP (12 mths) mmHg	**Group1:** 18.6 ± 0.9 **Group 2:** 18.7 ± 1.1	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)	**Group1:** 5.6 ± 0.8 **Group 2:** 5.3 ± 0.5 **p value:** between group using ANOVA for repeated measures = 0.16	
			Number of patients with local ocular side effects	**Group1:** NR **Group 2:** NR	
			Number of patients with cardiovascular systemic side effects	**Group1:** NR **Group 2:** NR	
			Reasons for withdrawals (dropouts)	**Group1:** • Inadequate IOP control = 2 • Allergic blepharoconjunctivitis = 1 **Group 2:** • Inadequate IOP control = 2	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 5 **Group 1** **N:** 22 **Age (mean):** 61.9 ± 8.6 **M/F:** NR **Drop outs:** 3 **Group 2** **N:** 22 **Age (mean):** 60.0 ± 9.4 **M/F:** NR **Drop outs:** 2				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 11 Miotics vs. beta-blockers

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Drance, 1998[36] **Study design:** RCT Single masked **Evidence level:** 1 + **Duration of follow-up:** 24 months	**Patient group:** COAG (early glaucoma including pseudoexfoliative and pigmentary glaucomas) **Setting:** single centre, Canada **Inclusion criteria:** • IOP ≥ 24 mmHg • Disc and field abnormality • Field abnormality include localised scotomata but not to preclude reliable follow up <10 dB • Previous glaucoma therapy discontinued 4 weeks prior to start of study **Exclusion criteria:** • Previous ocular trauma, uveitis, inflammatory disease or infections • Previous laser or surgical treatments within 3 or 6 months respectively • History of retinal disease • Current contact lens wearers • Premenopausal women not on birth control • Severe or unstable cardiovascular or pulmonary disease • Chronic renal failure • Cerebrovascular disease • Systemic use of glucocorticoids and other medications affecting IOP • Contraindications or hypersensitivity to either of the drugs in trial **<u>All patients</u>** **N:** 68 **Age (mean):** 63 **M/F:** NR **Drop outs:**	**Group 1** Betaxolol 0.5% 2/day **Group 2** Timolol 0.5% 2/day **Group 3** Pilocarpine 2% 4/day **Examination methods:** Follow up at 3,6,12,18,24 months and all patients visual fields tests on Octopus perimeter or 30-2 Humphrey blue/yellow, Snellen acuity, tonometry, blood pressure, pulse and optic disc evaluation	**Incidence of visual field progression defined as Least-squares mean defect (dB change from baseline)**	**Group 1:** 0.98 dB **Group 2:** 0.87 dB **Group 3:** 0.83 dB **T v P =** 0.95 **not signif.** **B v P =** 0.85 **not signif.**	**Funding:** Alcon laboratories **Limitations:** • Randomisation method and allocation concealment were not reported • Timolol and betaxolol masked. Pilocarpine open label • Adverse events not reported in details **Additional outcomes:** **Notes:**
			IOP at baseline mmHg	**Group 1:** 24.1 ± 3.8 **Group 2:** 23.9 ± 2.3 **Group 3:** 25.1 ± 4.1	
			Change in IOP from baseline *Estimated from line graph at 24 months*	**Group 1:** 4.1 ± NR **Group 2:** 4.5 ± NR **Group 3:** 4.8 ± NR **Not signif.**	
			Reasons for drop out:	**Group 1: 3** inadequate IOP control = 2 adverse event = 1 **Group 2: 7** inadequate IOP control = 2 patient decision = 2 other = 3 **Group 3: 3** Unacceptable local side effects = 3	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 27 **Age (mean):** 65.3 ± 12.5 **Baseline IOP ± SD mmHg:** 24.1 ± 3.8 **M/F:** 52/48 (%) **Mean MD (dB):** 5.2 ± 4.6 **Race:** White: 100% **Drop outs:** 3 **Group 2** **N:** 27 **Age (mean):** 59.6 ± 15.8 **Baseline IOP ± SD mmHg:** 23.9 ± 2.3 **M/F:** 67/33 (%) **Mean MD (dB):** 4.5 ± 2.3 **Race:** White: 89% **Drop outs:** 7 **Group 3** **N:** 14 **Age (mean):** 64.1 ± 7.7 **Baseline IOP ± SD mmHg:** 25.1 ± 4.1 **M/F:** 57/43 (%) **Mean MD (dB):** 3.9 ± 2.8 **Race:** White: 86% **Drop outs:** 3				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Miotics vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Sponsel, 1987[141] & Dallas et al., 1988[29] **Study design:** RCT **Evidence level:** 1 + **Duration of follow-up:** 17 months - 2 years	**Patient group:** COAG **Setting:** single centre, UK **Inclusion criteria:** • IOP ≥ 21 mmHg on 2 occasions • Optic disc cupping supportive of glaucoma • Visual field loss typical of nerve fibre bundle damage **Exclusion criteria:** • Co-existing pathology • Substantive acuity deficit 6/9 or worse • Retinal problems likely to affect plotting • Contraindications to Timolol **<u>All patients</u>** **N:** 50* **Age (mean):** NR **M/F:** 60/40 (%) **Drop outs:** 14* **<u>Group 1</u>** **N:** 25 **Age (mean):** 62.5 ± NR **Baseline IOP ± SD mmHg**: 28.0 ± 6.3 **M/F:** NR **Drop outs:** 3 **<u>Group 2</u>** **N:** 25 **Age (mean):** 68.7 ± NR **Baseline IOP ± SD mmHg**: 27.6 ± 4.7 **M/F:** NR **Drop outs:** 11	**Group 1** Timolol 0.5% or 0.25% 2/day **Group 2** Pilocarpine 2% or 4% 2/day **Examination methods:** Patients followed every 3 months and visual field measured using Goldmann and Friedmann static suprathreshold perimetry and IOP measured using Goldmann tonometry	**Rate of VF loss in units/month. Friedmann analysis**	**Group 1:** 0.46 **Group 2:** 0.92 **Signif.**	**Funding:** Alcon laboratories **Limitations:** • Randomisation method and allocation concealment not reported. • Open label study • Masking of examiners is not reported • Adverse events not reported **Additional outcomes:** **Notes:** *Original randomised patients reported in the other paper Dallas et al., 1998[29] but dropouts were not clearly reported. Could be due to miotic intolerance but figures do not add up.
			IOP at baseline mmHg	**Group 1:** 28.0 ± 6.3 (n=22) **Group 2:** 27.6 ± 4.7 (n=14)	
			IOP at end point mmHg (Averaged 6 measurements over 24 month follow up)	**Group 1:** 21.2 ± 5.1 (n=22) **Group 2:** 20.9 ± 1.9 (n=14)	
			Change in IOP from baseline at end point	**Group 1:** 6.8 ± NR (n=22) **Group 2:** 6.7 ± NR (n=14)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Miotics vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Vogel et al., 1992[157] **Study design:** RCT Single masked **Evidence level:** 1 + **Duration of follow-up:** 2 years	**Patient group:** POAG **Setting:** multi-centre, international – USA, UK & Canada] **Inclusion criteria:** • IOP ≥ 22 mmHg on at least 1/5 measurements taken over 1 day after washout period of 7 days • Open angles • Visual field defect of ≥ 3 test points > 5 dB recorded by Octopus 30 programme • Optic disc cupping supportive of glaucoma • Visual field loss typical of nerve fibre bundle damage **Exclusion criteria:** • History of ocular trauma or intraocular surgery • Corneal ulcer, ocular infection or herpatic keratitis 3 months prior to study • Closed angle or secondary glaucoma • Bronchial asthma or COPD • >first degree heart block • Uncompensated heart failure • Bradycardia • Concomitant medications affecting IOP • Pregnant or nursing women • Contraindications to Timolol **<u>All patients</u>** **N:** 189 **Age (mean):** NR **M/F:** NR	**Group 1** Timolol 0.5% or 0.25% 2/day **Group 2** Pilocarpine 2% or 4% 2/day **Examination methods:** After washout period measurements of VF, IOP, slit lamp examination, gonioscopy, ophthalmoscopy, visual acuity. VF measured every 4 months on Octopus 30 programme. Patients withdrawn if IOP > 25 mmHg or VF worsened rapidly. Worse eye was used for efficiacy analysis or if both eyes the same the right eye was used.	**Difference in mean VF score dB at 24 months**	**Group 1:** + 0.5 dB **Group 2:** - 1.2 dB P < 0.01 **Signif.**	**Funding:** Alcon laboratories **Limitations:** • High drop out rate. Data on VF (51 patients) and IOP (91 patients) not collected at baseline • Randomisation method and allocation concealment not reported. • Baseline demographic data not reported • Open label study but observer masked • Adverse events not reported **Additional outcomes:** **Notes:** *Not clear from study what patients did not start study or reasons for dropout. IOP data at baseline only available for 98 patients. Visual field data only available at baseline for 138
			Mena visual field threshold at baseline dB	**Group 1:** 18.5 ± 6.2 (n=75) **Group 2:** 16.9 ± 5.7 (n=63)	
			Mean number of Test Points showing deterioration at 24 months	**≥5 dB** **Group 1:** 4.5 ± 5.3 (n=46) **Group 2:** 13.5 ± 13.6 (n=26) P <0.01 **≥7 dB** **Group 1:** 2.3 ± 3.2 (n=46) **Group 2:** 6.7 ± 9.4 (n=26) P <0.01 **≥10 dB** **Group 1:** 1.1 ± 1.7 (n=46) **Group 2:** 3.5 ± 5.7 (n=26) P <0.01	
			IOP at baseline mmHg	**Group 1:** 26.9 ± 3.6 (n=53) **Group 2:** 27.9 ± 5.1 (n=45)	
			IOP at 24 months mmHg	**Group 1:** 20.8 ± 2.6 (n=36) **Group 2:** 21.9 ± 2.7 (n=20) **Not signif.**	
			Change in IOP from baseline at end point	**Group 1:** 6.8 ± NR (n=36) **Group 2:** 6.7 ± NR (n=20)	
			Discontinuation due to lack of IOP control	**Group 1:** 14% **Group 2:** 35%	
			Discontinuations for other reasons	**Group 1: 16** Taking concomitant beta-blocker = 1 Lost to follow up = 5 Patient uncooperative = 1 Protocol deviation = 2 Study ended before 24 mths	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: * **<u>Group 1</u>** **N:** * **Age (mean):** NR **Baseline IOP ± SD mmHg:** **M/F:** NR **Drop outs:** * **<u>Group 2</u>** **N:** * **Age (mean):** NR **Baseline IOP ± SD mmHg: M/F:** NR **Drop outs:** *			completed = 6 VF unsatisfactory = 1 **Group 2: 19** Taking concomitant beta-blocker = 1 Developed exclusion criteria = 1 Developed angle closure = 1 Lost to follow up = 7 Protocol deviation = 4 Study ended before 24 mths completed = 4 VF unsatisfactory = 1	patients.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 12 Fixed combination vs. single medications

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Higginbotham et al., 2002[61] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months (double masked RCT part of study) Study continued for a further 6 months as an open-label study with everyone receiving the fixed combination treatment.	**Patient group:** COAG or OHT **Setting:** multi-centre (38 eye clinics) USA **Inclusion criteria:** • Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Aged 18 or older • Best corrected visual acuity measuring 20/200 • Pre-study IOP ≥30mmHg without IOP reducing medication OR ≥25mmHg with prior treatment • Previous latanoprost or timolol therapy permitted **Exclusion criteria:** • History of acute angle-closure or occludable angles • Use of contact lenses • Ocular surgery, argon laser trabeculoplasty or ocular inflammation or infection within 3 months of the pre-study visit • Hypersensitivity to benzalkonium chloride • Any other abnormal ocular condition or symptom that investigator determined precluded study enrolment • Presence of concomitant diseases	**Group 1** Fixed combination of Latanoprost 0.005% & timolol 0.5% 8am AND placebo 8pm **Group 2** Latanoprost 0.005% 8am AND placebo 8pm **Group 3** Timolol 0.5% 8am AND 8pm **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer. Each measurement taken in triplicate in each eye. Measurements taken at 8am, 10am and 4pm at baseline and weeks 2, 13, 26 and 52. Automated visual field examination performed at	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 23.1 ± 3.8 **Group 2:** 22.9 ± 4.1 **Group 3:** 23.7 ± 4.1	**Funding:** Pharmacia & Upjohn Inc.; Research to Prevent Blindness Inc. **Limitations:** Run in period 2 – 4 weeks with timolol 0.5 % 2/day prior to starting study Adverse events reported by area of eye they occur making it difficult to assess total no. of patients with a particular event. **Notes:** *Differences estimated (least square mean difference) using a repeated measures analysis of covariance with baseline IOP as a covariate; patient, treatment, visit and centre as main factors; and treatment group-by-visit and treatment group-by-centre interaction factors. **§** values not reported for group 2 to group 3 Intention to treat analysis for the first 6 months included all patients who received at least
			Mean ± SD diurnal IOP at 6 mths mmHg	**Group1:** 19.9 ± 3.4 **Group 2:** 20.8 ± 4.6 **Group 3:** 23.4 ± 5.4	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths §	**Group1 to Group 3:** -2.9 (95% CI: -3.5 to -2.3, p<0.001)* **Group 1 to Group 2:** -1.0 (95% CI: -1.7 to -0.3, p=0.005)*	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths	**Group 1:** 3.2 ± 3.16 ** **Group 2:** 2.1 ± 4.23** **Group 3:** 0.3 ± 4.20**	
			Percent of patients reaching IOP <15mmHg at of 6 mths §	**Group1:** 6 /130 **Group 2:** 4/128 **Group 3:** 1/129 **P value (group 1 to 3):** 0.06 **P value (group 1 to 2):** 0.56	
			Percent of patients reaching IOP <18mmHg at of 6 mths § *Used in met-analysis*	**Group1:** 28/130 **Group 2:** 30/128 **Group 3:** 8/129 **P value (group 1 to 3)** =0. 01 **P value (group 1 to 2)** =0. 65	
			Percent of patients reaching IOP <21mmHg at of 6 mths §	**Group1:** 68/130 **Group 2:** 63/128 **Group 3:** 39/129 **P value (group 1 to 3)** <0.001 **P value (group 1 to 2)** =0.36	
			Number of ocular side effects †	**Group1:** 86 **Group 2:** 86 **Group 3:** 59	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	that contraindicate adrenergic antagonist • Nursing mothers, pregnant women and women who were of childbearing potential not using adequate contraception for at least the previous 3 months • Patients who could not adhere to treatment or the visit plan • Patients who had participated in another clinical study within 1 month of previous visit **<u>All patients</u>** **N:** 418 **Age (mean):** NR **M/F:** 215/203 **Drop outs:** 73 **Ethnicity:** white 276, black 110, Hispanic 27, other 5 **Diagnosis:** POAG 278, pseudoexfoliative glaucoma 9, pigmentary glaucoma 13, OHT 109, mixed (different diagnosis in the two eyes) 8, none listed 1 **IOP reducing medication in last 3 months**: 351/418 **<u>Group 1</u>** **N:** 138 **Age (mean):** 61 ±12 **M/F:** 67/71 **Drop outs:** 13 **Ethnicity:** white 90, black 38, Hispanic 7, other 3 **Diagnosis:** POAG 94, pseudoexfoliative glaucoma 2,	baseline and weeks 13, 26 and 52. Visual acuity assessed and eye-lid slit lamp biomicroscopy performed at each visit. Ophthalmoscopy performed at pre-study visit and weeks 26 and 52.		† side effects include blephartis, hypertrichosis, irritation, melbomianitis, seborrhea, eye hyperaemia, chemosis, conjunctival discolouration, corneal disorder, keratitis, keratopathy, cataract, optic atrophy, errors of refraction, increased IOP, vision decreased, visual field defect, conjunctivitis, epiphora, eye pain, photophobia, vision blurred	one drop of medication. For IOP measurements the last available IOP measurement was carried forward. ** Standard deviations (SD) for fixed v monotherapy calculated using the Cochrane method for imputed SDs from the mean correlation coefficients calculated from Ozturk 2007[115] (CAI + BB v PGA) Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation
			Visual field defects	**Group1:** 7/130 **Group 3:** 4/128	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	pigmentary glaucoma 4, OHT 36, mixed 2, none listed 0 **IOP reducing medication in last 3 months**: 117/138 **Group 2** **N:** 140 **Age (mean):** 63 ±13 **M/F:** 80/60 **Drop outs:** 36 **Ethnicity:** white 90, black 35, Hispanic 14, other 1 **Diagnosis:** POAG 95, pseudoexfoliative glaucoma 4, pigmentary glaucoma 5, OHT 33, mixed 3, none listed 0 **IOP reducing medication in last 3 months**: 117/140 **Group 3** **N:** 140 **Age (mean):** 63 ±12 **M/F:** 68/72 **Drop outs:** 24 **Ethnicity:** white 96, black 37, hispanic 6, other 1 **Diagnosis:** POAG 89, exfoliative glaucoma 3, pigmentary glaucoma 4, OHT 40, mixed 3, none listed 1 **IOP reducing medication in last 3 months**: 117/140				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Fixed combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ozturk et al, 2007[115] **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG or OHT **Setting:** ophthalmology clinic, Turkey **Inclusion criteria:** • IOP ≥21mmHg without medication Washout period for topical medications prior to baseline visit (CAI – 1 week, beta-blockers – 4 weeks, prostaglandins – 6 weeks) **Exclusion criteria:** • IOP >35mmHg • History of chronic or recurrent inflammatory eye disease • Ocular trauma • Ocular infection • Severe retinal disease • Previous intraocular or laser surgery • Any condition preventing reliable applanation tonometry • Use of any systemic medication that might affect IOP • Unstable cardiopulmonary disease **All patients** **N:** 65 **Group 1** **N:** 30 **Age (mean):** 64.9 (48-78) **M/F:** 15/14 **Drop outs:** 1	**Group 1** Fixed combination of dorzolamide & timolol (Cosopt, Merck, USA) 2/day (concentrations not reported) **Group 2** Bimatoprost 0.03% 1/day **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer. Mean of 3 consecutive measurements used. Bilateral POAG or OHT patients had eye with higher IOP selected, if eyes had equal IOP then right eye was selected. Measurements for baseline and 6 month visits taken at 8am, 12pm and 4pm.	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 24.1 ± 2.1 (n=29) **Group 2:** 23.7 ± 2.0 (n=34) **P value:** 0.38	**Funding:** not reported **Limitations:** Randomisation method and allocation concealment not reported. Adverse events poorly reported. **Additional outcomes:** Also reported IOP taken at 12.00 hours at day 15, and months 1 and 3. **Notes:** Investigators assessing IOP masked to treatments. † Reported adverse events: burning/stinging, conjunctival hyperaemia, bitter taste, dry eye, eyelid eczema, breathlessness
			Mean ± SD diurnal IOP at 6 mths mmHg	**Group1:** 17.6 ± 2.9 (n=29) **Group 2:** 17.5 ± 2.3 (n=34) **P value:** 0.89	
			Mean reduction in IOP at 6 mths	**Group1:** 6.5 ± 2.3 (n=29) **Group 2:** 6.2 ± 1.8 (n=34) **P value:** 0.89	
			No. of ocular & systemic adverse events by group (some patients had more than 1 ocular events)	**Group1:** 11 **Group 2:** 28	
			No. of patients with conjunctival hyperaemia	**Group1:** 2/29 **Group 2:** 18/34 **P value:** 0.02	
			No of patients with breathlessness	**Group1:** 0/29 **Group 2:** 1/34 **P value:** 0.47	
			Total no. dropouts	**Group1:** 1/30 **Group 2:** 1/35 **P value:** 0.71	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Ethnicity: NR **Diagnosis:** POAG 22, ocular hypertension 7, **Group 2** **N:** 35 **Age (mean):** 61.9 (48-75) **M/F:** 13/21 **Drop outs:** 1 **Ethnicity:** NR **Diagnosis:** POAG 26, ocular hypertension 8				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Fixed combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Pfeiffer, 2002[116] European Latanoprost Fixed Combination Study Group **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months Plus a 6 month open-label study with all patients using the fixed combination of latanoprost and timolol	**Patient group:** COAG or OHT **Setting:** multicentre - 37 centres, Germany **Inclusion criteria:** • Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Aged 18 or older • IOP ≥25mmHg with prior therapy • IOP ≥30mmHg without prior therapy **Exclusion criteria:** • History of angle-closure glaucoma • Previous ocular surgery, argon laser trabeculoplasty or ocular inflammation or infection 3 months prior to pre-study visit • Patients with a known hypersensitivity or contraindication to any component of study drugs **All patients** **N:** 436 **Age (mean):** NR **M/F:** 196/240 **Drop outs:** 72 **Ethnicity:** NR **Diagnosis: :** POAG 336, pseudoexfoliative glaucoma 22, pigmentary glaucoma 8, ocular hypertension 64, mixed (different diagnosis in the two eyes) 6 **Previous IOP reducing medication**: 401 **Group 1**	**Group 1** Fixed combination of latanoprost 0.005% & timolol 0.5% am, placebo pm **Group 2** Latanoprost 0.005% 1/day am, placebo pm **Group 3** Timolol 0.5% 2/day **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer at pre-study visit. Method of measurement for other visits not stated. Each measurement taken three times in each eye. Measurements for each visit taken at 8am, 10am and 4pm. Also determined at each visit: best corrected visual	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 21.6 ± 3.8 **Group 2:** 22.5 ± 4.0 **Group 3:** 22.5 ± 4.1	**Funding:** Pharmacia Inc **Limitations:** Adverse events poorly reported. Randomisation method and allocation concealment were not reported. Although patients were masked it is not clear whether examiners were masked. **Additional outcomes:** Also reported mean diurnal IOP at week 2 and 13; no. of patients switching to open-label trial on fixed combination. **Notes:** † Reported ocular adverse events: eye irritation, visual field change (suspected), hypertrichosis, hyperaemia, vision decreased, increased iris pigmentation, corneal disorder, cataract, optic atrophy, conjunctivitis, iritis, change in refraction, blepharitis. Gives number of patients for each adverse event. § Reported non-ocular adverse events: cardiovascular disorder,
			Mean ± SD diurnal IOP at 6 mths mmHg	**Group1:** 19.0 ± 3.5 **Group 2:** 20.4 ± 4.9 **Group 3:** 21.4 ± 5.4 **P values:** not reported	
			Mean ± SD reduction in diurnal IOP at 6 mths	**Group 1:** 1.7 ± 3.19** **Group 2:** 2.1 ± 3.76** **Group 3:** 1.1 ± 4.20**	
			Percent of patients reaching IOP <15mmHg at 6 mths or up to treatment failure	**Group1:** 14/140 **Group 2:** 8/147 **Group 3:** 7/149 **P values:** not significant	
			Percent of patients reaching acceptable IOP <18mmHg at 6 mths or up to treatment failure *Used in meta-analysis*	**Group1:** 54/140 **Group 2:** 48/147 **Group 3:** 37/149 **P values:** Group 1 to 3 p<0.05	
			Percent of patients reaching IOP <21mmHg at 6 mths or up to treatment failure	**Group1:** 110/140 **Group 2:** 101/147 **Group 3:** 83/149 **P values:** not significant	
			No. of ocular adverse events by group seen in ≥1% of any treatment group (NB not no. of patients) §	**Group1:** 34 **Group 2:** 41 **Group 3:** 21	
			No. of non-ocular adverse events by group seen in ≥1% of	**Group1:** 22 **Group 2:** 18 **Group 3:** 19	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 140 **Age (mean):** 64 ±13 **M/F:** 67/73 **Drop outs:** 12 **Ethnicity:** NR **Diagnosis:** POAG 106, pseudoexfoliative glaucoma 2, pigmentary glaucoma 3, ocular hypertension 27, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication**: NR **Group 2** **N:** 147 **Age (mean):** 63 ±12 **M/F:** 77/70 **Drop outs:** 28 **Ethnicity:** NR **Diagnosis:** POAG 112, pseudoexfoliative glaucoma 13, pigmentary glaucoma 4, ocular hypertension 16, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication in last**: NR **Group 3** **N:** 149 **Age (mean):** 64 ±10 **M/F:** 52/97 **Drop outs:** 32 **Ethnicity:** NR **Diagnosis:** POAG 118, pseudoexfoliative glaucoma 7, pigmentary glaucoma 1, ocular hypertension 21, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication in last**: NR	acuity and slit lamp examination. Refraction recorded, ophthalmoscopy performed and Colour Polaroid photographs taken at 6 months.	**any treatment group (NB not no. of patients) §**		influenza-like symptoms, metabolic disorders, respiratory disorders, cerebrovascular disorders, vertigo, sleep disorders, headache, liver/biliary disorders Patients switched medications to the fixed combination used in for group 1 if treatment failure occurred. Treatment failure defined as increased IOP ≥10% of the mean IOP from baseline and an IOP of ≥23mmHg on two examinations within 2 weeks. Study reports numbers by group. If treatment still did not work patients were withdrawn. ** Standard deviations (SD) for fixed v monotherapy calculated using the Cochrane method for imputed SDs from the mean correlation coefficients calculated from Ozturk 2007[115] (CAI + BB v PGA)
			No. of patients not completing 6 months in randomised group *	**Group1:** 12/140 **Group 2:** 28/147 **Group 3:** 32/149 **P value group 1 to 2:** =0.006 **P value group 1 to 3:** =0.001 **P value group 2 to 3:** =0.10	
			No. of patients not completing 6 months in randomised group OR in open label trial	**Group1:** 10/140 **Group 2:** 14/147 **Group 3:** 16/149 **P values:** not significant	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Fixed combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Sherwood et al, 2006[135] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** Bilateral COAG or OHT **Setting:** ophthalmology centre, USA **Inclusion criteria:** • Baseline IOP (after washout) between 24 & 34 mmHg in each eye with no more than 5 mmHg difference between eyes • Best corrected visual acuity of 20/100 • Aged 18 and over Continuation of long-term systemic therapy that could affect IOP was allowed as long as doses were constant throughout the trial **Exclusion criteria:** • Active ocular disease • Functionally significant or progressive visual field loss in the previous year • Abnormally low or high blood pressure or pulse rate • Contraindications or sensitivity to any component of the study treatments • Use of other topical medications or other therapies that might have a substantial effect on IOP • Ocular surgery in previous 3 months • Women not using 'effective means of contraception' or who were	**Group 1** Fixed combination of brimonidine 0.2% & timolol 0.5% 2/day & placebo for 3rd administration **Group 2** Brimonidine 0.2% 3/day * **Group 3** Timolol 0.5% 2/day & placebo for 3rd administration Washout periods for previous medications: CAI & parasympathometic 4 days, sympathometics 2 weeks, beta-blockers & prostaglandins 4 weeks **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer. The mean of two	**Mean baseline diurnal IOP mmHg (8am, 10am, 3pm, 5pm)**	**Group1:** 24.7, 23.3, 22.1, 21.8 (n=385) **Group 2:** 24.9, 23.5, 22.5, 22.2 (n=382) **Group 3:** 25.0, 23.5, 22.5, 22.4 (n=392) **P values:** not significant	**Funding:** Allergan Inc provided funding, had a primary role in study design, management and analysis of the data, and in the preparation of the manuscript. . **Limitations:** No measurements given for IOP or IOP change throughout the study, only graphs shown. **Additional outcomes:** **Notes:** * Brimonidine 3/day used to see whether the added dose of brimonidine provided additional IOP lowering effects. † Reported adverse events: conjunctival hyperaemia, ocular stinging, eye pruritus, allergic conjunctivitis, conjunctival folliculosis, oral dryness,
			Total no. of patients with treatment related adverse events with an incidence of ≥5% in any group and a statistically significant between group difference †	**Group1:** 204/385 **Group 2:** 240/382 **Group 3:** 160/392 **P value group 1 to 2:** =0.006 **P value group 1 to 3:** <0.001 **P value group 2 to 3:** <0.001	
			Total no. of dropouts	**Group1:** 99/385 **Group 2:** 169/382 **Group 3:** 58/392 **P value group 1 to 2:** <0.001 **P value group 1 to 3:** <0.001 **P value group 2 to 3:** <0.001	
			No. of dropouts due to adverse events	**Group1:** 55/385 **Group 2:** 117/382 **Group 3:** 20/392 **P value group 1 to 2:** <0.001 **P value group 1 to 3:** <0.001 **P value group 2 to 3:** <0.001	
			'Treatment related serious' adverse events	**Group1:** 0/385 **Group 2:** 0/382 **Group 3:** 2/392 -(respiratory distress secondary to emphysema & tachycardia, sweating & nausea) **P values:** not significant	
			Mortality	**Group1:** 2/385 **Group 2:** 2/382 **Group 3:** 1/392 **P value:** not significant	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	pregnant or nursing **<u>All patients</u>** **N:** 1159 **Age (mean):** 62.6 (23-89) **M/F:** 518/641 **Drop outs:** 326 **Ethnicity:** white 879, African Americans 187, Hispanic 78, Asian 11, Other 4 **Diagnosis:** POAG 762, ocular hypertension 384, mixed (different diagnosis in the two eyes) 13 **No. patients requiring washout due to previous medication**: 795 **<u>Group 1</u>** **N:** 385 **Age (mean):** 62.0 ±12.2 **M/F:** 181/204 **Drop outs:** 99 **<u>Group 2</u>** **N:** 382 **Age (mean):** 63.8 ±11.8 **M/F:** 151/231 **Drop outs:** 169 **<u>Group 3</u>** **N:** 392 **Age (mean):** 62.0 ±12.3 **M/F:** 186/206 **Drop outs:** 58	consecutive measurements were used for each eye. The median of 3 measurements for each eye was used if the first 2 measurements differed by >2mmHG. Each measurement of IOP was taken four times in each eye at 8am, 10am, 3pm and 5pm. Adverse events meausured using Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART)	**Total number of dropouts**	**Group1:** 99/385 **Group 2:** 169/382 **Group 3:** 58/392 **P value group 1 to 2:** <0.001 **P value group 1 to 3:** <0.001 **P value group 2 to 3:** <0.001	conjunctival allergy/inflammation (includes any combination of conjunctival hyperaemia, eye pruritus, follicular conjunctivitis, allergic conjunctivitis, conjunctivitis, chemical conjunctivitis, conjunctival adema and blepharoconjunctivitis. Gives number of patients for each adverse event. Significantly more events with fixed combination of brimonidine-timolol than with timolol alone for conjunctival allergy/inflammation adverse events.
			Number of patients with an acceptable IOP <17.5 mmHg	**Group1:** 202/385 **Group 2:** 105/382 **Group 3:** 127/392	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 13 Separate combination vs. single medications

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Bucci, 1999[13] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG **Setting:** Multi-centre centre, Italy **Inclusion criteria:** • Diagnosis of unilateral or bilateral POAG or Pseudoexfoliation glaucoma (PXF) • Uncontrolled IOP on current beta blocker therapy • Age >18 years **Exclusion criteria:** • Current therapies other than beta adrenergic agonists • Closed anterior angle glaucoma • Severe trauma • Previous ocular inflammation in last 3 months • Any condition affecting IOP measurement • Pregnant, nursing or patients considering pregnancy • **<u>All patients</u>** **N:** 99 **<u>Group 1</u>** **N:** 49 **Age (mean ± SD):** 63 ± 12 **M/F:** 21/28 **POAG:** 43 **PXF:** 6 **Drop outs:** 4	**Group 1** Latanoprost 0.005% 1/day + Timolol 0.5% 2/day **Group 2** Latanoprost 0.005% 1/day **Examination methods:** IOP measured at baseline, 2 weeks, 3 months and 6 months using a Goldmann tonometer. 3 (9am, 12 pm and 4pm) measurements were taken in each eye and mean value used in statistical analysis.	**Mean ± SD baseline diurnal IOP mmHg**	**Group 1:** NR **Group 2:** NR	**Funding:** Not reported. Conducted at Clinica Oculistica, Universita di Roma Tor Vergata **Limitations:** • Randomisation method not described. • Open label design • Masking of outcome assessment not mentioned • No washout period for latanoprost monotherapy. • Patients were selected for inadequate IOP control on various medications including timolol + clonidine and timolol + dipivefrine • **Significance testing between arms does not appear to be on an ITT basis. **Additional outcomes:** Timolol + pilocarpine study arm
			Mean ± SD end point diurnal IOP at 6 mths	**Group 1:** NR **Group 2:** NR	
			Mean ± SD reduction in IOP mmHg at 6mths (baseline – end point) SD = SE*√n	**Group 1:** 6.1 ± 2.10 **Group 2:** 5.5 ± 2.12 P between arm difference = not signif (using ANCOVA)**	
			% patients achieving an acceptable 30% reduction in IOP *<20% reduction from baseline (~21 mmHg) is approx <18 mmHg*	**Group 1:** 30/45 (not ITT) **Group 2:** 32/46 (not ITT)	
			Total number of local ocular side effects by group	**Group 1:** 21 **Group 2:** 17 Includes itching, stinging, conjunctivitis, vision disturbance and conjunctival hyperaemia	
			Total number of systemic side effects by group	**Group 1:** 1 **Group 2:** 4	
			Total number of patients with hyperaemia	**Group 1:** 8/49 **Group 2:** 4/50	
			Reasons for withdrawals	**Group 1:** • Inadequate IOP control = 1 • Conjunctivitis = 1 • Hyperaemia = 1 • Self-withdrawal = 1 **Group 2:** • Conjunctivitis = 1 • Hyperaemia = 1	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 50 **Age (mean ± SD):** 59 ± 13 **M/F:** 28/22 **POAG:** 50 **PXF:** 1* **Drop outs:** 4 * patient had different diagnosis in each eye			• Self-withdrawal = 2	**Notes:** If 2 eyes used in study, mean IOP was taken.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Separate combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Manni et al., 2004[91] **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG **Setting:** Single centre, Italy **Inclusion criteria:** • COAG • At least 6 months current treatment with timolol 0.5% 2/day • Age >18 years • Best corrected visual acuity 20/80 or better • IOP ≥ 21 mmHg in at least 1 eye but at least 20 % lower than before any IOP lowering treatment. • Repeatable VF defect in same eye • **Exclusion criteria:** • Uncontrolled systemic diseases • Allergy to treatment medications • Severe trauma • Previous ocular surgery in last 6 months • Any condition affecting IOP measurement such as corneal abnormalities • Pregnant, nursing or patients considering pregnancy • **<u>All patients</u>** **N:** 61 **Age (mean ± SD):** 59.4 ± 14.1	**Group 1** Latanoprost 0.005% (pm) 1/day + Timolol 0.5% (am) 1/day **Group 2** Bimatoprost 0.03% 1/day evening **Examination methods:** IOP measured at baseline, 2 weeks and every month months using a Goldmann tonometer. 3 (8am, 12 pm, 4pm) measurements were taken in each eye and mean value used in statistical analysis. Photographs of lids and periocular area were taken at baseline to compare to end point	**Mean ± SD baseline diurnal IOP mmHg**	**Group 1:** 24.1 ± 4.6 **Group 2:** 23.5 ± 3.2	**Funding:** Not reported. Conducted at Clinica Oculistica, Universita di Roma Tor Vergata **Limitations:** • No washout period for bimatoprost monotherapy. • Patients were selected for inadequate IOP control on timolol 0.5% • *Significance testing between arms does not appear to be on an ITT basis – only 28 patients counted per group **Additional outcomes:** Occurrence of hyperaemia and eyelash growth **Notes:** Investigators were masked to treatment allocation and randomisation performed using computer generated sequence.
			Mean ± SD end point diurnal IOP at 6 mths	**Group 1:** 16.8 ± 1.4 **Group 2:** 17.0 ± 2.1	
			Mean ± SD reduction in IOP mmHg at 6mths (baseline – end point)	**Group 1:** 7.3 ± 5.59** **Group 2:** 6.5 ± 3.98** P = not significant*	
			Total number of patients reporting ocular side effects	**Group 1:** NR **Group 2:** NR	
			Total number of cardiovascular systemic side effects by group	**Group 1:** NR **Group 2:** NR 6 patients in group 1 reported a headache	
			Reasons for withdrawals	**Group 1:** • Inadequate IOP control = 2 • Ocular allergy = 2 **Group 2:** • Inadequate IOP control = 2 • Ocular allergy = 3 • Self-withdrawal = 2	
			Hyeperaemia at baseline	**Group 1:** 10/30 **Group 2:** 9/31 **P value:** 0.20	
			Hyeperaemia at 90 days	**Group 1:** 24/30 **Group 2:** 14/31 **P value:** 0.004	
			Hyeperaemia at 180 days	**Group 1:** 19/30 **Group 2:** 14/31 **P value:** 0.08	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 30 **Age (mean ± SD):** 59.7 ± 13.5 **M/F:** 16/14 **Drop outs:** 4 **Group 2** **N:** 31 **Age (mean ± SD):** 59.2 ± 14.7 **M/F:** 14/17 **Drop outs:** 7				**Standard Deviations were estimated using the precise p values reported in the study following the method detailed in the Cochrane Handbook

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Separate combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Orengo-Nania et al, 2001[114] **Study design:** RCT, masked (subjects, investigators and study staff) **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG or OHT **Setting:** Multi-centre, USA **Inclusion criteria:** • Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma (PG), pseudoexfoliation glaucoma (PXF) or OHT • Completed 3 weeks timolol 0.05% 2x/d • IOP in at least one eye of 24-36mmHg at 8am AND 21-36mmHg at 10am & 4pm; all 3 measurements on 2 eligibility days **Exclusion criteria:** • Best corrected visual acuity worse than 0.6 logMAR • chronic or recurrent severe inflammatory eye disease • ocular trauma in past 6 months • ocular infection or ocular inflammation in past 3 months • clinically significant progressive retinal disease • inability to undergo applanation tonometry • ocular disease precluding the use of beta-blockers or prostaglandins • cup to disc ratio >0.8 in either eye • severe central visual field loss • intraocular surgery in past 6 months • laser surgery in past 3 months • severe hypersensitivity to study	**Group 1** Travoprost 0.004% 1/day + timolol 0.5% 2/day * **Group 2** Placebo 1/day and timolol 0.5% 2/day * **Examination methods:** Mean IOP measured by calibrated Goldmann applanation tonometer at 8am, 10am and 4pm for the patient's eye with the highest reading. Hyperaemia measured by comparing photographs of subjects' eyes with a standard set of photographs depicting ocular hyperaemia. Hyperaemia and iris and eyelash	**Mean ± SD baseline diurnal IOP (mmHg)**	**Group 1:** 25.0 ± NR **Group 2:** 25.2 ± NR **P value:** not significant	**Funding:** Alcon Research Ltd, manufacturers of travoprost **Limitations:** Reporting of discontinuations was not clear for each group. 24 discontinued due to inadequate IOP control 21 in timolol group and 3 across both travoprost groups. Standard deviations were not provided with the IOP data. ***Timolol was open label*** **Additional outcomes:** Data for travoprost 0.0015% not included in study (dosage not in BNF) Eye lash changes also mentioned, no patient stopped treatment due to these. No reported iris
			Mean IOP at end point (6 months)	**Group 1:** 19.6 (8am), 18.3 (10am), 18.9 (4pm) **Group 2:** 23.8 (8am), 23.0 (10am), 23.1 (4pm)	
			Mean diurnal IOP at end point (6 months)	**Group 1:** 18.9 ± NR **Group 2:** 23.3 ± NR (calculated as mean across 3 times)	
			Mean change in IOP from baseline mmHg at 6 months (end point – baseline	**Group 1:** 6.1 ± NR **Group 2:** 1.9 ± NR P = 0.0001 (ANOVA – repeated measures)	
			Percent of patients with ≥6mmHg decrease in IOP OR ≤20mmHg at 6 mths	**Group1:** 73.0–86.9% **Group 2:** 23.1-43.3% (per protocol data)	
			Percent of patients with acceptable decrease ≥30% in IOP OR ≤17mmHg at 6 mths	**Group 1:** 55/114 (47.8%) **Group 2:** 11/112 (9.9%) **P value groups 1 to 2:** <0.0001 (per protocol data)	
			No. of ocular adverse events by group seen in ≥2% of any treatment group (NB some patients may have had more than one adverse event	**Group 1:** 78 **Group 2:** 34 Includes: aqueous flare, anterior chamber cells, blurred vision, discomfort, dry eye, foreign body sensation, hyperaemia, keratitis, lid disorder, pain, photophobia, pruritus, tearing, visual acuity decreased	
			No. of non-ocular adverse events by group seen in ≥2% of any treatment group	**Group 1:** 19 **Group 2:** 13 Includes: cold syndrome, infection, sinusitis, surgical/medical procedure,	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	medications or 'vehicle' • severe, unstable or uncontrolled cardiovascular, hepatic or renal disease in which the use of beta-blockers is contraindicated • bronchial asthma or COPD • Starting any medication that might affect IOP <1 month prior to study entry, glucocorticosteroid use during eligibility phase, current use of NSAIDs • glaucoma other than open-angle or ocular hypertension • anterior chamber angle grade < 2 • inability to use medication in both eyes • women who were not 1 year post-menopausal or had not been surgical sterilised 3 months before study **All patients** **N:** 271 **Group 1** **N:** 145 **Age (mean):** 63.9 ±11.1 **M/F:** 65/72 **Drop outs:** 8 **Black/Non-black:** 35/105 **COAG/OHT**: 123/14 **Group 2** **N:** 139 **Age (mean):** 63.3 ±11.3 **M/F:** 56/78 **Drop outs:** 5 **Black/Non-black:** 32/102 **COAG/OHT**: 121/13	changes were assessed by masked ophthalmologists.	(NB some patients may have had more than one adverse event)	urinary tract infection.	pigmentation changes or clinical visible cystoid macular oedema reported **Notes:** All subjects who qualified stopped any ocular hypotensive medication (other than timolol) and were placed on timolol 0.05% 2/day for 3 weeks. Run in phase Randomisation sequence was computer generated. Allocation concealment in sealed but not necessarily opaque envelopes.
			Number of patients with hyperaemia (assessed on a scale. 1=none/trace, 2=mild, 3=moderate, 4=severe. Mean hyperaemia score in all groups <0.50)	**Group 1:** 52/145 **Group 2:** 13/139 **P value groups 1 to 2**: <0.001	
			Reasons for withdrawals	**Group 1:** • NR **Group 2:** • Inadequate IOP control = 21	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Separate combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Polo et al., 2005[117] **Study design:** RCT **Evidence level:** 1 + **Duration of follow-up:** 24 months	**Patient group:** COAG **Setting:** Single centre, Italy **Inclusion criteria:** • POAG + Pseudoexfoliative Glaucoma (PXF) • Patients on monotherapy with beta blocker • Age >18 years • IOP ≥ 22 mmHg • Optic nerve head showing signs of glaucomatous damage **Exclusion criteria:** • Previous treatment of dorzolamide or latanoprost • Ocular infection or inflammatory disease in last 3 months • Allergy to treatment medications or preservative • Closed Angle Glaucoma • Previous ocular surgery or laser treatment in last 3 months • Cardiovascular or bronchial disease • Pregnant, nursing or patients considering pregnancy **<u>All patients</u>** **N:** 61 **<u>Group 1</u>** **N:** 30 **Age (mean ± SD):** 67.9 ± 11.2 **M/F:** 60%/40% eyes	**Group 1** Dorzolamide 2% 2/day + Timolol 0.5% 2/day **Group 2** Latanoprost 0.005% 1/day **Examination methods:** At eligibility testing, automated perimetry (Humphrey 30-II STATPAC 2) was used to measure visual field, stereo photographs used to assess glaucomatous damage (neuroretinal rim loss, haemorrhage etc), visual acuity, refraction, slit lamp examination also performed and IOP measurement technique was not specified. Examination schedule was at baseline, 2 wks and every 3 months.	**Mean ± SD baseline diurnal IOP mmHg**	**Group 1:** 23.8 ± 2.3 **Group 2:** 23.9 ± NR	**Funding:** Not reported. Conducted at Department of Ophthalmology, "Miguel Servet" University Hospital, Zaragoza, Spain **Limitations:** • Randomisation method not explained and no allocation concealment • Unmasked study, no placebo. • 3 week run in period on timolol • No drop out figures reported for patients • Not ITT analysis **Additional outcomes:** **Notes:** Data analyses use data per eye rather than patient. ** Standard deviations (SD) for fixed v monotherapy calculated using the Cochrane
			Mean ± SD end point diurnal IOP at 6 mths	**Group 1:** 18.2 ± 3.2 **Group 2:** 17.1 ± 2.4	
			Mean ± SD end point diurnal IOP at 24 mths	**Group 1:** 18.4 ± 1.9 **Group 2:** 15.9 ± 2.04	
			Mean ± SD reduction in IOP mmHg at 6 mths (baseline – end point)	**Group 1:** 5.6 ± 2.53** **Group 2:** 6.8 ± 1.94**	
			Mean ± SD reduction in IOP mmHg at 24 mths (baseline – end point)	**Group 1:** 5.4 ± 1.87** **Group 2:** 8.0 ± 1. 81** P < 0.05	
			Eyes reaching acceptable IOP of ≥ 20% reduction from baseline after 24 mths (<21 mmHg) *Figures estimated from Kaplan-Meier graph*	**Group 1:** 17/30 (56%) **Group 2:** 37/45 (82%)	
			Total number of patients reporting ocular side effects	**Group 1:** NR **Group 2:** NR	
			Total number of patients reporting cardiovascular systemic side effects	**Group 1:** NR **Group 2:** NR	
			Reasons for withdrawals	**Group 1:** NR **Group 2:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	1 eye/2eyes: 2/28 **Family history:** 24% eyes **POAG/PXF:** 23/8 **Drop outs:** 26/58 eyes (45%) **<u>Group 2</u>** **N:** 31 **Age (mean ± SD):** 64.6 ± 19.1 **M/F:** 64%/36% eyes **1 eye/2eyes:** 3/28 **Family history:** 29% eyes **POAG/PXF:** 25/5 **Drop outs:** 14/59 eyes (24%)				method for imputed SDs from the mean correlation coefficients calculated from Ozturk 2007[115] (CAI + BB v PGA)

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Separate combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rismanchian et al, 2008[121] **Study design:** RCT Observer masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** Newly diagnosed bilateral POAG **Setting:** single centre, ophthalmology department, Isfahan University of Medical Science, Feiz Hospital, Isfahan, Iran **Inclusion criteria:** • Diagnosis of unilateral or bilateral POAG with either visual field defects or optic nerve damage and elevated IOP ≥ 22 mmHg • Aged 18 or older • No previous treatment **Exclusion criteria:** • History of acute angle-closure or occludable angles • Contraindication to beta-blockers • Ocular surgery or argon laser trabeculoplasty • History of asthma, COPD, cardiac failure, sinus brachycardia, second or third degree atrioventricular block. • Severe renal impairment and hyperchloremic acidosis • Pregnant or breast feeding women • History of non-compliance or hypersensitivity to study drugs • Use of systemic medications affecting IOP **<u>All patients</u>** **N:** 120 **Age (mean ± SD):** 57.3 ± 13.15 (range 21-80) **M/F:** 60/60 **Drop outs:** NR **Group 1** **N:** 60	**Group 1** Dorzolamide 2% 3/day* & timolol 0.5% 2/day. *Note: normal dosage of dorzolamide if used with timolol is 2/day (BNF) **Group 2** Latanoprost 0.005% 1/day **Examination methods:** At baseline best corrected visual acuity, refraction, visual field testing, ophthalmoscopy, IOP measurement and slit lamp examination were performed. Goldmann applanation tonometry was used to measure IOP at 1, 3 and 6 months by same masked observer	**Mean ± SD IOP at 6 mths mmHg** **Mean ± SD change in IOP from baseline at 6 mths mmHg**	**Group1:** 22.9 ± 5.81 **Group 2:** 22.4 ± 5.42 **Group1:** 7.4 ± 2.32 **Group 2:** 7.1 ± 2.71 **p value:** 0.52 (calculated by NCC-AC team using t test with equal variances and ITT analysis)	**Funding:** Not reported **Limitations:** Randomisation method and allocation concealment not reported Dropouts were not reported so unclear if all patients completed study **Notes:** If both eyes qualified for study worse eye was used. No serious adverse events were observed.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean ± SD): 54.8 ± 15.49 (range 21-80) **M/F:** 28/32 **Drop outs:** NR **Mean Cup disc ratio ± SD:** 0.60 ± 0.15 **Mean baseline IOP ± SD mmHg:** 30.4 ± 6.58 **Group 2** **N:** 60 **Age (mean ± SD):** 52.7 ± 10.84 (range 35-80) **M/F:** 32/28 **Drop outs:** NR **Mean Cup disc ratio ± SD:** 0.60 ± 0.08 **Mean baseline IOP ± SD mmHg:** 29.6 ± 5.81				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 14 Adverse events associated with topical medications

Study details	Patients	Interventions/ exposures	Outcome measures	Effect size	Comments
Kirwan et al, 2002[74] and Kirwan et al, 2004[75] **Country of study:** UK **Study design:** Retrospective cohort study **Evidence level:** 2+ **Duration of follow-up:** 12 months	**Patient group:** Elderly glaucoma patients with no previous diagnosis of airways obstruction identified from the Mediplus database. **Inclusion criteria:** • elderly patients but age not given **Exclusion criteria:** None reported **All patients** **N:** 11,739 **Age (mean):** NR **M/F:** NR **Additional risk factors:** NR **Exposed group:** **n:** 2645 **Age (mean):** 68.6 **Unexposed group:** **n:** 9094 **Age (mean):** 67.5	**Exposed group:** Patients who had used topical beta-blockers **Control group:** Patients randomly selected, loosely matched by age and gender to exposed group. Validated against a random sample of 40 full longitudinal records of exposed and unexposed patients.	**Patients given a new prescription of a drug for reversible airways obstruction for first time in the 12 months after treatment**	**Exposed:** 81/2645 (3.1%) **Control:** 112/9094 (1.2%) **Unadjusted hazard ratio:** 2.39 (95% CI: 1.79 to 3.20) * **Adjusted hazard ratio:** 2.29 (95% CI: 1.71 to 3.07) † **NNH:** 55 (95% CI: 29 to 85)	**Funding:** Not reported **Limitations:** Age cut off not given to describe elderly. Respiratory problems may not have always been done with an objective test . Consequently, the study reports that there may have been a certain rate of missed diagnosis or misdiagnosis diagnosis which may have underestimated the the true risk. **Notes:** * Adjusted analysis used a proportional hazards model, corrected for age, sex, use of systemic beta-blockers, use of non-steroidal anti-inflammatory drugs, use of nitrates, smoking, season of presentation, and number of visits to general practitioners. † Number of patients needed to be treated with topical beta-blockers to cause one case of airways obstruction during that time period.
			Patients given a new prescription of a drug for reversible airways obstruction for first time in the 6 months after treatment	**Exposed:** 49/2645 (1.9%) **Control:** 55/9094 (0.6%) **Unadjusted hazard ratio:** 2.83 (95% CI: 1.91 to 4.20) * **Adjusted hazard ratio:** 2.79 (95% CI: 1.88 to 4.15) † **NNH:** 84 (95% CI: 51 to 131)	
			Patients given a new prescription of a drug for reversible airways obstruction for first time in the 12 months after treatment AND a new Read code for asthma or COPD	**Exposed:** 191/2645 (7.2%) **Control:** 354/9094 (3.9%) **Unadjusted hazard ratio:** 1.81 (95% CI: 1.50 to 2.16) * **Adjusted hazard ratio:** 1.77 (95% CI: 1.48 to 2.12) † **NNH:** 30 (95% CI: 22 to 42)	
			Patients given a new prescription of a drug for reversible airways obstruction for first time in the 6 months after treatment AND a new Read code for asthma or COPD	**Exposed:** 115/2645 (4.3%) **Control:** 172/9094 (1.9%) **Unadjusted hazard ratio:** 2.16 (95% CI: 1.70 to 2.76) * **Adjusted hazard ratio:** 2.18 (95% CI: 1.71 to 2.79) † **NNH:** 42 (95% CI: 30 to 60)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Adverse events associated with topical medications (continued)

Study details	Patients	Interventions/ exposures	Outcome measures	Effect size	Comments
Kaiserman et al, 2006[68] **Country of study:** UK **Study design:** Cohort **Evidence level:** 2+ **Duration of follow-up:** All data for the years 2001 and 2003 assessed	**Patient group:** All patients aged over 20 who filled at least 6 consecutive antiglaucoma prescriptions at least once every 2 months in an Israeli health district. **<u>All patients</u>** **N:** 6597 **Age (mean):** NR **M/F:** NR **Additional risk factors:** NR **<u>Exposed group</u>:** **n:** 5846 **Age (mean):** 73.2 ±10.4 **M/F:** 2511/3335 **<u>Unexposed group</u>:** **n:** 751 **Age (mean):** 73.2 ±11.7 **M/F:** 331/420	**Exposed group:** Patients using beta-blockers alone or with another glaucoma medication Medications used include: Timolol, Betaxolol, Levobunolol or Dorzolamide-Timolol **Control group:** Patients using glaucoma medications other than beta-blockers Medications used include: Brimonidine, Dorzolamide, Latanoprost, Travoprost, Bimatoprost, Pilocarpine and others	**No. patients taking at least 4 prescriptions of anti-depressants**	**Exposed group:** 715/5846 **Control group:** 95/751 **p value:** 0.74 **Odds ratio (95% CI):** 0.96 (0.77 to 1.21)	**Funding** not reported **Additional outcomes reported:** Compared results by different age groups as age could be a confounder for glaucoma and depression. No significant differences were found between age groups. **Notes:** Included patients using at least 4 prescriptions of anti-depressants in order to dicount patients prescribed anti-depressants for brief reactive events.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 15 Laser treatment for COAG

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rolim & Paranhos, 2007[124] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum treatment 6 months but collected outcomes at 12 and 24 months where possible.	**Patient group:** POAG, primary & secondary pigmentary glaucoma, pseudoexfoliative glaucoma. **Inclusion criteria:** Any age, gender or nationality. RCTs only comparing laser trabeculoplasty with no intervention, with medical treatment, with surgery or comparing different modalities. **Exclusion criteria:** Studies with OHT patients **Primary Outcomes:** 1. Failure to control IOP 2. Failure to stabilise visual field 3. Failure to stabilise optic neuropathy **Secondary Outcomes:** 1. Necessity of adding or changing therapy or intervention when IOP is uncontrolled 2. Adverse Events (severe/minor) including: IOP spikes, Uveitis, cyclitis, hypoema, PAS formation, corneal oedema, persistent IOP elevation, loss of vision, bronchial spasm	**Comparison 2:** Argon laser trabeculoplasty (ALT) v medication in newly diagnosed participants **Studies included:** Gandolfi 2005, Moorfields (Migdal) 1994. **Comparison 3:** ALT v medication in participants already on maximal medical therapy. **Studies included:** Moriarty 1988 and Sherwood 1987. **Comparison 4:** ALT v trabeculectomy **Studies included:** AGIS 2002, Watson 1984 and Moorfields (Migdal) 1994. **Comparison 6:** Selective laser trabeculoplasty (SLT) v ALT **Studies included:** Damji 2006 Comparisons 2, 3, 4 and 6 are relevant to the clinical question "What is the effectiveness (and comparative effectiveness) of Laser Trabeculoplasty (ALT or SLT) in lowering IOP in patients with suspected or definite COAG (including POAG & NTG) **Intervention Details:**	**Comparison 2:** ALT v medication in newly diagnosed participants		**Funding:** Not stated. Conducted at the Universidade Federal de São Paulo, Brazil **Limitations:** Excludes OHT patients **Notes:** Literature search date to June 2007. Studies included in Rolim 2007 that are excluded from guideline **Bergea 1992** as both study arms received additional stepped medications including with timolol and acetazolamide. **Glaucoma Laser Trial (GLT)** because fellow eyes were randomised to ALT or medications
			Failure to Control IOP ≥22mmHg for Moorfields 1994 and Gandolfi 2005	***Relative Risk at 0-24 months*** Moorfields 1994 1.36 (95% CI: 0.50, 3.66) ***Relative Risk at 0 – 5 years*** Moorfields 1994 1.83 (95% CI: 0.93, 3.61) ***Relative Risk at 3-4 years*** Gandolfi 2005 1.20 (95% CI: 0.46, 3.15) (data not presented in Rolim)	
			Bronchial reactivity	Gandolfi. At 3 and 4 years there was a tendency for a reduced risk ratio in the ALT group but the figure was not statistically significant.	
			Comparison 3: ALT + Medication v Medication		
			Failure to Control IOP ≥21mmHg for Sherwood 1987 and ≥ 22mmHg for Moriarty 1988	***Relative Risk at 0-24 months*** Sherwood 1987 1.08 (95% CI: 0.02, 0.31) ***Relative Risk at 0-24 months*** Moriarty 1988 0.41 (95% CI: 0.22, 0.77)	
			Comparison 4: ALT v trabeculectomy		
			Failure to Control IOP ≥22mmHg for Moorfields 1994 and need for second intervention in sequence	***Relative Risk at 0-6 months*** AGIS & Moorfields 3.4 (95% CI: 1.60, 6.18) ***Relative Risk at 0-24 months*** AGIS & Moorfields 2.03 (95% CI: 1.38, 2.98)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	3. Quality of life measures 4. Economic data	ALT mainly performed with 50 µm spot, 50 – 100 burns, 0.8 to 2.0 Watts.0.1 sec exposure. **Quality Assessment:** ***Selection Bias*** – randomisation was adequately concealed in Watson 1984, AGIS, Moorfields (Migdal) 1994 and Damji 2006 ***Performance Bias*** - care providers and recipients could not be masked to intervention in most comparisons so criteria was not used ***Detection Bias*** - assessment of outcomes masked for AGIS and Gandolfi 2005 ***Attrition Bias*** – ITT analysis performed for AGIS and Damji 2006 and follow up described. Watson 1984 did not report loss to follow up. Moorfields (Migdal) 1994 was not an ITT analysis.	Optic neuropathy progression	Optic disc was photographed in Moorfields and Watson study but not reported	
			Comparison 6: Selective laser trabeculoplasty (SLT) v ALT		
			Failure to Control IOP	***Relative Risk at 12 months*** Damji 2006 1.27 (95% CI: 0.84, 1.90)	
			Mean ± SD score of flare in anterior chamber	SLT – 1.00 ± 0.6 ALT – 0.8 ± 0.6. Not signif.	

Abbreviations: NR=not reported, NA=not applicable, Signif =statistically significant at 5%, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE=Standard Error, AGIS – Advanced Glaucoma Intervention Study, Trab – Trabeculectomy, TAT – Trab then ALT then Trab, ATT – ALT then Trab then Trab, PAS - Peripheral Anterior Synechiae, ITT – Intention to Treat, FU – Follow Up

RCTs included in ROLIM 2007 that meet guideline inclusion criteria

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
AGIS 2002[1] [USA]	TAT v ATT	5 years	National Eye Institute, NIH, USA	Advanced POAG	591 (789)	67 median (35 - 80)	ALT: 24.0 ± 4.7 Trab: 24.6 ± 6.1	56 / 38	Selection: A Detection: D Attrition – FU: A Attrition – ITT: A Low risk of bias	Rolim includes results after 1st intervention in sequence only. Data obtained from study authors. Failure criterion is need for 2nd intervention in sequence
Damji et al., 2006[30] [Canada]	SLT V ALT	12 months	Lumenis (manufacturer of SLT)	COAG Uncontrolled IOP > 16 mmHg on max medication (38% previous ALT)	152 (176)	69.1 ± 10.52	ALT: 23.4 ± 4.2 SLT: 23.8 ± 4.9	NR/ NR	Selection: A Detection: D Attrition – FU: B Attrition – ITT: A Low risk of bias	Patients remained on current medications throughout follow up. Unacceptable IOP criteria ≥ 20 mmHg
Gandolfi et al., 2005[45] [Italy]	ALT V Timolol 0.5% 2/day	4 years	Research, Science & technology University, Rome	POAG with IOP ≥ 22 mmHg	32	44-67	ALT: 24.5 ± 2.0 Meds: 24.4 ± 1.5	NR/ NR	Selection: B Detection: D Attrition – FU:B Attrition – ITT: A Low risk of bias	Looks at respiratory adverse events but reports change in IOP from baseline. Number of patients with unacceptable IOP > 22mmHg excluded from study.
Migdal et al., 1994[98] Moorfields [UK]	ALT v Trab v Medical	6 mths - 8 years	Charity – Frost Foundation	COAG 29% early 23% middle 48% late	168 55 laser 57 Trab 56 Meds	63.5	ALT: 35.0 ± 8.7 Meds: 35.0 ± 5.4 Trab: 34.0 ± 5.4	6 / NR	Selection: A Detection: D Attrition – FU: A Attrition – ITT: B Low risk of bias	Data obtained from study authors Pilocarpine included in medications Unacceptable IOP criteria ≥ 22 mmHg
Moriarty et al., 1988[102] [Jamaica]	ALT + Medication V Medication	12 months	NR	POAG with IOP ≥22mmHg	30 (48)	62 (27-77)	ALT: 32.3 ± NR Meds: 29.2 ± NR	100/NR	Selection: B Detection: D Attrition – FU: C Attrition – ITT: A High risk of bias	Medication - pilocarpine 4% & oral acetazolamide 250mg; 4 patients also used timolol 0.5% Unacceptable IOP criteria ≥ 22 mmHg

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
Sherwood et al., 1987[136] [UK]	ALT + Medication V Medication	35 (30-40) months	Locally organised research scheme (GMC)	POAG with IOP >21mmHg	25 (50)	72.54 (50-90)	ALT: 23.8 ± NR Meds: 23.8 ± NR	NR/NR	Selection: A Detection: D Attrition – FU:A Attrition – ITT: A Low risk of bias	Medication - between minimum of 2 and maximum of 4 of the following: timolol, pilocarpine, sympathomimetics and acetazolamide Failure criteria ≥ 21 mmHg
Watson et al., 1984[159] [UK]	ALT v Trab	6 months	2 UK hospitals (Addenbrookes + Sunderland Eye Infirmary)	Severe COAG or evidence of progression not responding to medications	61 (95)	70 (38 – 86)	Site 1 ALT: 25.2 ± 5.5 Trab: 30.4 ± 8.6 Site 2 ALT: 33.7 ± 10.1 Trab: 39.5 ± 10.6	NR/ NR	Selection: A Detection: D Attrition – FU: C Attrition – ITT: C Moderate risk bias	Reports change in IOP from baseline for each treatment by hospital

Abbreviations: NR=not reported, NA=not applicable, Signif =statistically significant at 5%, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE=Standard Error, AGIS – Advanced Glaucoma Intervention Study, Trab – Trabeculectomy, TAT – Trab then ALT then Trab, ATT – ALT then Trab then Trab, PAS - Peripheral Anterior Synechiae, ITT – Intention to Treat, FU – Follow Up

Evidence Table 16 Trabeculectomy vs. pharmacological treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Burr et al., 2004[15] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum length of follow-up was 12 months.	**Patient group:** POAG, NTG, pigmentary glaucoma, Pseudo-exfoliative glaucoma. **Inclusion criteria:** • Any gender or nationality • >18 years only **Possible interventions:** • Trabeculectomy ± MMC or 5F • Non-penetrating surgery ± MMC or 5F • Other surgery including drainage • Trans-scleral cytophotocoagulation (TSCPC) **Exclusion criteria:** Studies where medical arm included laser. **Primary Outcomes:** 4. Progressive visual field loss according to criteria described for each trial 5. Quality of Life **Secondary Outcomes:**	**Comparison 2:** Medications v trabeculectomy **Intervention Details:** **Surgery** Trabeculectomy in 3 Studies. Migdal 1994 (Moorfields Trial), Jay 1988 (Glasgow trial), Lichter 2001 (CIGTS trial) **Medications** Migdal 1994 (Moorfields Trial)- miotics, Sympathomimetic or beta-blocker + oral CAI Jay 1988 (Glasgow trial) - miotics, Sympathomimetic or beta-blocker + oral CAI Lichter 2001 (CIGTS trial) – Beta blockers + other not specified. **Quality Assessment:** ***Selection Bias*** – randomisation was adequately concealed in Lichter 2001 (CIGTS trial), Jay 1988 (Glasgow trial), Migdal 1994 (Moorfields Trial), ***Performance Bias*** - NR	**Comparison 1:** Medications v Scheie's procedure ***(no longer performed)***		**Funding:** Non industry funded (Cochrane Review). **Limitations:** • Includes Studies with miotics (pilocarpine). • Outcome assessment was not masked • Migdal 1994 (Moorfields) and Jay1988 (Glasgow trial) were not ITT analyses as the treatment failures had been excluded. **Notes:** Literature search date to August 2003. An updated search was run in February 2005 but no new studies were found. **Additional Outcomes:** Optic disc change (Jay 1988)
			Comparison 2: Medications v trabeculectomy		
			Progressive Visual Field Loss (Mean change in visual field score from baseline)	**Jay 1988 (Glasgow trial)** At 4.6 years mean follow-up 27/57 medical patients and 13/50 trab patients had progressed by at least one stage. **Migdal 1994 (Moorfields Trial)** Friedman Visual field analysis 3.92 (95% CI: 2.02 – 5.82) favours Trab. Signif Humphrey automated perimetry (introduced 2yrs after start of study) Medical: 25/40 (63%) progressed Trab:34/48 (71%) progressed OR:0.69 (95% CI: 0.29 – 1.67) No significant difference **Lichter 2001 (CIGTS trial)** VF Score change from baseline – 1yr -0.5 (95% CI: -1.10 – 0.10) VF Score change from baseline – 5yr 0.30 (95% CI: -0.45 – 1.05) No significant difference at 1 or 5yrs ANOVA Mean VF score difference between treatment groups over follow up time -0.36 (95% CI: -0.67 to -0.05) Adjusting for cataract mean VF: -0.28 (95% CI: -0.59 to 0.03) No significant difference Logistic Regression (adjusting for baseline VR, age, sex, race, diagnosis, diabetes and time in study) Risk of progressive VFL of at least 3 units from baseline	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	5. Change in IOP 6. Progression of optic disc or nerve fibre damage 7. Reduction of LogMAR score ≥ 0.3 (Snellen visual acuity ≥ 2 lines) 8. Adverse Events (severe/minor) including: mortality, loss of eye due to infection or inflammation, severe irreversible reduction in vision, visually significant cataract, incidence of cataract surgery, need for additional surgery or medication, transient decrease in central vision from complications, systemic side effects (cardiovascular and COPD, CNS defects), local side effects (eye irritation, watering, redness, discomfort) 9. Economic data	***Detection Bias*** - Assessment of outcomes was not masked for any of the Studies apart from QoL in CIGTS – telephone administered questionnaire ***Attrition Bias*** Jay 1988 (Glasgow trial): 25/57 in medication group and 30/50 not available for final analysis. IOP analysis not ITT Migdal 1994 (Moorfields Trial): IOP and VF analysis not ITT. Lichter 2001 (CIGTS trial): at 5 years 37/607 lost to follow-up. Analysis was ITT		between treatment groups: OR= 0.74 (95% CI: 0.54 – 1.01) Adjusted for cataract: OR = 0.75 (95% CI: 0.55 – 1.02) No significant difference	Health related quality of life in Lichter 2001 (CIGTS trial) Economic measures in Migdal 1994 (Moorfields Trial) Visual Acuity Loss (All studies) Burr 2004 reported OR for VF progression for CIGTS and also Number of patients with unacceptable IOP for Moorfields but did not did not actual dichotomous outcome figures so they could not be included in the meta-analysis. Jampel et al., 2005[64] paper describes perioperative complications for the CIGTS study and reports number of trabs with no augmentation = 177/465 eyes, Number with 5FU = 266/465 eyes and number with MMC = 22/465 eyes
			Mean reduction in IOP from baseline mmHg	**Jay 1988 (Glasgow trial) [short term only]** 6.0 (95% CI:2.64 – 9.36) **Migdal 1994 (Moorfields Trial)** **Short term** (51/56 Medical/Surgery) 6.2 (95% CI: 3.92 – 8.48) **Medium term** (50/56 Medical/Surgery) 1.6 (95% CI: -0.69 – 3.89) **Long term** (46/56 Medical/Surgery) 3.4 (95% CI: 1.04 – 5.76) [Both above studies exclude failures from the point of failure]. **Lichter 2001 (CIGTS trial)** At year one (595 pts) 3.6 (95% CI: 2.78 – 4.42) Favours Trab Signif At 5 years (384 pts) 1.9 (95% CI: 0.85 – 2.95) Favours Trab. No significant difference.	
			Adverse Events	**1) Mortality** **Jay 1988 (Glasgow trial)** At last follow up (mean 4.6yrs) 12/112 (14%) of recruited pts died. 7in the medical group, 8 in the Trab group and 1 unknown. **2) Severe irreversible reduction in vision** **Jay 1988 (Glasgow trial)** At one year, 6/46 (13%) eyes in the medical group had lost central fixation and in the following 2 years, a further 2 in the same group. No pts in the Trab group lost central fixation over mean follow up of 33 months. **3) Visually significant cataract** **Total from all Studies** 57/403 for trabeculectomy	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
				24/416 for medications. RR: 2.45 (95% CI: 1.55 to 3.87)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

RCTs included in BURR 2004 that meet guideline inclusion criteria

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
Jay & Murray, 1988[65] Glasgow [UK]	Trab v Medical	7yrs max (mean 4.6yrs)	NR	Newly diagnosed POAG 65% moderate 35% severe	107 50 Trab 57 Meds	NR	Meds: 37.8 ± NR Trab: 37.8 ± NR	0/ NR	Selection: A Detection: C Attrition – FU: B Attrition – ITT: C Moderate risk of bias	*Outcome assessment was not masked* *Pilocarpine included in medication* *Treatment failures excluded from analysis*
Lichter et al., 2001[89] CIGTS **[USA]**	Trab v Medical	Min 5 yrs	Non industry – National Institutes of Health, National Eye Institute grants	91% POAG (mean visual field defects 4.8units on a scale of 0 to 20) C/D range 0.6-0.7 Mild glaucoma	607 300 Trab 307 Meds	57.5 (range 28-75)	Meds: 27 ± NR Trab: 27 ± NR	44 / NR	Selection: A Detection: C Attrition – FU: A Attrition – ITT: A Low risk of bias	*Main medication was beta-blockers*
Migdal et al., 1994[98] Moorfields [UK]	ALT v Trab v Medical	6 mths - 8 yrs	Charity – Frost Foundation	COAG 29% early 23% middle 48% late	168 55 laser 57 Trab 56 Meds	63.5	ALT: 35.0 ± 8.7 Meds: 35.0 ± 5.4 Trab: 34.0 ± 5.4	6 / NR	Selection: A Detection: C Attrition – FU: B Attrition – ITT: C Moderate risk of bias	*Outcome assessment was not masked* *Data obtained from study authors* *Pilocarpine included in medications* *Failure criteria ≥ 22 mmHg* *Treatment failures excluded from analysis*

Cochrane Quality Assessment Grades: A =Acceptable, B=Unclear, C=inadequate

Evidence Table 17 Trabeculectomy plus pharmacological augmentation vs. trabeculectomy

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Wilkins et al., 2005[161] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum follow up 12 months	**Patient group:** POAG, pigmentary glaucoma, pseudoexfoliative glaucoma, closed-angle glaucoma and other secondary glaucomas – congenital, neovascular etc 3 population sub-groups considered: 1. High risk of failure – previous drainage surgery, cataract surgery or with secondary glaucomas 2. Combined surgery with extra-capsular cataract extraction and intraocular lens implantation. 3. Primary trabeculectomy **Inclusion criteria**: RCTs with intraoperative Mitomycin C (MMC) administered at any concentration or dose compared to placebo or control. **Primary Outcomes:** 6. Proportion of failed surgeries at 12 months post-surgery (failure defined as repeat surgery or uncontrolled IOP despite additional medications) 7. Mean IOP at 12 months **Secondary Outcomes:** 10. Wound leaks detected by positive Seidel test	**Intervention Details:** Surgery was performed with or without Mitomycin C delivered intraoperatively at concentrations of 0.1 – 0.5 mg/ml saline for between 1 and 5 minutes. **Quality Assessment:** ***Selection Bias*** – randomisation and allocation concealment was graded as A adequate, B unclear or C inadequate, only studies with A or B were included ***Performance Bias*** - checking whether recipients or those providing care were masked to treatment allocation. If not then study deemed as high risk of bias. ***Detection Bias*** - checking whether assessment of outcomes was masked. If not then study deemed as high risk of bias. ***Attrition Bias*** – checking	**Failure at 12 months Primary Trabeculectomy** (338 patients)	Costa 1996, Martini 1997, Robin 1997, Szymanski 1997 **Relative Risk**: 0.37 in favour of MMC **Signif.** (CI 95% 0.26 – 0.51) **p value**: 0.00004	**Funding:** MRC and Moorfields Eye Hospital **Limitations:** • Includes trials a proportion of patients with closed-angle glaucoma (CACG). • Includes secondary glaucomas such as congenital, neovascular, uveitic, traumatic etc **Notes:** Latest literature search to March 2005 Studies included in Wilkins 2005 that are excluded from guideline **Andreanos 1997** includes high patients with previous surgery **Carlson 1997** includes combination cataract surgery **Shin 1995** includes combination cataract surgery **Shin 1998** includes high patients with previous surgery and combination cataract surgery **Cohen 1996** includes CACG but proportion is not defined **Turacli 1996** – includes 17% closed-angle glaucoma patients & 22% secondary glaucomas (congenital, neovascular etc) **Wu 1996** – secondary glaucomas
			Mean IOP at 12 months Primary Trabeculectomy	Costa 1996, Martini 1997, Szymanski 1997 **Weighted Mean Difference:** 5.41 mmHg in favour of MMC **Signif.** (CI 95% 7.34 – 3.49) **p value**: <0.00001 Robin 1997 did not report IOP at 12 months	
			Wound leak	**Primary Trabeculectomy** Szymanski 1997 **Odds Ratio**: 1.65 in favour of control **Not signif.** (CI 95% 0.16 – 17.47) **p value**: 0.7	
			Hypotony	**Primary Trabeculectomy** Costa 1996, Martini 1997, Szymanski 1997 **Odds Ratio**: 1.05 in favour of control **Not signif.** (CI 95% 0.23 – 4.68) **p value**: 1.0	
			Expulsive Haemorrhage	***No events reported***	
			Cataract	**Primary Trabeculectomy** Costa 1996, Martini 1997, Szymanski 1997, Robin 1997 **Relative Risk**: 1.93 in favour of control **Not signif.** (CI 95% 0.98 – 3.80) **p value**: 0.6	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	11. Hypotony IOP < 5 mmHg 12. Late endophthalmitis infection 13. Expulsive or choriodal haemorrhage 14. Shallow anterior chamber 15. Cataract – reduction in optical clarity 16. Quality of Life assessments and patients perspectives	whether analysis was done on an ITT basis and if rates of follow up were similar in each group. If not then study deemed as high risk of bias.	**Shallow Anterior Chamber**	**Primary Trabeculectomy** Costa 1996, Martini 1997 **Odds Ratio**: 1.14 in favour of control **Not signif.** (CI 95% 0.42 – 3.07) **p value**: 0.8	(congenital, neovascular etc)

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Wormald et al., 2001[162] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum follow up 12 months	**Patient group:** POAG, pigmentary glaucoma, pseudoexfoliative glaucoma, closed-angle glaucoma and other secondary glaucomas – congenital, neovascular etc 3 population sub-groups considered: 4. High risk of failure – previous drainage surgery, cataract surgery or with secondary glaucomas 5. Combined surgery with extra-capsular cataract extraction and intraocular lens implantation. 6. Primary trabeculectomy **Inclusion criteria:** RCTs with postoperative 5-Fluorouracil (5-FU) administered injections at any concentration or dose compared to placebo or control. **Primary Outcomes:** 8. Proportion of failed surgeries at 12 months post-surgery (failure defined as repeat surgery or uncontrolled IOP > 22 mmHg despite additional medications) **Secondary Outcomes:** 17. Wound leaks detected by positive Seidel test 18. Hypotony IOP < 5 mmHg 19. Late endophthalmitis infection 20. Expulsive or choroidal haemorrhage	**Intervention Details:** Surgery was performed with or without postoperative injections of 5-FU in 0.1 or 0.5 ml saline solution **Quality Assessment:** A quality score was applied to each study 1. Clear description of inclusion/exclusion criteria (YES-1/NO-0) 2. Was study randomised? (YES with description-2/ONLY STATED – 1/NO-0) 3. Was study double blind? (YES with description-2/ONLY STATED – 1/NO-0) 4. Was there a description of withdrawals & dropouts? (YES-1/NO-0) 5. Were statistics methods described? (YES-	**Failure at 12 months Primary Trabeculectomy** (338 patients)	Goldenfeld 1994, Ophir 1992 **Relative Risk**: 0.21 in favour of 5-FU **Signif.** (CI 95% 0.06 – 0.68) **p value**: 0.009	**Funding:** Moorfields Eye Hospital **Limitations:** • Includes trials a proportion of patients with closed-angle glaucoma (CACG). • Includes secondary glaucomas such as congenital, neovascular, uveitic, traumatic etc **Notes:** Latest literature search to January 2008 – no new studies to add Studies included in Wormald 2001 that are excluded from guideline **Gandolfi 1997** includes combination cataract surgery **Loftfield 1991** conference abstract **FFSSG 1996** 32% Secondary angle-closure glaucoma and 33% other types including secondary open-angle, pigmentary glaucoma and primary angle closure glaucoma (proportions not specified) **O'Grady 1993** includes combination cataract surgery **Ruderman 1987** includes 69% secondary glaucomas (congenital, neovascular etc)
			Mean IOP at 12 months Primary Trabeculectomy	Goldenfeld 1994, Ophir 1992 **Weighted Mean Difference:** 4.67 mmHg in favour of 5-FU **Signif.** (CI 95% 2.74 – 6.60) **p value**: <0.00001	
			Wound leak	**Primary Trabeculectomy** Goldenfeld 1994, Ophir 1992 **Relative Risk:** 0.47 in favour of 5-FU **Not Signif.** (CI 95% 0.04 – 4.91) **p value:** 0.5	
			Hypotonous maculopathy	**Primary Trabeculectomy** Goldenfeld 1994, **Relative Risk:** 2.82 in favour of control **Not Signif.** (CI 95% 0.12 – 66.62)	
			Endophthalmitis	***No events reported***	
			Cataract	**Primary Trabeculectomy** Chaudhry 2000 **Relative Risk**: 6.00 in favour of control **Not signif.** (CI 95% 0.76 – 47.49)	
			Shallow Anterior Chamber	**Inconsistently reported among trials**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	21. Shallow anterior chamber 22. Corneal and conjunctive epithelial erosions	1/NO-0) Allocation concealment was also assessed as A-adequate, B-unclear, C-inadequate			**Wong 1994** includes combination cataract surgery

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Egbert et al., 1993[39] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** Mean approx. 9 months	**Patient group:** West African patients with advanced POAG, CACG & traumatic glaucoma **Setting:** single centre - Ghana **Inclusion criteria:** • Non-phakic glaucoma **Exclusion criteria:** NR **All patients** **N:** 59 (61 eyes) **Age (mean ± SD):** NR **M/F:** 35/20 **Mean IOP:** NR **Drop outs:** NR **Group 1** **N:** 31 **Age (mean ± SD):** 58.9 (range 22-83) **M/F:** 23/8 **Eyes with previous operations:** 4 **Mean IOP:** 33.4 (range 16-76) **Drop outs:** NR **Group 2** **N:** 24 **Age (mean ± SD):** 60.6 (range 36-76) **M/F:** 12/12 **Mean IOP:** 29.2 (range 18-46) **Drop outs:** NR	**Group 1** Trabeculectomy **Group 2** Trabeculectomy + Intraoperative 5-Flourouracil (5-FU) 50 mg/ml for 5 minutes on surgical sponge **Examination methods:** ***Preoperative:*** Visual acuity, slit lamp examination, Goldmann tonometry, gonioscopy and ophthalmoscopy. ***Postoperative:*** Visual acuity, slit lamp examination, Goldmann tonometry Day 1, and over 1st week. Other follow-up visits were irregular.	**Mean IOP at final visit (mean follow-up 9 months)**	**Group 1:** 24.5 (range 4-74) **Group 2:** 17.3 (range 6-35) **p value:** 0.05 (Mann-Whitney U test)	**Funding:** Partially funded by Research to Prevent Blindness - USA **Limitations:** • West African population only • Includes 4% CACG patients & 4% traumatic glaucoma patients • 61 eyes started study but only 55 were included in the analysis. Dropouts per group not reported. • Follow up time is limited. Complications such as bleb infections could increase in the 5-FU group with longer follow up. • Randomisation method, allocation concealment and masking of outcome assessment were not mentioned. **Additional outcomes:** Visual acuity **Notes:** No postoperative 5FU injections were performed
			Number of eyes with acceptable IOP (<20 mmHg without medications at 12 months	**Group 1:** 10/31 **Group 2:** 17/24 **p value:** 0.02 **signif.**	
			Number of eyes with unacceptable IOP >20mmHg at end point (9 mths)	**Group 1:** 21/31 **Group 2:** 7/24 **p value:** NR	
			Number of eyes with unacceptable IOP >15mmHg at end point (9 mths)	**Group 1:** 26/31 **Group 2:** 13/24 **p value:** NR	
			Number of patients on postoperative medications	**Group 1:** 16 (46%) **Group 2:** 5 (24%) **p value:** 0.02 (Chi-squared) **signif.**	
			Hyphaema	**Group 1:** 1/31 **Group 2:** 0/24 **p value:**	
			Cataract progression	**Group 1:** 3/31 **Group 2:** 4/24 **p value:**	
			Flat anterior chamber	**Group 1:** 2/31 **Group 2:** 2/24 **p value:**	
			Conjunctival wound leak	**Group 1:** 2/31 **Group 2:** 4/24 **p value:** Not signif.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			Corneal epithelial defects	**Group 1:** 0/31 **Group 2:** 0/24 **p value:**	

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Leyland et al., 2001[88] **Study design:** RCT **Evidence level:** 1+ Double blind **Duration of follow-up:** 30	**Patient group:** POAG, chronic closed-angle glaucoma & pseudoexfoliative glaucoma **Setting:** single centre - UK **Inclusion criteria:** • POAG, CACG (13%), PXF • Established disc cupping and glaucomatous field loss • Uncontrolled IOP • ≥ 18 years **Exclusion criteria:** • Other glaucomas such as congenital, uveitic, traumatic • Previous surgery • Laser treatment within last 6 months • Pregnant women **<u>All patients</u>** **N:** 39 (43 eyes) **Age (mean ± SD):** NR **M/F:** 35/20 **Mean IOP:** NR **Drop outs:** 3 **<u>Group 1</u>** **N:** 17 **Age (mean ± SD):** 66.7 ± 11.4 **M/F:** 10/7 **Mean IOP:** 28.1 ± 6.8 **Visual Field (Mean Db):** -15.1 ± 10.1 **Drop outs:** 2 **<u>Group 2</u>**	**Group 1** Trabeculectomy + 0.9% Sodium Chloride for 5 minutes on surgical sponge **Group 2** Trabeculectomy + Intraoperative 5-Flourouracil (5-FU) 25 mg/ml for 5 minutes on surgical sponge **Examination methods:** ***Postoperative:*** Visual acuity, bleb appearance, IOP, lens clarity and fundus appearance monitored at each visit at 1 day, 1 week, 1, 3, 6, 12 months.	**Mean IOP at 12 months**	**Group 1:** 15.3 ± NR **Group 2:** 14.7 ± NR **p value:** Not signif.	**Funding:** NR **Limitations:** • Includes 5/40 (13%) CACG patients • Primary outcomes not reported **Additional outcomes:** Bleb analysis **Notes:** 1 postoperative 5FU injections was performed on a patient in group 1 Double blind study with allocation concealment
			Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	**Group 1:** NR **Group 2:** NR **p value:**	
			Cataract progression (late surgery)	**Group 1:** 4/17 **Group 2:** 5/23 **p value:**	
			Shallow anterior chamber	**Group 1:** 3/17 **Group 2:** 7/23 **p value:** 0.06	
			Conjunctival wound leak	**Group 1:** 3/17 **Group 2:** 7/23 **p value:**	
			Corneal punctate epithelial keratopathy	**Group 1:** 3/17 **Group 2:** 5/23 **p value:**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 23 **Age (mean ± SD):** 64.8 ± 12.2 **M/F:** 10/7 **Mean IOP:** 27.7 ± 5.7 **Visual Field (Mean Db):** -14.4 ± 9.1 **Drop outs:** 1				

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
RASHEED, 1999[118] **Study design:** RCT (single blind) **Evidence level:** 1 + **Duration of follow-up:** 18 months	**Patient group:** POAG & CACG **Setting:** single-centre - Egypt **Inclusion criteria:** Bilateral POAG or CACG (16%) uncontrolled on medical therapy **Exclusion criteria:** None detailed **All patients** **N:** 25 (50 eyes) **Age (mean):** 50.3 ± 14.1 **M/F:** 12/13 **Mean IOP:** NR **Drop outs:** 0 **Group 1** **N:** 25 **Age (mean):** see above **M/F:** see above **Mean IOP:** 28.1 ± 3.14 **Pre-op Medications:** 3.7 ± 0.3 **Drop outs:** 0 **Group 2** **N:** 25 **Age (mean):** see above **M/F:** see above **Mean IOP:** 28.0 ± 3.19 **Pre-op Medications:** 3.7 ± 0.6 **Drop outs:** 0	**Group 1** Trabeculectomy **Group 2** Trabeculectomy + Mitomycin C. 0.3 – 0.4 mg/ml for 4 minutes depending on risk of failure **Examination methods:** Not clearly stated but infer that IOP, changes in optic disc and VF progression measured.	**Mean IOP during last 6 months of study (months 12-18)**	**Group 1:** 16.1 ± 5.1 **Group 2:** 10.2 ± 3.9 **p value:** NR	**Funding:** NR **Limitations:** • Includes 4/25 (16%) CACG patients • States as single blind though no details given • Some discrepancies in the statistical tests • Allocation concealment and masking of outcome assessment not reported **Additional outcomes:** Argon laser suture lysis **Group 1:** 21/25 **Group 2:** 13/25 **Notes:** Computerised randomisation Fellow eyes randomised
			Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	**Group 1:** 12/25 (48%) **Group 2:** 21/25 (84%) **p value:** NR *p = 0.016 Fishers Exact calculated by NCC-AC as ITT (n=25 in both groups)*	
			Number of eyes with unacceptable IOP >20mmHg at 12 months	**Group 1:** 17/25 **Group 2:** 7/25 **p value:** NR	
			Hyphaema	**Group 1:** 2/25 **Group 2:** 2/25 **p value:**	
			Cataract progression	**Group 1:** 1/25 **Group 2:** 1/25 **p value:**	
			Wound leak	**Group 1:** 3/25 **Group 2:** 10/25 **p value:** 0.44 (Chi-squared) *p = 0.051 Fishers Exact calculated by NCC-AC as ITT (n=25 in both groups)*	
			Bleb scarring	**Group 1:** 6/25 **Group 2:** 1/25 **p value:** 0.04 (Chi-squared) *p = 0.1 Fishers Exact calculated by NCC-AC as ITT (n=25 in both groups)*	

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Summary of RCTs included in WORMALD 2001 and WILKINS 2005 that met guideline inclusion criteria

STUDY	Intervention MMC	Duration (months)	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
Costa et al., 1996[26] [Brazil]	0.2 mg/ml for 3 minutes v Placebo	18	NR	Medically uncontrolled POAG + ***14% CACG***	28 (28)	67.0	MMC: 26.35 ± 6.68 Placebo: 24.92 ± 7.07	32 / NR	Allocation concealment – B unclear	Primary trabeculectomy Randomisation unclear Double masked Failure criteria >15 mmHg without medication
Goldenfeld et al., 1994[49] [Israel]	5 x 1/day 5 mg injections over first 15 postoperative days	20	Partially by Research to Prevent Blindness	Medically uncontrolled POAG or PXF	62 (62)	67.3 range (46 - 84)	5-FU: 25.0 ± 6.22 NT: 27.4 ± 12.05	10 / NR	Quality Score = 4 Allocation concealment – B unclear	Randomisation was adequate but, allocation concealment and masking of outcome assessment were not reported. Failure criteria >21 mmHg with medications
Martini et al., 1997[94] [Italy]	0.1 mg/ml for 3 minutes v NT	12	NR	Medically uncontrolled COAG	48 (60)	65.5	MMC: 28.8 ± 7.4 NT: 28.4 ± 9.2	NR / NR	Allocation concealment – B unclear	Computer randomisation Investigator masked Failure criteria >18 mmHg with or without medication. Some patients had previous laser treatment
Ophir & Ticho 1992[113] [Israel]	5 x 1/day 5 mg injections over first 10 postoperative days	18	NR	Medically uncontrolled POAG + **18% CACG**	50 (50)	63.2	5-FU: 25.7 ± 2.1 NT: 25.9 ± 2.4	48 / NR	Quality Score = 1 Allocation concealment – B unclear	Randomisation, allocation concealment and masking of outcome assessment were not reported. Failure criteria >20 mmHg with medications
Robin et al., 1997[123] [USA]	MMC 1 - 0.2 mg/ml for 2 mins MMC 2 - 0.2 mg/ml for 4 mins MMC 3 – 0.4 mg/ml for 2 mins	12	NR	Medically uncontrolled COAG + ***39% CACG***	300 (300)	57	T: 29.1 ± NR MMC 1: 28.1 ± NR MMC 2: 30.6 ± NR MMC 3: 30.9 ± NR	NR / NR	Allocation concealment –A adequate	Double masked study Failure criteria >19 mmHg with or without medication. Some patients had previous laser treatment
Szymanski et al., 1997[147] [Poland]	0.2 mg/ml or 0.5 mg/ml for 5 min v Placebo	18	NR	Medically uncontrolled POAG	29 (29)	47.8	All: 21.6 ± 4.2	NR / NR	Allocation concealment – B unclear	Randomisation, allocation concealment, masking of outcome assessment not reported. IOP control is not primary outcome Failure criteria >15 mmHg with medication

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Evidence Table 18 Trabeculectomy plus antimetabolite drug MMC vs. antimetabolite drug 5-FU

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Singh et al., 1997[138] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** mean 10.0±4.41 months (difference between groups p=0.70)	**Patient group:** West African POAG patients **Setting:** Cape Coast Christian Eye Clinic, Ghana **Inclusion criteria:** Diagnosis of POAG based on visual acuity, slit lamp examination, Goldmann applanation tonometry, gonioscopy and post dilation ophthalmoscopy **Exclusion criteria:** NR **<u>All patients</u>** **N:** 81 **Age (mean ± SD):** 53.6 P-value for diff = 0.73 **M/F:** 49/32 P-value for diff = 0.29 **Mean IOP:** 30.1 (17-55) P-value for diff = 0.46 **Drop outs:** 0 **<u>Group 1</u>** **N:** 44 **Age (mean ± SD):** 54.1 **M/F:** 29/15 **Mean IOP:** 30.7 (20-47) **Drop outs:** 0	**Group 1** Primary trabeculectomy with intraoperative use 0.5mg/ml MMC for 3.5 minutes on a soaked surgical sponge wedged between the flap and the conjunctiva. **Group 2** Primary trabeculectomy with intraoperative use 50 mg/ml 5-FU for 5 minutes on a soaked surgical sponge wedged between the flap and the conjunctiva. **Examination methods:** 90-diopter lens at the slit lamp examination and applanation tonometry. Indirect ophthalmoscopy was reserved for eyes with unexplained vision loss or shallow anterior chamber. Visits were at 3, 7, and 14 days postoperatively.	**Mean (range) IOP at follow-up (mmHg) at mean follow-up of 10 months**	**Group 1:** 13.7 (2-30) **Group 2:** 16.3 (4-36) **p value:** 0.05 (Chi-square test)	**Funding:** NR **Limitations:** • Patients and medical staff were not kept blind • Only partially applicable (West African patients) • Only 81 of the 85 patients randomised were followed up for at least 3 months postoperatively. **Notes:** The surgical technique and postoperative care did not vary for individual surgeons based on choice of antimetabolites. Randomisation by coin flipping prior to surgery **Additional outcomes:** 22/44 in the MMC group and 23/37 in the FU group had preoperative visual acuity of 6/60 or worse in the treated eye. .
			IOP success (with or without medications – not explicitly stated) at mean follow-up of 10 months	**IOP < 21mmHg** **Group 1:** 41/44 (93.2%) **Group 2:** 27/37 (73.0%) **p value:** 0.01 (Chi-square test) **IOP < 18mmHg** **Group 1:** 31/44 (70.5%) **Group 2:** 21/37 (56.8%) **p value:** 0.21 (Chi-square test) **IOP < 15mmHg** **Group 1:** 28/44 (63.6%) **Group 2:** 19/37 (51.4%) **p value:** 0.26 (Chi-square test)	
			Number of patients with unacceptable IOP (with or without medications – not explicitly stated) at mean follow-up of 10 months	**IOP > 21mmHg** **Group 1:** 3/44 (93.2%) **Group 2:** 10/37 (73.0%) **p value:**	
			Proportion of patients taking IOP-lowering medication at final follow-up	**Group 1:** 10/44 **Group 2:** 9/37 **p value:** 1 (Fisher's exact calculated by NCC-AC)	
			Eyes with no change in postoperative visual acuity	**Group 1:** 32/44 **Group 2:** 27/37 **p value:** 0.96 (Chi-square test)	
			Eyes with more than two-line decrease in	**Group 1:** 6/44 **Group 2:** 7/37	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 37 **Age (mean ± SD):** 52.7 **M/F:** 20/17 **Mean IOP:** 32.0 (22-45) **Drop outs:** 0		**visual acuity**	**p value:** 0.53 (Chi-square test)	
			Flat anterior chamber	**Group 1:** 1/44 **Group 2:** 0/37 **p value:** 1 (Fisher's exact calculated by NCC-AC)	
			Cataract	**Group 1:** 3/44 **Group 2:** 3/37 **p value:** 1 (Fisher's exact calculated by NCC-AC)	
			Hypotony (IOP<6mmHg)	**Group 1:** 2/44 **Group 2:** 2/37 **p value:** 1 (Fisher's exact calculated by NCC-AC)	
			Persistent wound leak	**Group 1:** 0/44 **Group 2:** 0/37 **p value:** NA	
			Endophthalmitis	**Group 1:** 0/44 **Group 2:** 0/37 **p value:** NA	

Abbreviations: NR=not reported, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, IOP=intra-ocular pressure, POAG=primary open-angle glaucoma, MMC=mitomycin, 5-FU=5-Fluorouracil, VA=visual acuity

Trabeculectomy plus antimetabolite drug MMC vs. antimetabolite drug 5-FU (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Zadok et al., 1995[165] **Study design:** RCT Investigator who followed up the patients was masked to intervention. **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG **Setting:** Single centre in Israel. **Inclusion criteria:** Adult patients with medically uncontrolled POAG. **Exclusion criteria:** NR **<u>All patients</u>** **N:** 20 (20 eyes) **Age (mean):** NR **M/F:** 11/9 **Mean IOP:** see below. P-value for diff = 0.22. **Drop outs:** 0 **<u>Group 1</u>** **N:** 10 **Age (mean):** 70.8±8.0 **M/F:** 7/3 **Mean IOP:** 24.0±1.9 **Drop outs:** 0 **<u>Group 2</u>** **N:** 10 **Age (mean):** 66.6±7.6 **M/F:** 4/6 **Mean IOP:** 25.7±3.8 **Drop outs:** 0	**Group 1** Cairn's filtering procedure in which a surgical sponge soaked in a 0.2mg/ml MMC was placed between the conjunctiva and episclera for five minutes. The tissues were then rinsed with 100ml of balanced salt solution. **Group 2** Cairn's filtering procedure in which 5 mg of 5-FU (0.5ml of a 10 mg/ml solution) were injected subconjunctivally 180 degrees from the filtering site once daily up to seven times during the first week after surgery. **Examination methods:** NR IOP measured at 1week, 2 weeks, 1 month, 2 months, 6 months and 12 months.	**Mean post-operative IOP (mmHg)**	***6 months:*** **Group 1:** 11.1 ± 4.8 **Group 2:** 14.1 ± 4.9 **p value:** 0.1 (Student's t test) ***12 months:*** **Group 1:** 11.6 ± 4.2 **Group 2:** 14.3 ± 3.7 **p value:** 0.1 (Student's t test)	**Funding:** NR **Limitations:** • Randomisation method not clear • Surgeon and patients unblinded • Examination methods NR • Small sample size • Inclusion/exclusion criteria for patients enrolment NR **Additional outcomes:** Visual acuity at 12 months was stable within 1 line of baseline in all eyes in both groups. Mean change in IOP rate at 12 months was 53.4% ± 20.3% with MMC and 43.4% ± 21.3% with 5-FU **Notes:**
			Mean change in IOP from baseline at postoperative measurement	***6 months:*** **Group 1:** 12.9 ± NR **Group 2:** 11.6 ± NR **p value:** NR ***12 months:*** **Group 1:** 12.4 ± NR **Group 2:** 11.4 ± NR **p value:** NR	
			Number of patients with acceptable IOP (<20 mmHg without medications) at 12 months	**Group 1:** 8/10 **Group 2:** 7/10 **p value:** 1 (Fisher's exact calculated by NCC-AC)	
			Number of patients with unacceptable IOP > 20 mmHg at 12 months	**Group 1:** 2/10 **Group 2:** 3/10	
			Corneal epithelial defect	**Group 1:** 0/10 **Group 2:** 3/10 **p value:** 0.2 (Fisher's exact calculated by NCC-AC)	
			Wound leakage	**Group 1:** 2/10 **Group 2:** 2/10 **p value:** 0.6 (Fisher's exact calculated by NCC-AC)	
			Shallow anterior chamber	**Group 1:** 1/10 **Group 2:** 1/10	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
				p value: 1 (Fisher's exact calculated by NCC-AC)	
			Hypotony (IOP between 4 and 6 mmHg)	**Group 1:** 0/10 **Group 2:** 1/10 **p value:** 1 (Fisher's exact calculated by NCC-AC)	

Abbreviations: NR=not reported, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, Sig=<0.05, IOP=intra-ocular pressure, POAG=primary open-angle glaucoma, MMC=mitomycin, 5-FU=5-Fluorouracil

Evidence Table 19 Viscocanalostomy vs. deep sclerectomy

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Egrilmez et al, 2004[40] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG **Setting:** single setting - Turkey **Inclusion criteria:** • POAG + Pigmentary glaucoma (PG) + Pseudoexfoliation glaucoma (PXF) • Uncontrolled IOP on maximal medical therapy **Exclusion criteria:** • Previous intraocular surgery • <21 years **<u>All patients</u>** **N:** 34 (34 eyes) randomised **Age (mean):** 61.7 ± 10.9 **M/F:** 21/13 **Mean IOP:** NR **Drop outs:** 4 (2 drop outs and 2 due to cataract surgery) **POAG:** 20 **PG:** 3 **PXF:** 7 **White:** 30 **<u>Group 1</u>** **N:** 12 **Age (mean):** 60.35 ± 12.96 **M/F:** NR **Mean IOP:** 31.09 ± 12.53 **Drop outs:** 1 **<u>Group 2</u>**	**Group 1** Trabeculectomy (Cairns) **Group 2** NDPS + T-flux non-absorbable implant **Group 3** Viscocanalostomy **Examination methods:** Baseline examinations included visual acuity, Humphrey VF measurement, biomicroscopy, gonioscopy, Goldmann tonometry, autokeratorefreactometry and corneal topography. Measurements of astigmatism, IOP and visual acuity at 1 day, 1 month, 3 months and 6 months Antimetabolites were not used	**Mean IOP ± SD at 6 months** **Mean change in IOP from baseline at 6 months**	**Group 1:** 15.09 ± 3.36 (n=11) **Group 2:** 14.13 ± 2.85 (n=8) **Group 3:** 17.28 ± 3.44 (n=8) **p value:** 0.103 Kruskal-Wallis test **Group 1:** 16.0 ± 11.23* **Group 2:** 11.91 ± 9.19* **Group 3:** 10.08 ± 3.92* **p value:** NR	**Funding:** NR (requested info from author but no response) **Limitations:** • Randomisation method was not clear • Allocation concealment was not reported • Masking of outcome assessment was not reported • No adverse events reported • IOP control is not the primary outcome **Additional outcomes:** Visual acuity Induced astigmatism **Notes:** *As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 10 **Age (mean):** 61.25 ± 10.67 **M/F:** NR **Mean IOP:** 27.00 ± 5.35 **Drop outs:** 2 (1 lost to follow up after 1 month and 1 cataract surgery) **<u>Group 3</u>** **N:** 12 **Age (mean):** 63.36 ± 9.68 **M/F:** NR **Mean IOP:** 27.36 ± 11.26 **Drop outs:** 1				intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Evidence Table 20 Non-penetrating surgery vs. trabeculectomy

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Carassa et al., 2003[19] **Study design:** RCT Single-blind Surgeon was masked to treatment allocation **Evidence level:** 1+ **Duration of follow-up:** 24 months	**Patient group:** COAG (POAG + Pseudoexfoliative glaucoma (PXF) **Setting:** single centre - Italy **Inclusion criteria:** • POAG or PXF • Uncontrolled IOP > 21 mmHg on maximal medical therapy or IOP ≤ 21 mmHg with intolerance to current medications or poor compliance • ≥ 45 years **Exclusion criteria:** • Other ocular disease including congenital glaucoma or angle closure glaucoma • Previous ocular surgery • Abnormality preventing reliable tonometry **<u>All patients</u>** **N:** 50 (50 eyes) **Age (mean):** NR **M/F:** 20/30 **Mean IOP:** NR **Drop outs:** 1 **<u>Group 1</u>** **N:** 25 eyes **Age (mean ± SD):** 68 ± 10.5 **M/F:** 10/15 **Mean ± SD IOP:** 22.88 ± 7.18	**Group 1** Trabeculectomy + 5FU ** **Group 2** Viscocanalostomy (Stegmann) **Examination methods:** Baseline IOP measured using slit lamp mounted applanation tonometer. Postoperative visits at 1 day, 1 week, 1, 2, 3 months and every months thereafter	**Mean IOP ± SD at 6 months**	**Group 1:** 12.76 ± 2.44 **Group 2:** 16.46 ± 4.96 **p value:**	**Funding:** Self funded (confirmed by author) **Limitations:** • Randomisation method was not reported • Masking of outcome assessment was not reported • Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve **Additional outcomes:** • Ocular discomfort score at 12 months • Reduction in visual acuity at end point **Notes:** **9 eyes received postoperative 5-FU injections and 2 eyes received argon laser suture lysis but these were allowed in treatment protocol and not considered as a treatment failure For group 2, any further intervention was
			Mean IOP ± SD reduction at 6 months	**Group 1:** 10.12 ± 6.32* **Group 2:** 8.29 ± 4.81*	
			Mean IOP ± SD at 12 months	**Group 1:** 13.04 ± 3.08 (n=25) **Group 2:** 16.38 ± 5.05 (n=24) **p value:** 0.01 (unpaired t-test) **signif.** *p = 0.0074 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean IOP ± SD reduction at 12 months	**Group 1:** 9.84 ± 6.24* **Group 2:** 8.37 ± 4.82*	
			Mean IOP ± SD at 24 months	**Group 1:** 14.04 ± 4.64 (n=25) **Group 2:** 16.29 ± 5.10 (n=24) **p value:** 0.11 (unpaired t-test) *p = 0.12 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean change in IOP from baseline at 24 months	**Group 1:** 8.76 ± NR **Group 2:** 8.46 ± NR **p value:** NR	
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications) at 12 months	**Group 1:** 80% (n=20) (22/25) **Group 2:** 76% (n=19) (19/25) **p value:** 0.6 (log rank test)	
			Kaplan-Meier cumulative % Failure to control IOP without medications at 12 months	**Group 1:** 3/25 **Group 2:** 6/25	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Visual acuity: 0.42 ± 0.3 **White:** 25 **Preoperative medications**: 3.06 (range 2-5) **POAG**: 22 **PXF**: 3 **Drop outs:** 0 **<u>Group 2</u>** **N:** 25 eyes **Age (mean ± SD):** 67.4 ± 15.8 **M/F:** 10/15 **Mean ± SD IOP:** 24.75 ± 6.73 **Visual acuity**: 0.56 ± 0.34 **White:** 25 **Preoperative medications**: 3.12 (range 2-5) **POAG**: 24 **PXF**: 1 **Drop outs:** 1 eye converted to trab but considered as withdrawal		**Kaplan-Meier cumulative % probability of IOP success (<16 mmHg without medications) at 24 months**	**Group 1:** 72% (n=18) **Group 2:** 56% (n=14) **p value:** 0.17 (log rank test)	considered a failure. * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.
			Number of eyes requiring re-operation (treatment failure)**	**Group 1:** 0/25 **Group 2:** 4/25 **p value:** NR *p = 0.12 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in both groups)*	
			Number of eyes requiring additional medications (treatment failure)**	**Group 1:** 5/25 **Group 2:** 2/25 **p value:** NR *p = 0.42 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in both groups)*	
			Hyphaema (1-2 mm)	**Group 1:** 1/25 (4%) **Group 2:** 3/24 (12.5%)	
			Hypotony	**Group 1:** 5/25 (20%) **Group 2:** 0/24 (0%)	
			Choroidals	**Group 1:** 1/25 (4%) **Group 2:** 0/25 (0%)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Chiselita, 2001[20] **Study design:** RCT Single Blind **Evidence level:** 1+ **Duration of follow-up:** 18 months	**Patient group:** POAG **Setting:** single centre - Romania **Inclusion criteria:** • Symmetrical POAG with uncontrolled IOP on maximal medical therapy • Both eyes > 23 mmHg on at least 2 medications • > 40 years old **Exclusion criteria:** • Asymmetrical POAG • Secondary OAG • Angle-closure glaucoma • Previous eye surgery • Previous argon laser treatment within 30 days **<u>All patients</u>** **N:** 17 (34 eyes) **Age (mean):** 60.17 ± 7.3 **M/F:** 9/8 **Mean IOP:** NR **Drop outs:** 0 **<u>Group 1</u>** **N:** 17 **Age (mean):** see above **M/F:** see above **Mean IOP:** 27.29 ± 2.08 **Visual Acuity:** 0.47 ± 0.26 **C/D Ratio:** 0.75 ± 0.11 **Drop outs:** 0	**Group 1** Trabeculectomy (Cairns) **Group 2** Non-penetrating Deep Sclerectomy **Examination methods:** ***Preoperative:*** Visual acuity, biomicroscopy, gonioscopy, Goldmann applanation tonometry, Humphrey VF analysis, fundus examination, C/D ratio ***Postoperative:*** Included visual acuity, Humphrey VF analysis, C/D ratio repeated every 3 months. Diurnal IOP curves measured at 1, 2, 3, 6, 12, 18 months. All measurements performed by same physician masked to allocation	**Mean IOP ± SD at 18 months**	**Group 1:** 17.27 ± 1.2 (n=17) **Group 2:** 20.90 ± 4.0 (n=17) **p value:** <0.0015 ANCOVA	**Funding:** NR **Limitations:** • Randomisation method unclear • Allocation concealment not reported • Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve **Additional outcomes:** Kaplan-Meier cumulative probability for achieving postoperative IOP >30% less than preoperative IOP **Notes:** No antimetabolite use or postoperative goniopuncture. Fellow eyes randomised * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from
			Mean IOP ± SD at 6 months	**Group 1:** 16.41 ± 1.8 **Group 2:** 19.17 ± 3.6	
			Mean change in IOP from baseline at 6 months	**Group 1:** 10.88 ± 1.96* **Group 2:** 8.53 ± 2.40*	
			Mean IOP ± SD at 12 months	**Group 1:** 16.78 ± 1.6 **Group 2:** 20.35 ± 4.5	
			Mean change in IOP from baseline at 12 months	**Group 1:** 10.51 ± 2.56* **Group 2:** 7.35 ± 3.35*	
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications) at 12 months	**Group 1:** 92.59% (16/17) **Group 2:** 44.57% (8/17) **p value:** 0.00034 (Cox's F Test) **signif.**	
			Kaplan-Meier cumulative % probability number of eyes with unacceptable IOP without medications at 12 months	**Group 1:** 1/17 **Group 2:** 9/17 **p value:**	
			Number requiring postoperative medications	**Group 1:** 6/17 **Group 2:** 9/17 **p value:** Not signif.	
			Hyphaema	**Group 1:** 7/17 **Group 2:** 0/17 **p value:** 0.003 (Chi-squared)	
			Inflammation	**Group 1:** 2/17 **Group 2:** 0/17	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 17 **Age (mean):** see above **M/F:** see above **Mean IOP:** 27.70 ± 2.22 **Visual Acuity:** 0.48 ± 0.23 **C/D Ratio:** 0.75 ± 0.12 **Drop outs:** 0			**p value:** not signif. (Chi-squared)	baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook.
			Cataract	**Group 1:** 4/17 **Group 2:** 0/17 **p value:** 0.0279 (Chi-squared)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Cillino et al., 2005[22] & Cillino et al., 2008[21] **Study design:** RCT Single Blind **Evidence level:** 1+ Single blind **Duration of follow-up:** 12 months	**Patient group:** POAG and pseudoexfoliative glaucoma (PXF) **Setting:** single centre - Itlay **Inclusion criteria:** • IOP > 21 mmHg on maximal medications • Visual field deterioration **Exclusion criteria:** • Cataract • Other ocular diseases • Previous eye surgery **<u>All patients</u>** **N:** 40 (40 eyes) **Age (mean):** NR **M/F:** 20/20 **Mean IOP:** NR **Drop outs:** 3 **<u>Group 1</u>** **N:** 21 **Age (mean):** 68.9 ± 6.4 **M/F:** 10/11 **Mean IOP:** 28.0 ± 6.0 **POAG:** 15 **PXF:** 6 **Drop outs:** 0 **<u>Group 2</u>** **N:** 22 **Age (mean):** 71.9 ± 7.1 **M/F:** 10/9	**Group 1** Punch Trabeculectomy (Crozafon-De Laage) + Mitomycin C (MMC) 0.2 mg/ml for 2 minutes **Group 2** Non-penetrating Deep Sclerectomy (DS) + Mitomycin C (MMC) 0.2 mg/ml for 2 minutes **Examination methods:** ***Preoperative:*** Goldmann applanation tonometry, Humphrey VF analysis, slit lamp examination ***Postoperative:*** IOP measured at each visit at 1 day, 1, 2, 3 weeks, 1, 3, 6, 9 & 12 months. Investigators were blinded	**Mean IOP ± SD at 6 months**	**Group 1:** 13.8 ± 4.0 **Group 2:** 14.4 ± 2.6 **p value:** 0.78 ANOVA	**Funding:** NR **Limitations:** • Allocation concealment not reported **Additional outcomes:** **Notes:** Author confirms use of computer to generate randomisation sequence NdYAG: goniopuncture was performed in 4/19 eyes in the DS group * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. **A paper with longer term data was published by the same
			Mean change in IOP from baseline at 6 months	**Group 1:** 14.2 ± 5.29* **Group 2:** 15.2 ± 4.39*	
			Mean IOP ± SD at 12 months	**Group 1:** 16.1 ± 3.8 (n=21) **Group 2:** 14.5 ± 4.0 (n=19) **p value:** 0.53 ANOVA	
			Mean change in IOP from baseline at 12 months	**Group 1:** 11.9 ± 6.94* **Group 2:** 15.1 ± 4.14* **p value:** NR	
			Mean IOP ± SD at 24 months**	**Group 1:** 16.9 ± 2.4 **Group 2:** 16.8 ± 3.4 **p value:** 0.99 ANOVA	
			Mean IOP ± SD at 48 months**	**Group 1:** 17.8 ± 3.6 **Group 2:** 17.6 ± 3.4 **p value:** 0.97 ANOVA	
			Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	**Group 1:** 15/21 (71%) **Group 2:** 15/19 (79%) **p value:** 0.72 (Fishers exact test)	
			Number of eyes with acceptable IOP (<17 mmHg without medications at 12 months	**Group 1:** 13/21 (62%) **Group 2:** 12/19 (63%) **p value:** 0.81 (Fishers exact test)	
			Failure to control IOP without medications at 12 months	**Group 1:** 6/21 **Group 2:** 3/19	
			Hypotony (<5 mmHg for > 2 weeks)	**Group 1:** 8/21 **Group 2:** 0/19 **p value:** 0.003 (Fishers exact test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Mean IOP: 29.6 ± 5.8 **POAG:** 12 **PXF:** 7 **Drop outs:** 3			**signif**	author in 2008[21]. The outcome data have been reported in this evidence table but they do not affect the main outcome data reported at 12 months.
			Hyphaema	**Group 1:** 9/21 **Group 2:** 4/19 **p value:** 0.26 (Fishers exact test)	
			Inflammation	**Group 1:** 4/21 **Group 2:** 1/19 **p value:** 0.49(Fishers exact test)	
			Flat anterior chamber	**Group 1:** 2/21 **Group 2:** 0/19 **p value:** 0.046 (Fishers exact test)	
			Shallow anterior chamber	**Group 1:** 7/21 **Group 2:** 1/19 **p value:** 0.046 (Fishers exact test)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Egrilmez et al, 2004[40] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG **Setting:** single setting - Turkey **Inclusion criteria:** • POAG + Pigmentary glaucoma (PG) + Pseudoexfoliative glaucoma (PXF) • Uncontrolled IOP on maximal medical therapy **Exclusion criteria:** • Previous intraocular surgery • <21 years **All patients** **N:** 34 (34 eyes) randomised **Age (mean):** 61.7 ± 10.9 **M/F:** 21/13 **Mean IOP:** NR **Drop outs:** 4 (2 drop outs and 2 due to cataract surgery) **POAG:** 20 **PG:** 3 **PXF:** 7 **White:** 30 **Group 1** **N:** 12 **Age (mean):** 60.35 ± 12.96 **M/F:** NR **Mean IOP:** 31.09 ± 12.53 **Drop outs:** 1 **Group 2** **N:** 10	**Group 1** Trabeculectomy (Cairns) **Group 2** NDPS + T-flux non-absorbable implant **Group 3** Viscocanalostomy **Examination methods:** Baseline examinations included visual acuity, Humphrey VF measurement, biomicroscopy, gonioscopy, Goldmann tonometry, autokeratorefreactometry and corneal topography. Measurements of astigmatism, IOP and visual acuity at 1 day, 1 month, 3 months and 6 months Antimetabolites were not used	**Mean IOP ± SD at 6 months** **Mean change in IOP from baseline at 6 months**	**Group 1:** 15.09 ± 3.36 (n=11) **Group 2:** 14.13 ± 2.85 (n=8) **Group 3:** 17.28 ± 3.44 (n=8) **p value:** 0.103 Kruskal-Wallis test **Group 1:** 16.0 ± 11.23* **Group 2:** 11.91 ± 9.19* **Group 3:** 10.08 ± 3.92* **p value:** NR	**Funding:** NR (requested info from author but no response) **Limitations:** • Randomisation method was not clear • Allocation concealment was not reported • Masking of outcome assessment was not reported • No adverse events reported • IOP control is not the primary outcome **Additional outcomes:** Visual acuity Induced astigmatism **Notes:** *As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 61.25 ± 10.67 **M/F:** NR **Mean IOP:** 27.00 ± 5.35 **Drop outs:** 2 (1 lost to follow up after 1 month and 1 cataract surgery) **<u>Group 3</u>** **N:** 12 **Age (mean):** 63.36 ± 9.68 **M/F:** NR **Mean IOP:** 27.36 ± 11.26 **Drop outs:** 1				similar enough to viscocanalostomy to produce an equivalent effect size.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
El Sayyad et al., 2000[41] **Study design:** RCT **Evidence level:** 1 + **Duration of follow-up:** 12 months	**Patient group:** POAG **Setting:** single centre – Saudi Arabia **Inclusion criteria:** • Symmetrical POAG with uncontrolled IOP > 21 mmHg on maximal medical therapy • > 35 years old **Exclusion criteria:** • Previous eye surgery • Patients with significant posterior segment eye disorders **<u>All patients</u>** **N:** 39 (78 eyes) **Age (mean):** 53.4 ± 9.6 **M/F:** 24/15 **Mean IOP:** NR **Drop outs:** 0 (patients failing sclerectomy procedure were replaced) **<u>Group 1</u>** **N:** 39 **Age (mean):** see above **M/F:** see above **Mean IOP:** 28.2 ± 4.7 **Pre-op glaucoma meds:** 2.6 ± 0.6 **Drop outs:** 0 **<u>Group 2</u>** **N:** 39 **Age (mean):** see above	**Group 1** Trabeculectomy **Group 2** Non-penetrating Deep Sclerectomy **Examination methods:** ***Preoperative:*** Visual Acuity, applanation tonometry, slit lamp examination & ophthalmoscopy ***Postoperative:*** Details of examinations not reported but measurements taken at 1 day, 1 week, 1 month then at 3, 6, 9 and 12 months	**Mean IOP ± SD at 6 months**	**Group 1:** 13.7 ± 5.4 (n=39) **Group 2:** 14.9 ± 4.3 (n=39) **p value:** 0.28 (unpaired t test)	**Funding:** NR **Limitations:** • Randomisation method was not clear • Allocation concealment was not reported • Masking of outcome assessment was not reported **Additional outcomes:** Postoperative glaucoma meds at 12 months **Group 1:** 0.27 ± 0.5 **Group 2:** 0.30 S 0.4 Visual Acuity (Snellen lines) at 12 months No significant difference **Notes:** Fellow eyes randomised Goniopuncture with Nd:YAG laser was performed in 4/39 eyes in NPDS group and Argon laser suture lysis was performed in 17/39 eyes in trabeculectomy group. 5-FU was used
			Mean change in IOP from baseline at 6 months	**Group 1:** 14.5 ± 5.1 **Group 2:** 13.2 ± 4.2 **p value:** 0.16 (unpaired t test)	
			Mean IOP ± SD at 12 months	**Group 1:** 14.1 ± 4.6 (n=39) **Group 2:** 15.6 ± 4.2 (n=39) **p value:** 0.13 (unpaired t test)	
			Mean change in IOP from baseline at 12 months	**Group 1:** 14.1 ± 6.4 **Group 2:** 12.3 ± 4.2 **p value:** 0.15 (unpaired t test)	
			Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	**Group 1:** 33/39 (85%) **Group 2:** 31/39 (79%) **p value:** 0.55 (Chi squared)	
			Failure to control IOP <21 mmHg without medications	**Group 1:** 6/39 **Group 2:** 8/39	
			Hyphaema	**Group 1:** 3/39 **Group 2:** 1/39 **p value:** 0.6 (Chi-squared)	
			Hypotony	**Group 1:** 1/39 **Group 2:** 0/39 **p value:** 0.9 (Chi-squared)	
			Intensive Uveitis	**Group 1:** 2/39 **Group 2:** 0/39 **p value:** 0.47 (Chi-squared)	
			Cataract	**Group 1:** 1/39 **Group 2:** 0/39 **p value:** 0.9 (Chi-squared)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: see above **Mean IOP:** 27.9 ± 5.9 **Pre-op glaucoma meds:** 2.4 ± 0.7 **Drop outs:** 0				postoperatively 17/39 eyes of the NPDS group and 15/39 in the trabeculectomy group

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Jonescu-Cuypers et al., 2001[67] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** POAG (all white patients) **Setting:** single centre - Germany **Inclusion criteria:** • Uncontrolled high tension glaucoma on maximal medications • IOP > 30 mmHg with or without medication • Glaucomatous damage defined by VF loss or progressive cupping **Exclusion criteria:** • Those with previous ocular surgery • Legally blind fellow eye • Corneal abnormalities preventing applanation tonometry **<u>All patients</u>** **N:** 20 patients (20 eyes) **Age (mean):** 62.5 ± 13.1 **M/F:** 11/9 **Mean IOP:** 29.65 ± 6.45 **Drop outs:** 0 **All white patients** **<u>Group 1</u>** **N:** 10 **Age (mean):** NR **M/F:** NR **Mean IOP:** 28.1 ± 5.84 **C/D ratio:** 0.67 ± 0.26 **Drop outs:** 0 **<u>Group 2</u>**	**Group 1** Trabeculectomy (Cairns modification) **Group 2** Viscocanalostomy (Stegmann)** **Examination methods:** ***Preoperative*** IOP measurement, visual acuity, gonioscopy, slit lamp biomicroscopy, indirect ophthalmoscopy of the retina, biomorphometry of papilla by laser scanning, VF testing with Humphrey and ultrasonography for scleral thickness. ***Postoperative*** IOP measurement, biomorphometry of papilla by laser scanning, VF testing with Humphrey. Examinations monthly for 6-8 months after surgery **2/10 in the viscocanalostomy group had trabeculectomies with mitomycin C and 1/10 in same group had a sclerectomy due to IOP spikes	**Mean postoperative IOP ± SD - Follow-up time not specified**	**Group 1:** 15.6 ± 3.17 (n=10) **Group 2:** 18.3 ± 5.03 (n=10) **p value:** NR *p = 0.17 2-sided t-test with equal variances calculated by NCC-AC as ITT (n=10 in both groups)*	**Funding:** NR (emailed author) **Limitations:** • Randomisation method not clear • Outcome assessment was not masked **Additional outcomes:** **Notes:** *As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.
			Mean change in IOP from baseline mean follow up of 6 months (range 6-8 months)	**Group 1:** 12.5 ± 5.06* **Group 2:** 12.29 ± 4.97* **p value:**	
			Number of eyes with acceptable IOP (<20 mmHg without medications or need for re-operation) at follow up of 6 months (range 6-8 months)	**Group 1:** 5/10 (50%) **Group 2:** 0/10 (0%) **p value:** NR *p = 0.03 2-sided Fishers exact test calculated by NCC-AC as ITT (n=10 in both groups)*	
			Failure to control IOP without medications or a need for further surgery at follow up of 6 months (range 6-8 months)	**Group 1:** 5/10 (50%) **Group 2:** 10/10 (100%)	
			Bleeding into conjunctiva	**Group 1:** 0/10 **Group 2:** 1/10 **p value:** NR	
			Leaking Bleb	**Group 1:** 1/10 **Group 2:** 0/10 **p value:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 10 **Age (mean):** NR **M/F:** NR **Mean IOP:** 31.2 ± 6.96 **C/D ratio:** 0.85 ± 0.13 **Drop outs:**				

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kobayashi et al., 2003[77] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG **Setting:** single setting - Japan **Inclusion criteria:** • IOP ≥ 22mmHg on maximal medical therapy **Exclusion criteria:** • Angle-closure, post-traumatic, uveitic, neovascular or dysgenetic glaucoma • Patients needing combined cataract procedures **<u>All patients</u>** **N:** 25 (50 eyes) **Age (mean):** 62..5 ± 7.4 **M/F:** 11/14 **Mean IOP:** NR **Drop outs:** 0/25 **<u>Group 1</u>** **N:** 25 eyes **Age (mean):** see above **M/F:** see above **Mean IOP:** 24.8 ± 2.6 **VF Mean Deviation:** -12.81 ± 5.6 **Drop outs:** 0 **<u>Group 2</u>** **N:** 25 eyes **Age (mean):** see above **M/F:** see above **Mean IOP:** 25.0 ± 2.2	**Group 1** Trabeculectomy (Cairns) with 0.04% MMC sponges after dissection Laser suture lysis was performed if bleb was flat or target IOP not reached **Group 2** Viscocanalostomy (Stegmann) Goniopuncture with Nd:YAG laser performed after if target pressure not reached **Examination methods:** ***Baseline examinations:*** Humphrey VF test, gonioscopy, scanning laser tomography. IOP measured at 3 visits in 2 week period prior to study and 3 measurements averaged. ***Postoperative examinations:*** Patients reviewed at 1, 3 days, 1, 2 weeks and 1, 2, 3, 4, 5, 6, 9, 12 months after surgery.	**Mean IOP ± SD at 6 months**	**Group 1:** 11.8 ± 4.6 (n=25) **Group 2:** 16.9 ± 2.8(n=25) **p value:** <0.0001 student t-test	**Funding:** Self-funded. **Limitations:** • Allocation concealment was not reported • Masking of outcome assessment was not reported **Additional outcomes:** VF change as Mean Deviation at 12 months **Group 1**: -0.30 ± 0.85 **Group 2**: -0.21 ± 0.28 Change in visual acuity at 12 months **Notes:** Eyes randomised. Patient received viscocanalostomy in 1 eye and trabeculectomy in the fellow eye. "nd procedure was performed 1-2 weeks after the first. 14/25 (56%) viscocanalostomy eyes received goniopuncture with Nd:YAG laser post surgery.
			Mean change in IOP from baseline at 6 months	**Group 1:** 13.0 ± 5.4 **Group 2:** 8.1 ± 3.5 **p value:** <0.0001 student t-test **signif.** *p = 0.0005 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean IOP ± SD at 12 months	**Group 1:** 12.6 ± 4.3 (n=25) **Group 2:** 17.1 ± 1.5 (n=25) **p value:** <0.0001 student t-test	
			Mean change in IOP from baseline at 12 months	**Group 1:** 12.3 ± 5.2 **Group 2:** 7.8 ± 3.1 **p value:** <0.0001 student t-test **signif.** *p = 0.0006 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Number of eyes with acceptable IOP (<20 mmHg & change in IOP or >30% without medications) at 12 months	**Group 1:** 22/25 (88%) **Group 2:** 15/25 (60%) **p value:** 0.024 (Chi-squared) *p = 0.051 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in both groups)*	
			IOP < 16 mmHg without medication at 12 months	**Group 1:** 20/25 (80%) **Group 2:** 10/25 (40%) **p value:** 0.0039 (Chi-squared) *p = 0.009 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in both groups)*	
			Failure to control IOP without medications or a need for further surgery at 12 months	**Group 1:** 3/25 **Group 2:** 10/25	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	VF Mean Deviation: -13.72 ± 4.97 **Drop outs:** 0	3 IOP measurements taken in each eye and mean used. Optic nerve was examined with Goldmann lens and tomography performed at 1 year interval. V F measured at 6 months and 12 months.	**Complete failure defined by need for further surgery or loss of Visual Function**	**Group 1:** 0/25 **Group 2:** 1/25 **p value:** Not signif.	
			Hypotony	**Group 1:** 5/25 (20%) **Group 2:** 0/25 **p value:** 0.0184 (Chi-squared).	
			Hypaema	**Group 1:** 4/25 (16%) **Group 2:** 0/25 **p value:** 0.0371	
			Failed Bleb	**Group 1:** 2/25 (8%) **Group 2:** NR **p value:** NR	
			Bleb Formation	**Group 1:** NR **Group 2:** 5/25 **p value:** NR	
			Cataract formation	**Group 1:** 2/25 **Group 2:** 0/25 **p value:** Not signif.	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Luke et al., 2002[90] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG, pseudoexfoliative glaucoma (PXF) & pigmentary glaucoma (PG) **Setting:** single centre - Germany **Inclusion criteria** • Uncontrolled IOP on maximal medications • >21 years old **Exclusion criteria:** • Previous ocular surgery **<u>All patients</u>** **N:** 60 (60 eyes) **Age (mean):** 61.4 ± 17.6 **M/F:** 57/31 **Mean IOP:** 27.1 ± 7.1 **Drop outs:** 0 **POAG:** 33 **PXF:** 20 **PG:** 7 **<u>Group 1</u>** **N:** 30 **Age (mean):** NR **M/F:** NR **Mean IOP:** 26.9 ± 7.4 **Drop outs:** 0 **Number of Medications:** 2.5 ± 1.1 **<u>Group 2</u>** **N:** 30 **Age (mean):** NR **M/F:** NR **Mean IOP:** 27.2 ± 6.9	**Group 1** Trabeculectomy (Cairns) **Group 2** Viscocanalostomy **Examination methods:** ***Preoperative:*** Visual acuity, VF examination using Humphrey, biomicroscopy, gonioscopy, Goldmann applanation tonometry ***Postoperative:*** Visual acuity, VF examination using Humphrey, biomicroscopy, gonioscopy, Goldmann applanation tonometry performed daily for 1 week, then at 1, 6, 12 months Laser suture lysis was performed on 11/30 eyes in trabeculectomy group if IOP was uncontrolled	**Mean IOP ± SD at 6 months**	**Group 1:** 15.5 ± 3.0 **Group 2:** 16.0 ± 4.1 **p value:** 0.15 student t-test	**Funding:** Not reported **Limitations:** • Randomisation method is unclear • Allocation concealment was not reported • Masking of outcome assessment was not reported • Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve **Additional outcomes:** **Notes:** *As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter
			Mean change in IOP from baseline at 6 months	**Group 1:** 16.78 ± 6.45* **Group 2:** 11.2 ± 4.98* **p value:** NR	
			Mean IOP ± SD at 12 months	**Group 1:** 15.0 ± 3.5 **Group 2:** 17.1 ± 5.4 **p value:** 0.15 student t-test	
			Mean change in IOP from baseline at 12 months	**Group 1:** 11.9 ± 6.41* **Group 2:** 10.1 ± 3.87* **p value:** NR	
			Kaplan-Meier cumulative % probability of IOP success (<22 mmHg without medications) at 12 months	**Group 1:** 56.7% (n=30) (17/30) **Group 2:** 30% (n=30) (9/30) **p value:** 0.041 (log rank test) **signif.**	
			Kaplan-Meier cumulative % probability of number of eyes with unacceptable IOP without medications or a need for further surgery at 12 months	**Group 1:** 13/30 **Group 2:** 21/30	
			Hyphaema	**Group 1:** 8/30 (26.7%) **Group 2:** 3/30 (10%) **p value:** 0.095 (Chi-squared)	
			Hypotony (<6 mmHg)	**Group 1:** 11/30 (36.7%) **Group 2:** 6/30 (20%) **p value:** 0.152 (Chi-squared)	
			Cataract Progression	**Group 1:** 2/30 (6.7%) **Group 2:** 0/30 **p value:** 0.15 (Chi-squared)	
			Bleb formation	**Group 1:** 30/30 **Group 2:** 17/30	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 0 **Number of Medications:** 2.9 ± 0.9			**p value:** <0.001 (Chi-squared)	intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Yalvac et al., 2004[163] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 36 months (mean follow up 18 months range 6-38)	**Patient group:** POAG **Setting:** single centre - Turkey **Inclusion criteria:** • Uncontrolled POAG on maximal medical therapy **Exclusion criteria:** • Congenital glaucoma, angle closure glaucoma, neovascular glaucoma, traumatic glaucoma & uveitic glaucoma • Previous ocular surgery **<u>All patients</u>** **N:** 50 (50 eyes) **Age (mean):** NR **M/F:** 36/14 **Mean IOP:** NR **Drop outs:** 0 **<u>Group 1</u>** **N:** 25 eyes **Age (mean ± SD):** 66.8 ± 10.2 **M/F:** 19/6 **Mean ± SD IOP:** 37.7 ± 9.0 **Preoperative medications:**: 3 (range 2-4) **Drop outs:** 0 **<u>Group 2</u>** **N:** 25 eyes **Age (mean ± SD):** 63.6 ± 12.6 **M/F:** 17/8	**Group 1** Trabeculectomy (Cairns) **Group 2** Viscocanalostomy (similar to Stegmann) **Examination methods:** ***Preoperative:*** IOP measurement by applanation tonometry, visual acuity, gonioscopy, slit lamp biomiscroscopy, indirect ophthalmoscopy of the optic nerve, VF examination using Humphrey 24-2. ***Postoperative:*** IOP measurement by Goldmann applanation tonometry, visual acuity, gonioscopy, slit lamp biomiscroscopy, fundoscopy Patients were examined at 1 day, 1 week, 1, 3 & 6 months, 1, 2 & 3 years. No antimetabolites were used	**Mean IOP ± SD at 6 months**	**Group 1:** 16.0 ± 5.3 (n=25) **Group 2:** 18.1 ± 5.2 (n=25) **p value:** 0.206 (unpaired t-test) *p = 0.16 2-sided t-test with equal variances calculated by NCC-AC as ITT (n=25 in both groups)*	**Funding:** NR (requested info from author but no response) **Limitations:** • Randomisation method was not clear • Allocation concealment not reported • Masking of outcome assessment was not reported • Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve **Notes:** * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep
			Mean change in IOP from baseline at 6 months	**Group 1:** 24.1 ± 7.84* (n=25) **Group 2:** 15.7 ± 5.73* (n=25)	
			Mean IOP ± SD at 12 months	**Group 1:** 16.3 ± 3.9 (n=25) **Group 2:** 20.3 ± 5.6 (n=25) **p value:** 0.027 (unpaired t-test) **signif.** *p = 0.005 2-sided t-test with equal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean change in IOP from baseline at 12 months	**Group 1:** 24.1 ± 7.82* (n=25) **Group 2:** 15.7 ± 5.71* (n=25)	
			Mean IOP ± SD at 24 months	**Group 1:** 18.6 ± 4.3 (n=25) **Group 2:** 21.6 ± 10.8 (n=25) **p value:** 0.43 (unpaired t-test) *p = 0.21 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean IOP ± SD at 36 months	**Group 1:** 16.0 ± 7.1 (n=25) **Group 2:** 17.8 ± 4.6 (n=25) **p value:** 0.69 (unpaired t-test) *p = 0.29 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications)	**Group 1:** 17/25 66.2% **Group 2:** 13/25 52.9% **p value:** 0.311 (log rank test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Mean ± SD IOP: 36.0 ± 8.0 **Preoperative medications:** 3.1 (range 2-4) **Drop outs:** 0		**at 6 months**		sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size. **Additional outcomes:** Visual acuity change
			Kaplan-Meier cumulative % probability of number of eyes with unacceptable IOP without medications or need for further surgery at 6 months	**Group 1:** 8/25 **Group 2:** 12/25	
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications) at 3 years	**Group 1:** 14/25 55.1% **Group 2:** 9/25 35.3% **p value:** 0.228 (log rank test)	
			Number of eyes requiring additional medications postoperatively	**Group 1:** 10/25 (40%) **Group 2:** 13/25 (52%) *p = 0.40 2-sided Fishers calculated by NCC-AC as ITT (n=25 in both groups)*	
			Transient early Hypotony IOP < 5 mmHg	**Group 1:** 7/25 (28%) **Group 2:** 1/25 (4%) **p value:** 0.002 (Chi-squared) **signif.** *p = 0.049 2-sided Fishers calculated by NCC-AC as ITT (n=25 in both groups)*	
			Hyphaema	**Group 1:** 2/25 (8%) **Group 2:** 1/25 (4%)	
			Bleb encapsulation	**Group 1:** 3/25 (12%) **Group 2:** 1/25 (4%)	
			Cataract	**Group 1:** 7/25 (28%) **Group 2:** 2/25 (8%) **p value:** 0.002 (Chi-squared) **signif.** *p = 0.14 2-sided Fishers calculated by NCC-AC as ITT (n=25 in both groups)*	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Yarangumeli et al., 2005[164] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG, chronic angle closure glaucoma (CACG) and pseudoexfoliative glaucoma (PXF) **Setting:** single centre - Turkey **Inclusion criteria:** • Uncontrolled high tension glaucoma on maximal medications **Exclusion criteria:** • High risk patients requiring antimetabolites such as those with previous ocular surgery • Secondary or developmental glaucoma • < 40 years old • History of ocular inflammation or trauma **All patients** **N:** 22 (44 eyes) **Age (mean):** 64.3 ± 10.5 **M/F:** 12/10 **Mean IOP:** NR **Drop outs:** 0 **POAG:** 7 **PXF:** 11 **CACG:** 4 **Group 1** **N:** 22 **Age (mean):** see above **M/F:** see above **Mean IOP:** 39.3 ± 11.9	**Group 1** Trabeculectomy (Cairns/Watson modification) **Group 2** Viscocanalostomy (Stegmann) **Examination methods:** IOP measured by Goldmann tonometry by same observer. Preoperatively and at 1, 2, 4 and 12 weeks postoperatively then every 3 months for 1st year and 6 month intervals thereafter. No antimetabolites in either group	**Mean IOP ± SD at 6 months**	**Group 1:** 9.6 ± 3.8 **Group 2:** 12.6 ± 4.0 **p value:** 0.026 (repeated measures ANOVA)	**Funding:** Self-funded (confirmed by author) **Limitations:** • **4/22 patients had CACG but these were excluded from the Number of patients with unacceptable IOP results • Outcome assessment was not masked **Additional outcomes:** • Diffuse elevated blebs • Thin walled, multi-cystic blebs • Low-lying, localised blebs **Notes:** One eye randomised using coin tossing to first treatment group. Less than 2 months later fellow eye received remaining procedure. Eye to be randomised to 1st treatment was the one with most severe glaucoma, otherwise coin used to select eye. * As standard deviations for the change in IOP from baseline were not reported they were imputed using
			Mean change in IOP from baseline at 6 months	**Group 1:** 29.7 ± 10.53* **Group 2:** 26.0 ± 9.89* **p value:**	
			Mean IOP ± SD at 12 months	**Group 1:** 9.6 ± 3.8 **Group 2:** 12.6 ± 4.0 **p value:** 0.026 (repeated measures ANOVA)	
			Mean change in IOP from baseline at 12 months	**Group 1:** 29.7 ± 10.53* **Group 2:** 26.0 ± 10.41* **p value:**	
			Number of eyes with acceptable IOP (<18 mmHg without medications) at 12 months	**Group 1:** 14/22 (64%) **Group 2:** 13/22 (59%) **p value:** 0.75 (Chi-squared)	
			Number of eyes with unacceptable IOP without medications at 12 months	**Group 1:** 7/18** **Group 2:** 8/18**	
			Hyphaema	**Group 1:** 1/22 **Group 2:** 1/22 **p value:** NR	
			Persistent hypotony	**Group 1:** 2/22 **Group 2:** 1/22 **p value:** NR	
			Cataract progression	**Group 1:** 7/22 **Group 2:** 2/22 **p value:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 0 **<u>Group 2</u>** **N:** 22 **Age (mean):** see above **M/F:** see above **Mean IOP:** 38.6 ± 12.5 **Drop outs:** 0				correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Evidence Table 21 Non-penetrating surgery plus augmentation vs. non-penetrating surgery

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Neudorfer et al., 2004[111] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** At least 24 months. Clinical visits that extended longer than 27 months were considered as 2 year postoperative follow ups.	**Patient group:** POAG **Setting:** single centre - Israel **Inclusion criteria:** Open angle glaucoma patients: • IOP ≥ 22 mmHg with maximal medications • Glaucomatous disc cupping • Visual field defect • Open angles on gonioscopy **Exclusion criteria:** • Secondary glaucoma, neovascular or juvenile glaucomas • iridocorneal endothelial syndrome • uveitis **<u>All patients</u>** **N:** 26 (26 eyes) **Age (mean ± SD):** NR **M/F:** 13/13 **Mean IOP:** **Drop outs:** 0 **<u>Group 1</u>** **N:** 13 **Age (mean ± SD):** 65.8 ± 6.8 **M/F:** 5/8 **Mean IOP:** 26.5 ± 2.5 **Drop outs:** 0	**Group 1** Deep Sclerectomy with collagen implant only **Group 2** Deep Sclerectomy with collagen implant + MMC 0.3mg/ml for 3 minutes **Examination methods:** IOP. Best corrected visual acuity for distance based on the results of retinoscopy and manifest refraction.	**Mean preoperative IOP**	**Group 1:** 26.5 ± 2.5 **Group 2:** 31.5 ± 5.7 **p value: significant**	**Funding:** NR **Limitations:** • Mean preoperative IOP significantly higher in the MMC group than in control despite randomisation. • Patients receiving MMC had been taking significantly greater mean number of medications preoperatively. • Study was underpowered to detect a difference between the groups • Randomisation method, allocation concealment and masking of outcome assessment were not reported **Additional outcomes:** **Visual acuity deterioration (>2 lines on the Snellen chart)** Group 1: 0/13 Group 2: 0/13
			Mean IOP at 12 months	**Group 1:** 17.2 ± 3.9 **Group 2:** 15.6 ± 3.5 **p value:** significant baseline-12 months for each group not between groups	
			IOP % difference from baseline to 12 months	**Group 1:** 34.8 ± 15.3 **Group 2:** 47.8 ±18.1 **p value:** not significant between groups	
			Mean IOP at 24 months	**Group 1:** 17.8 ± 2.8 **Group 2:** 15.8 ± 5.6 **p value:** significant baseline-24 months for each group not between groups	
			IOP % difference from baseline to 24 months	**Group 1:** 32.1 ± 12.2 **Group 2:** 48.1 ± 17.2 **p value:** p = 0.01 significant	
			IOP success <21 mmHg without medications	**Group 1:** 5/13 **Group 2:** 4/13 **p value:** not significant	
			Number of patients with unacceptable IOP ≥ 21 mmHg (with or without meds) at 12 months	**Group 1:** 2/13 **Group 2:** 0/13	
			Number of patients with unacceptable IOP ≥ 21 mmHg (with or without meds) at 24 months	**Group 1:** 1/13 **Group 2:** 1/13	
			Mean number of medications at baseline	**Group 1:** 2.9 ± 0.6 **Group 2:** 3.7 ± 0.6 **p value:** p < 0.05 significant	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 13 **Age (mean ± SD):** 68.1 ± 8 **M/F:** 8/5 **Mean IOP:** 31.5 ± 5.7 **Drop outs:** 0		**Mean number of medications at 12 months**	**Group 1:** 1.3 ± 1.2 **Group 2:** 1.8 ± 1.5 **p value:** significant baseline-12 months for each group not between groups	**Visual acuity deterioration (1 line on the Snellen chart due to cataract formation)** Group 1: 1/13 Group 2: 2/13 **Notes:**
			Mean number of medications at 24 months	**Group 1:** 1.8 ± 0.9 **Group 2:** 2.0 ± 1.5 **p value:** significant baseline- 24 months for each group not between groups	
			Complications at 24 months	**Postoperative Hyphaema** Group 1: 1/13 Group 2: 2/13 **Filtering blebs** Group 1: 2/13 Group 2: 3/13 Neither bleb leak nor hypotony were present in any of the patient groups.	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Evidence Table 22 Service Provision

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Azuara-Blanco et al., 2007[6] **Study design:** Prospective observational Observer masked	**Patient group:** 671 referrals from community optometrists in Grampian, Scotland. **Inclusion criteria:** >18 years **<u>All patients</u>** **N:** 100 (165 randomised, 65 chose not to participate) **Age (mean):** 67 **M/F:** 52/48 **Mean IOP (mmHg):** 26 **Family history:** 24 **Black:** 1 **Glaucoma diagnosis (management decisions **) by consultant** 1. Normal & discharged: **35** 2. Suspect or OHT requiring review: **32** 3. Suspect or OHT requiring treatment: **8** 4. Glaucoma: **23** 5. Glaucoma requiring urgent treatment: **2**	**Group 1:** 3 community optometrists (CO) that had received in-house training by a consultant ophthalmologist and glaucoma specialist as part of glaucoma optometric service. Training included practical sessions, glaucoma clinics, teaching on diagnostic interventions **Group 2:** Junior (trainee) ophthalmologist **Group 3:** Consultant ophthalmologist **Examination methods:** Each CO examined all 671 referrals for: • Visual acuity (Snellen chart) • VF (threshold strategy 24-2 SITA) • Corneal thickness (ultrasound pachymetry) • Slit lamp biomicroscopy to assess anterior segment and optic disc • Goldmann tonometry • Gonioscopy • Refraction • Risk factors The junior doctor and consultant ophthalmologist examined the 100 patients randomised into the study in	**Inter-observer** (consultant-optometrist) **agreement for *all management decisions* (1-5)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.53** (0.39 - 0.67) **(moderate)** 95% CI calculated by NCC-AC using SE 0.07 from study	**Funding:** Scottish Executive Health Department **Limitations:** The method of weighting of the kappa statistic was not clearly defined and the kappa value agreement scale was not mentioned. It was assumed to be from (Landis and Koch 1977) **Additional Outcomes:** **Notes:** The community optometrists were masked to randomised patient selection. Participants were required not to disclose details of previous consultations.
			Inter-observer (junior doctor–consultant) **agreement for *all management decisions* (1-5)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.45** (0.31 - 0.59) **(moderate)** 95% CI calculated by NCC-AC using SE 0.07 from study	
			Inter-observer (junior doctor–optometrist) **agreement for *all management decisions* (1-5)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.45** (0.31 - 0.59) **(moderate)** 95% CI calculated by NCC-AC using SE 0.07 from study	
			Inter-observer (consultant-optometrist) **agreement for *diagnosis* of glaucoma (4-5 v 1-3)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.70** (0.54 - 0.87) **(substantial)** 95% CI calculated by NCC-AC using SE 0.083 from study	
			Inter-observer (junior doctor–consultant) **agreement for *diagnosis* of glaucoma (4-5 v 1-3)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.54** (0.35 - 0.73) **(moderate)** 95% CI calculated by NCC-AC using SE 0.098 from study	
			Inter-observer (junior doctor–optometrist) **agreement for *diagnosis* of glaucoma (4-5 v 1-3)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.22** (0.02 - 0.42) **(fair)** 95% CI calculated by NCC-AC using SE 0.101 from study	
			Inter-observer (consultant-optometrist) **agreement for *treatment required* (3-5 v 1-2)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.72** (0.57 - 0.86) **(substantial)** 95% CI calculated by NCC-AC using SE 0.076 from study	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		the hospital out patient department with same tests except for IOP measurements	**Inter-observer** (junior doctor–consultant) **agreement for *treatment required* (3-5 v 1-2)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.55** (0.37 - 0.73) **(moderate)** 95% CI calculated by NCC-AC using SE 0.09 from study	
			Inter-observer (junior doctor–optometrist) **agreement for *treatment required* (3-5 v 1-2)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.62** (0.45 - 0.79) **(substantial)** 95% CI calculated by NCC-AC using SE 0.088 from study	
			Diagnosis of glaucoma (with reference standard defined by consultant)	**Group 1** Sensitivity: **0.76** (95% CI: 0.57-0.89) Specificity: **0.93** (95% CI: 0.85-0.97) **Group 2** Sensitivity: **0.66** (95% CI: 0.48-0.81) Specificity: **0.89** (95% CI: 0.80-0.95)	
			Treatment of glaucoma (with reference standard defined by consultant)	**Group 1** Sensitivity: **0.73** (95% CI: 0.57-0.85) Specificity: **0.96** (95% CI: 0.88-0.99) **Group 2** Sensitivity: **0.64** (95% CI: 0.47-0.78) Specificity: **0.90** (95% CI: 0.80-0.95)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat e**tc**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments

Banes et al., 2000[8]
 	
Study design: Prospective observational
 	
Observer masked
	Patient group: patients from general glaucoma clinic. Moorfields Eye Hospital
	Some patients had other ocular pathologies. Most patients had a diagnosis of POAG and were on medical treatment
	
	Inclusion criteria:
	NR
	
	<u>All patients</u>
	N: 54
	Age (mean): NR
	M/F: NR
	No demographic data was reported
		Group 1:
		1 senior optometrist
		
		Group 2:
		1 general ophthalmologist (research fellow)
		
		Examination methods:
		Visual fields were carried out by a technician before assessment.
		Both optometrist and research fellow carried out the following:
		• Clinical history of medication including adverse events
		• Slit lamp biomicroscopy to assess anterior segment and optic disc
		  ○ VCD
		  ○ Drawing of disc
		  ○ Haemorrhages
		  ○ Disc size
		• VF (24-2) plots were considered
		  ○ Stable
		  ○ Progressive
		  ○ Non-glaucoma
		  ○ Unreliable
		• Goldmann tonometry
		• Gonioscopy
		• Management of patient according to clinical state was assessed
		  ○ Continue with treatment
		  ○ Change treatment
		  ○ Stop treatment
		  ○ Consider surgery
		• Length of time to next
			Inter-observer agreement for visual field assessment (right eyes)
			kappa statistic κ* (% agreement)
				= **0.81 (very good)** (92%)
				(3 eyes had missing data and 4 eyes were disagreed upon)
					Funding:
					NR
					
					Limitations:
					• No confidence intervals for kappa
					• The kappa value agreement scale was not mentioned. It was assumed to be from (Landis and Koch 1977)
					
					Additional Outcomes:
					
					Notes:
					* kappa was calculated excluding missing values
					Patients were randomly distributed to optometrist and research fellow by clerk but the optometrist did not see any postoperative or complicated cases.

			Inter-observer agreement for visual field assessment (left eyes) kappa statistic κ* (% agreement)	= **0.80 (good)** (91%)	
			Inter-observer agreement for management recommendations (right eyes) kappa statistic κ* (% agreement)	= **1.00 (very good)** (100%) (Group 2 had not recorded data for 3 eyes)	
			Inter-observer agreement for management recommendations (left eyes) kappa statistic κ* (% agreement)	= **0.93 (very good)** (98%) (6 eyes had missing data and 1 eye was disagreed upon)	
			Inter-observer agreement for follow up recommendations kappa statistic κ* (% agreement)	= **0.97 (very good)** (98%) (5 eyes had missing data and 1 eye was disagreed upon)	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		appointment ○ < 2 months ○ 3 months ○ 6 months ○ 1 year ○ Discharge			The research fellow was masked to the observations of the optometrist

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Banes et al., 2006[7] **Study design:** Prospective + Retrospective observational study	**Patient group:** 350 patients attending glaucoma outpatient services at Moorfields, UK **Inclusion criteria:** • Diagnosis of glaucoma (POAG, CACG, secondary and NTG) or OHT **Exclusion criteria:** • New and postoperative patients **<u>All patients</u>** **N:** 350 **Age (median):** NR **M/F:** NR Dropouts: 1 (one hospital record could not be retrieved) No demographic data was reported	**Group 1** 4 certified optometrists with a College of Optometry diploma in glaucoma in hospital setting with patient assessment and management experienced gained from 3 – 10 years of 1-2 half day sessions/week. Training consisted of patient assessments in supportive environment with access to an ophthalmologist. **Group 2** 3 medical clinicians (associate specialists) working part-time in glaucoma clinics for ≥ 10 years **Group 3** 2 consultant ophthalmologists **retrospectively** reviewed the patient records and clinical decisions and made independent management decisions **Examination methods:** Optic disc assessment for glaucomatous damage or normal disc was performed independently of the main study using 134 stereo pairs of disc photographs. Results were compared to previously published data. All patients had a visual field test performed by a technician before clinical assessment. The optometrists	**Detection of glaucomatous disc** using 134 stereo pairs (with glaucomatous damage defined checking against previously published data)	**Group 1** Sensitivity: range 77.8% - 88.2% Specificity: range 76.0% - 79.0% **Group 2** Sensitivity: range 64.7% - 74.2% Specificity: range 82.3% - 93.0%	**Funding:** NR **Limitations:** Mean kappa statistic not reported with confidence intervals **Additional outcomes:** **Notes:** Patients allocated by clinic clerk on a sequential basis to specialist ophthalmologist or optometrist (50 patients each) ***Weighted kappa statistic κ_w** Weights assigned for time to next clinical appointment: 1.0 = agreement; 0.75 = 1 step away disagreement; 0.5 = 2 steps away disagreement ; 0.25 = 3 steps away disagreement, 0 = 4 steps away disagreement and disagreement for discharge and missing data
			Inter-observer agreement for visual field status (kappa statistic & % agreement)	**Group 3 (Consultant 1) v Group 1** κ = 0.33 **fair** (55%) **Group 3 (Consultant 2) v Group 1** κ = 0.27 **fair** (54%) Mean κ = **0.30 fair** **Group 3 (Consultant 1) v Group 2** κ = 0.22 **fair** (44%) **Group 3 (Consultant 2) v Group 2** κ = 0.21 **fair** (43%) Mean κ = **0.22 fair**	
			Inter-observer agreement for clinical management 1 (kappa statistic & % agreement)	**Consultant 1 v Group 1** (certified optometrists) κ = 0.67 **good** (79%) N=199 (3% missing data) **Consultant 1 v Group 2** (general ophthalmologists) κ = 0.52 **moderate** (71%) N=150 (5.3% missing data)	
			% agreement for clinical management 2	Consider cataract surgery: **Group 3 (Consultant 1) v Group 1** 94% **Group 3 (Consultant 1) v Group 2** 91% Consider glaucoma surgery: **Group 3 (Consultant 1) v Group 1** 95% **Group 3 (Consultant 1) v Group 2** 99% Reinforce Compliance: **Group 3 (Consultant 1) v Group 1** 97% **Group 3 (Consultant 1) v Group 2** 99% Discuss with consultant:	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		and medical clinicians then performed a structured clinical assessment on each of their 50 patients then used the clinical data to make management decisions on 5 aspects of patient care: 1. Visual field status (stable, progression, unreliable, non-glaucoma, other) 2. Clinical management 1 (no treatment, continue, start/increase treatment, reduce) 3. Clinical management 2 (consider glaucoma surgery, consider cataract surgery, change treatment due to intolerance, reinforce compliance, discuss with consultant) 4. Planned tests (disc photographs, HRT, VF, IOP phasing 5. Time to next appointment in months (1-2, 3, 6 9 12, discharge)		**Group 3 (Consultant 1) v Group 1** 72% **Group 3 (Consultant 1) v Group 2** 81%	Kappa value agreement 0.00 to 0.2 = poor 0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = good 0.81 to 1.00 = very good
			% agreement for planning of tests	Visual Field: **Group 3 v Group 1** mean 62% (C1 & C2) **Group 3 v Group 2** mean 54% (C1 & C2) Imaging: **Group 3 v Group 1** mean 73% (C1 & C2) **Group 3 v Group 2** mean 61% (C1 & C2) Phasing: **Group 3 v Group 1** mean 98% (C1 & C2) **Group 3 v Group 2** mean 100% (C1 & C2) Disc Photo: **Group 3 v Group 1** mean 91% (C1 & C2) **Group 3 v Group 2** mean 100% (C1 & C2)	
			Next clinic appointment weighted kappa statistic κ_w * and % agreement	**Group 3 (Consultant 1) v Group 1** (certified optometrist) κ_w = 0.35 **fair** (79%) **Group 3 (Consultant 1) v Group 2** (general ophthalmologist) κ_w = 0.29 **fair** (73%)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Harper et al., 2000[56] **Study design:** Retrospective observational study	**Patient group:** 48 optic disc stereophotographs retrospectively selected from of glaucomatous and non glaucomatous patients attending glaucoma service in Greenwich Hospital, UK **Inclusion criteria:** Photographs that were representative of a wide range of disc appearances classified using a visual analogue scale (VAS) 0= definitely non-glaucomatous and 100= definitely glaucomatous by a glaucoma specialist. Matched visual field data was not available for the stereophotographs **<u>All patients</u>** **N:** 48 **Age (median):** NR **M/F:** NR **Glaucomatous damage (defined by VAS**): • **Definitely non-glaucomatous ≤10):** 11 • **Definitely glaucomatous ≥90):** 15 • **Suspicious (11-89):** 22 Patient demographics were not reported	**Group 1** 3 optometrists with 4 years accredited training ≥ 4 years post registration experience. None had specialist shared care expertise **Group 2** 2 general ophthalmologists. One SPR and one associate specialist in medical ophthalmology. Neither had sub-speciality training although the associate specialist had responsibility for reporting on fundus/disc photographs **Examination methods:** Photographs had been taken with a standard fundus camera with stereopsis achieved through decentration of camera angle. They were examined through a Carl-Zeiss 2x stereoscopic viewer and standard light box Each observer 1. Estimated vertical cup disc ratio (VCD) 2. Grading of narrowest rim width estimate 3. Haemorrhage present or absent Also graded using simple ranking/ordinal scales	**Inter-observer (ophthal-optom) agreement in estimating VCD** **weighted kappa statistic κ_w *** **Inter-observer (ophthal-optom) agreement in estimating VCD** **1 x standard deviation of difference scores** **Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio** **weighted kappa statistic κ_w *** **Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio** **1 x standard deviation of difference scores** **Inter-observer (ophthal-optom) detection of disc haemorrhage as present or absent** **(kappa statistic - unweighted)** **Inter-observer (ophthal-optom) agreement on neuroretinal rim pallor** **weighted kappa statistic κ_w**	Mean κ_w = **0.46 (moderate)** Range from 0.23 (fair) to 0.64 (substantial) Mean SD = 0.19 (range 0.13 – 0.22) (4/6 mean differences were significantly different $p<0.01$) Mean κ_w = NR Range from 0.29 (fair) to 0.65 (substantial) Mean SD = NR (range 0.09 – 0.15) (3/6 mean differences were significantly different $p<0.01$) Mean κ = **0.77 (substantial)** Range from 0.61 (substantial) to 0.91 (almost perfect) % agreement ranges from 90-98%) Mean κ_w = **0.23 (fair)**	**Funding:** College of optometrists **Limitations:** • No confidence intervals available for Mean weighted kappa statistic or SD • No patient demographics **Notes:** Observers were presented photographs in a masked and random fashion with at least 5 days between the 2 assessments of each photograph ***Weighted kappa statistic κ_w** Weights assigned to each observation for VCD were equal to 1 minus (difference between estimates). 0.0 difference = 1, 0.1 difference = 0.9 weight etc until 1.0 difference = 0. Smaller disagreements were weighted more heavily Kappa value agreement (Landis and Koch 1977)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		4. Focal pallor of neuroretinal rim 5. Extent of peri-papillary atrophy 6. Steepness of cup-edge 7. Cribriform sign as present or absent	*		-1.00 to 0 = poor 0.01 to 0.2 = slight 0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = substantial 0.81 to 0.99 = almost perfect +1.00 = perfect
			Inter-observer (ophthal-optom) agreement on peri-papillary atrophy **weighted kappa statistic κ_w ***	Mean κ_w = **0.45 (moderate)**	
			Inter-observer (ophthal-optom) agreement on steepness of cup edge **weighted kappa statistic κ_w ***	Mean κ_w = **0.50 (moderate)**	
			Inter-observer (ophthal-optom) agreement on cribriform sign **weighted kappa statistic κ_w ***	Mean κ_w = **0.48 (moderate)**	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Harper et al., 2001[55] **Study design:** Retrospective observational study	**Patient group:** 48 optic disc stereophotographs retrospectively selected from of glaucomatous and non glaucomatous patients attending glaucoma service in Greenwich Hospital, UK **Inclusion criteria:** Photographs that were representative of a wide range of disc appearances classified using a visual analogue scale (VAS) 0= definitely non-glaucomatous and 100= definitely glaucomatous by a glaucoma specialist. Matched visual field data was not available for the stereophotographs **<u>All patients</u>** **N:** 48 **Age (median):** NR **M/F:** NR **Glaucomatous damage (defined by VAS**): • **Definitely non-glaucomatous ≤10):** 11 • **Definitely glaucomatous ≥90):** 15 • **Suspicious (11-89):** 22 Patient demographics were not reported	**Group 1** 6 optometrists with 4 years accredited training. 2 had 1 year of post-registration experience, 2 had 4 years of post-registration experience and 2 had ≥ 10 years of post-registration experience. None had been involved in shared care schemes or had specialist training. All employed full or part-time in primary care optic role. **Group 2** 6 general ophthalmologists: 2 SPR and 2 SHOs and 2 consultants with subspecialty expertise in glaucoma. **Examination methods:** Photographs had been taken with a standard fundus camera with stereopsis achieved through decentration of camera angle. They were examined through a Carl-Zeiss 2x stereoscopic viewer and standard light box Each observer 1. Estimated vertical cup disc ratio (VCD) uncorrected for disc size 2. Grading of narrowest rim width estimate 3. Haemorrhage present or absent	**Inter-observer (ophthal-optom) agreement in estimating VCD** **weighted kappa statistic κ_w *** **Inter-observer (ophthal-optom) agreement in estimating VCD** **1 x standard deviation of difference scores** **Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio** **weighted kappa statistic κ_w *** **Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio** **1 x standard deviation of difference scores** **Inter-observer (ophthal-optom) detection of disc haemorrhage as present or absent** **(unweighted kappa statistic)**	Mean (95%CI) κ_w = **0.36** (0.31 - 0.41) **(fair)** Range for κ_w from 0.06 (slight) to 0.63 (substantial) Mean (95%CI) SD = 0.18 (0.17 - 0.20) Range 0.10 – 0.28 (25/36 mean differences were significantly different $p<0.01$ or <0.001 or <0.0001) Mean (95%CI) κ_w = **0.35** (0.29 - 0.41) **(fair)** Range for κ_w from -0.01 (poor) to 0.77 (substantial) Mean (95%CI) SD = 0.11 (0.11 - 0.12) Range 0.08 – 0.15 (23/36 mean differences were significantly different $p<0.01$ or <0.001 or <0.0001) Mean (95%CI) κ = **0.42** (0.37 – 0.47) **(moderate)** Range 0.12 (slight) to 0.72 (substantial)	**Funding:** NR **Limitations:** • No patient demographics **Notes:** Observers were presented photographs in a masked and random fashion with at least 5 days between the 2 assessments of each photograph ***Weighted kappa statistic** Weights assigned to each observation for VCD were equal to 1 minus (difference between estimates). 0.0 difference = 1, 0.1 difference = 0.9 weight etc until 1.0 difference = 0. Smaller disagreements were weighted

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		The features were discussed between each observer and the researcher prior to grading. All 12 observers had opportunity to read instructions for grading criteria			more heavily Kappa value agreement (Landis and Koch 1977) -1.00 to 0 = poor 0.01 to 0.2 = slight 0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = substantial 0.81 to 0.99 = almost perfect +1.00 = perfect

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Service Provision (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Spry, 1999[142] & Gray, 2000[52] [Bristol Shared Care Glaucoma Study] **Study design:** RCT **Evidence level:** + **Duration of follow-up:** 2 years Computer generated random numbers and allocation concealment	**Patient group:** glaucoma patients and glaucoma suspects attending glaucoma clinic **Setting:** Bristol Eye Hospital, UK **Inclusion criteria:** • 50 years • Glaucoma suspects • Stable (no change in visual field (VF) over last year) glaucoma • Primary open angle glaucoma • Pigment dispersion glaucoma • Pseudoexfoliative glaucoma • Informed consent • Ability to cooperate with examination • Snellen visual acuity (VA) ≥ 6/18 in both eyes **Exclusion criteria:** • <50 years • Unstable glaucoma • Normal tension glaucoma • Secondary glaucoma • Narrow angle glaucoma • Other coexisting ocular pathology • Extensive field loss (>66/12 missed points on Henson 132 point threshold related suprathreshold examination	**Group 1** Routine follow up** in Hospital Eye Service (HES) comprising by a general ophthalmologist: • VF analysis with Henson CFS2000/CFA3000 • Single IOP measurement using Goldmann Applanation Tonometry (GAT) • Vertical cup-disc ratio (VCD) using direct ophthalmoscopy or indirect binocular ophthalmoscopy **Group 2** Structured 6 monthly follow-up at specially trained (instruction through lectures and demonstrations from study researchers) Community Optometrist (CO) comprising: • VF analysis using Henson CFA 3000 132 point threshold related suprathreshold examination • Repeat VF examination on 50% patients • Single IOP measurement using GAT	**Mean number of points missed on visual field testing ± SD** ***Better Eye***	**Group 1:** 7.9 ± 12.0 **Group 2:** 6.8 ± 10.8 **Difference between means:** 0.07 (95% CI: -1.86, 2.04) **p value:** 0.94 **(ANCOVA)*** **not signif.**	**Funding:** MRC, International Glaucoma Association, R&D Directorate NHS Executive South and West and Avon Health Authority **Limitations:** **Notes:** ***ANCOVA**: analysis of covariance was performed for each outcome variable comparing the 2 follow up groups ***adjusting for baseline measurements***. Control was also considered for age, sex, time from recruitment to follow up, treatment at baseline, treatment at any time (any/none) and diagnosis (glaucoma suspect/established POAG) **$Adjusted Intraclass Correlation Coefficient (ICC):** The ICC is an equivalent to a quadratic weighted kappa statistic as a
			Mean number of points missed on visual field testing ± SD ***Worse Eye***	**Group 1:** 20.2 ± 21.6 **Group 2:** 18.3 ± 19.9 **Difference between means:** 0.04 (95% CI: -3.49, 3.40) **p value:** 0.98 **(ANCOVA)*** **not signif.**	
			Mean IOP (mmHg) ± SD ***Better Eye***	**Group 1:** 19.3 ± 5.1 **Group 2:** 19.3 ± 4.7 **Difference between means:** 0.26 ± (95% CI: -1.21, 0.68) **p value:** 0.59 **(ANCOVA)*** **not signif.**	
			Mean IOP (mmHg) ± SD ***Worse Eye***	**Group 1:** 19.1 ± 5.5 **Group 2:** 19.0 ± 5.3 **Difference between means:** 0.53 ± (95% CI: -1.58, 0.51) **p value:** 0.32 **(ANCOVA)*** **not signif.**	
			Cup disc ratio ± SD ***Better Eye***	**Group 1:** 0.72 ± 0.12 **Group 2:** 0.72 ± 0.13 **Difference between means:** 0.00 (95% CI: -0.02, 0.03) **p value:** 0.70 **(ANCOVA)*** **not signif.**	
			Cup disc ratio ± SD ***Worse Eye***	**Group 1:** 0.74 ± 0.13 **Group 2:** 0.74 ± 0.14 **Difference between means:** 0.00 (95% CI: -0.03, 0.03) **p value:** 0.70 **(ANCOVA)*** **not signif.**	
			VCD (inter centre agreement) ***Right Eye***	**Mean Difference:** -0.05 (95% CI: -0.03, -0.07) **$Adjusted ICC: 0.50** (moderate agreement) N=360	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	• Best corrected VA in either eye worse than 6/18 **<u>All patients</u>** **N:** 403 **<u>Group 1 (HES)</u>** **N:** 200 **Age (mean ± SD):** 69.4 ± 8.8 **M/F:** 115/85 **Mean glaucoma suspects** **Male:** 48 **Female:** 30 **Family history:** 35 **Previous cataract extraction:** 14 **LogMAR both eyes (mean ± SD):** 0.06 ± 0.18 **Drop outs:** 38 (died = 7, moved = 2, general health = 6, lost to follow up = 23) **<u>Group 2 (CO)</u>** **N:** 203 **Age (mean ± SD):** 68.0 ± 8.3 **M/F:** 103/100 **Mean glaucoma suspects** **Male:** 51 **Female:** 44 **Family history:** 48 **Previous cataract extraction:** 8 **LogMAR both eyes (mean ± SD):** 0.06 ± 0.17 **Drop outs:** 19 (died = 5, moved = 4, general health = 3, other = 7)	• VCD using direct ophthalmoscopy or indirect binocular ophthalmoscopy (dilated pupil) **Examination methods:** A research clinic reference standard (RCRS) examination was performed on each patient at baseline pre-randomisation and 2 year follow up comprising: • VF analysis using Henson CFA 3000 132 point threshold related suprathreshold examination • Repeat VF examination • Triple IOP measurement using GAT • VCD using direct ophthalmoscopy or indirect binocular ophthalmoscopy (dilated pupil) • Stereophotographic analysis of VCD by observer 1 • Stereophotographic analysis of VCD by observer 2	**VCD (inter centre agreement)** ***Left Eye***	**Mean Difference:** 0.05 (95% CI: 0.03, 0.07) **$Adjusted ICC: 0.54** (moderate) N=358	chance corrected measure of agreement which corrects for systematic bias, weighting discrepancies according to square of the differences between the paired measurements. **ICC = <0.2** "slight agreement"; **ICC = 0.21-0.40** "fair agreement"; **ICC = 0.41-0.60** "moderate agreement; **ICC = 0.61-0.80** "substantial agreement; **ICC = ≥ 0.80** "almost perfect agreement. **For HES group mean time to first follow up 10.7 ± 5.4 months (range 3 – 24 months) Median number of visits within 2 year period was 2.8 (range 0-8) **Additional outcomes:** RCRS v HES (all outcomes and RCRS v CO (all outcomes
			IOP mmHg (inter centre agreement) ***Right Eye***	**Mean Difference:** 0.4 (95% CI: -0.05, 0.85) **$Adjusted ICC: 0.45** (moderate) N=388	
			IOP mmHg (inter centre agreement) ***Left Eye***	**Mean Difference:** 0.6 (95% CI: 0.13, 1.07) **$Adjusted ICC: 0.40** (fair) N=388	
			VF points missed (inter centre agreement) ***Right Eye***	**Mean Difference:** 1.1 (95% CI: -0.38, 2.58) **$Adjusted ICC: 0.55** (moderate) N=287	
			VF points missed (inter centre agreement) ***Left Eye***	**Mean Difference:** 0.7 (95% CI: -0.80, 2.20) **$Adjusted ICC: 0.61** (substantial) N=287	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Theodossiades & Murdoch, 2001[148] **Study design:** Prospective observational	**Patient group:** Volunteers from Moorfields Eye Hospital glaucoma clinics, UK **Inclusion criteria:** Wide range of normal and glaucomatous disc features **<u>All patients</u>** **N:** 50 **Age (median):** NR **M/F:** NR **Glaucomatous damage (defined by consultant):** • **No glaucoma:** 27 • **Early glaucoma:** 4 • **Moderate glaucoma:** 5 • **Advanced glaucoma:** 14 Patient demographics were not reported	**Group 1** 8 community optometrists based in high street optometric practices. 6 also worked part-time in the hospital eye service but not for glaucoma. Optometrists received 2 hours of lectures on assessment of optic nerve head **Group 2** Consultant ophthalmologist with specialist interest in glaucoma **Examination methods:** Both undilated eyes of each patient were first examined by the consultant ophthalmologist using slit lamp biomicroscopy and one eye selected for examination by optometrist. Optometrists assessed one undilated eye through a direct ophthalmoscope of each patient for the following parameters: 1. Vertical disc diameter 2. Vertical cup disc ratio (VCD) 3. Neuroretinal configuration 4. Cup shape 5. Neuroretinal rim colour 6. Vessel configuration 7. Haemorrhage 8. Extent of peri-papillary atrophy 9. Health status of optic nerve head These were then used to give a final opinion on presence or absence of	**Inter-observer agreement in Vertical disc diameter** weighted kappa statistic κ_w *	Mean (95%CI) κ_w = **0.34** (0.26 - 0.42) **(fair)**	**Funding:** International Glaucoma Association **Limitations:** • No patient demographics • Weighting method for VCD and vertical disc diameter was not reported • Observer masking was not reported • Patients were not recruited in a randomised or consecutive fashion. **Notes:** Kappa value agreement based on (Landis and Koch 1977) 0.00 to 0.2 = poor 0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = good 0.81 to 1.00 = very
			Inter-observer agreement in VCD weighted kappa statistic κ_w *	Mean (95%CI) κ_w = **0.84** (0.81 - 0.87) **(very good)**	
			Inter-observer agreement in Neuroretinal configuration kappa statistic κ_w	Mean (95%CI) κ_w = **0.67** (0.58 - 0.76) **(good)**	
			Inter-observer agreement in Cup shape kappa statistic κ_w	Mean (95%CI) κ_w = **0.66** (0.58 - 0.74) **(good)**	
			Inter-observer agreement in Neuroretinal rim colour kappa statistic κ_w	Mean (95%CI) κ_w = **0.32** (0.25 - 0.38) **(fair)**	
			Inter-observer agreement in Vessel configuration kappa statistic κ_w	Mean (95%CI) κ_w = **0.53** (0.40 - 0.65) **(moderate)**	
			Inter-observer agreement in Haemorrhage kappa statistic κ_w	Mean (95%CI) κ_w = **0.67** (0.45 - 0.89) **(good)**	
			Inter-observer agreement in Peri-papillary atrophy kappa statistic κ_w	Mean (95%CI) κ_w = **0.22** (0.14 - 0.29) **(fair)**	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		glaucomatous damage	**Inter-observer agreement in Health status of optic nerve head** kappa statistic κ_w	Mean (95%CI) κ_w = **0.62** (0.53 - 0.70) **(good)**	good
			Health status of optic nerve head (reference standard defined consultant)	Sensitivity: **0.90** (95% CI: 0.86 - 0.94) Specificity: **0.73** (95% CI: 0.66 - 0.80)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Evidence Table 23 Patient Views

Study details	Patients	Intervention	Outcome measures	Effect size	Comments

Day et al., 2006[32]
 	
Study design: Prospective observational cohort
 	
Evidence level:
 	
Duration of follow-up: N/A
	Patient group: Consecutively recruited patients from outpatient clinics.
	
	Setting: USA
	
	Inclusion criteria:
	• > 18 years
	• POAG or OHT
	• On medication in at least 1 eye for 30 days prior to study
	• Adequate visual acuity
	• Mental ability to read and understand English
	
	Exclusion criteria:
	• Patients with clinically significant medical or psychiatric condition
	• Those who had participated in another trial within 30 days prior to study
	• Unable to give informed consent
	• Unable to understand trial procedures
	• Those with previous laser or surgery with previous 2 months
	
	<u>All patients</u>
	N: 250
		The **Treatment Satisfaction Survey-Intraocular Pressure (TSS-IOP)** - owned by Pfizer, Inc. - is a survey focussing on patient satisfaction and perception of their glaucoma medication and patient compliance. The survey consists of 15 validated questions falling under categories below:
		• Effectiveness (satisfaction scale)
		  ○ Preventing future vision problems
		  ○ Reducing current vision problems
		• Side effects – eye irritation (bother scale)
		  ○ Prolonged burning or stinging
		  ○ Grittiness or sandiness
		  ○ Stickiness or crustiness
		  ○ Dry eyes
		• Eye appearance – hyperaemia (bother scale)
		  ○ Peoples' reaction to red eye
		  ○ Self-consciousness of red eye
		  ○ Overall cosmetic appearance
		• Ease of administration (satisfaction scale)
		  ○ Number of times drops applied
		  ○ Time of day for application
		  ○ Ease of remembering to
			Treatment satisfaction and dosing frequency Mean TSS-IOP score ± SD	**TSS-IOP Effectiveness**
				Single medications (n=151) 79.1 ± 15.4
				Multiple medications (n=99) 73.7 ± 18.0 **P =0.01**
				TSS-IOP Side Effects
				Single medications (n=151) 93.4 ± 12.7
				Multiple medications (n=99) 88.7 ± 15.2 **P =0.01**
				TSS-IOP Irritation
				Single medications (n=151) 93.4 ± 11.1
				Multiple medications (n=99) 87.5 ± 17.8 **P =0.001**
				TSS-IOP Convenience of use
				Single medications (n=151) 82.54 ± 14.2
				Multiple medications (n=99) 77.1 ± 16.8 **P =0.007**
				TSS-IOP Ease of use NR
					Funding: Pfizer, Inc. CA, USA.
					
					Limitations:
					• Statistical analysis was not explained.
					• TSS-IOP scoring system was not clearly explained
					• Study reports correlation analysis between TSS-IOP items and items from an invalidated additional questionnaire
					
					Additional outcomes: Correlation between TSS-IOP items and physician reported ratings of IOP control, side effects, compliance and problems with

			Differences between specific single glaucoma medications (n=148) Mean TSS-IOP score ± SD	**TSS-IOP Convenience of use** Beta-blockers (n=34) 85.8 ± 14.5 PGA (n=80) 83.6 ± 14.0 CAI (n=22) 79.3 ± 14.3 Sympathomimetic (n=12) 73.6 ± 11.1 P values NR. NCC-AC calculate using *t* test with equal variance BB v PGA **p=Not signif.** BB v CAI **p=Not signif.** BB v sympathomimetics **p=0.01** PGA v CAI **p=Not signif.** PGA v sympathomimetics **p=0.02** CAI v sympathomimetics **p=Not signif.**	
			Differences between specific glaucoma medications Mean TSS-IOP score ± SD	**TSS-IOP Eye appearance** Beta-blockers (n=34) 99.3 ± 3.2 PGA (n=80) 90.7 ± 17.8 CAI (n=22) 93.6 ± 8.1 sympathomimetics (n=12) 88.2 ± 27.2 P values NR. NCC-AC calculate using *t* test	

Study details	Patients	Intervention	Outcome measures	Effect size	Comments
	Age (mean ± SD): 64.6 ± 13.1 **M/F:** 109/141 **History of elevated IOP (years):** 8.4 ± 7.8 **Race** White: 138 African-American: 109 Hispanic: 3 **Iris Colour** Brown: 142 Blue: 67 Other: 41 **Employment** Retired: 134 Full or part time: 99 Unemployed: 17 **Number of medications** **Monotherapy (n=148):** β-blockers: 34 PGA: 80 CAI: 22 Sympathomimetics: 12 **Adjunctive therapy (n=102):** β-blockers: 48 PGA: 85 CAI: 49 Sympathomimetics: 31	use • Convenience of use (satisfaction scale) ○ Ease of delivery of correct amount rather than missing or too much ○ Ease of angling head when sitting or standing to apply ○ Ease of consistently applying correct amount Items were scored on either a 5 or 7 point scale from 'Extremely satisfied' or 'Extremely Bothered' to 'Extremely dissatisfied' or "Not bothered' Patients had a full medical and ocular history taken and completed a supplemental non-validated questionnaire about their expectations of topical medication. Patients then completed the TSS-IOP validated questionnaire. Patients had a clinical examination as part of routine care and then completed a questionnaire regarding assessment of the patients' treatment, tolerance of medicine and compliance. 25 patients were asked to return for ±a second visit to complete the questionnaire again to evaluate test-retest reliability		with unequal variance BB v PGA **p=0.0001** BB v CAI **p=0.004** BB v sympathomimetics **p=0.19 Not ignif.** PGA v CAI **p=Not signif.** PGA v sympathomimetics **p=Not signif.** CAI v sympathomimetics **p=Not signif.**	self-administration **Notes:**

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Evidence Table 24 Economic Evidence

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kymes et al., 2006[80] USA **Economic analysis:** Cost Utility analysis **Study design** Decision analysis* **Time horizon:** Life-time **Discount rates:** Costs: 3% Effects: 3%	**Patient group:** patients between 40 and 80 with OHT (IOP between 24mm Hg and 32mm Hg in one eye and between 21mm Hg and 32mm Hg in the other eye, and normal VF and optic disk in both eyes) **<u>All patients</u>** * **N:** 1636 **N with glaucoma:** 0 **M/F:** 705/931 **Mean IOP at baseline (SD):** 24.9 (2.7) **Ethnic origin:** Asian 14, African American 408, Hispanic 59, White 1137, Other 18 **Drop outs:** 228	**Intervention 1:** Treat no one **Intervention 2:** Treat if IOP≥24 mm Hg and annual risk of developing POAG ≥5% **Intervention 3:** Treat if IOP≥24 mm Hg and annual risk of developing POAG≥2% **Intervention 4:** Treat everyone with IOP≥24 mm Hg	Mean QALYs gained per patient (determined by progression and development of cataract)	**intervention 1:** 13.537 **intervention 2:** 13.559 **Intervention 3:** 13.588 **Intervention 4:** 13.587 **p value:** NR	**Funding:** National Eye Institute; National Institutes of Health; Merck Research Laboratories; Pfizer, Inc; Research to prevent Blindness, Inc. **Limitations:** Treatment was a mixture **Notes:** * Based on the Ocular Hypertension Treatment Study
			Mean total life-time cost per patient 2006 US$, cost of medication, cataract surgery, cost associated with POAG progression, cost of blindness. Societal perspective	**Intervention 1: $**4,006 (£ 2,476) **Intervention 2: $**4,086 (£ 2,525) **Intervention 3:** $5,305 (£ 3,278) **Intervention 4:** $11,245 (£ 6,949) **p value:** NR	
			Cost-effectiveness Cost per QALY gained	Int 2 vs Int 1: $3,670 (£2,268) Int 3 vs Int 2: $42,430 (£ 26,222) Int 4 vs Int 3: Int 4 is dominated	
			Sensitivity analysis One-way SA	Sensitive factors were: incidence of POAG without treatment (if less than 1.5%, Int 2 more cost-effective), proportion of people with OHT to be treated, reduction in risk because of medical treatment (if <30% Int 2 more cost-effective), annual probability of progression of a POAG stage, cost of one medication, increased annual risk of cataract surgery, utility loss in stage 1 POAG.	
			Probabilistic sensitivity analysis (Monte Carlo simulation)	At the £20,000/QALY threshold, both Int 1 and Int 3 have a 30% probability of being the most cost-effective, while Int 2 has a 40% probability.	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Stewart et al., 2008[144] USA **Economic analysis:** Cost Utility **Study design** Decision model based on the Ocular Hypertension Treatment Study and Early Manifest Glaucoma Trial. **Time horizon:** 5 years **Discount rates:** Costs: 3% Effects: 0%	**Patient group:** patients with ocular hypertension from the Ocular Hypertension Treatment Study.	**Intervention 1:** No treatment **Intervention 2:** 1 medication for the first 2 years. In the last 3 years: - 1.4 medications in non-progressing patients - 2 medications in 75% of patients that progressed - 3 medications in 15% of patients that progressed Medications could be Prostaglandin Analogues, Beta-Blockers or Brimonidine.	QALYs	**Intervention 1:** 4.45 **Intervention 2:** 4.48 **p value:** NR	**Funding:** NR (one of the authors was employed by Pfizer). **Limitations:** - other relevant outcomes were omitted (e.g. blindness) - limited applicability (US cost data)
			Mean cost per patient 2007 US $, Cost of visits, medications, and tests (central corneal thickness, gonioscopy, IOP, optic disc imaging, refraction, automated visual field).	**Intervention 1:** $ 2,467 (£ 1,525) **Intervention 2:** $ 5,001 (£ 3,091) **p value:** NR	
			Cost-effectiveness incremental cost per QALY gained	Intervention 2 vs Intervention 1 $84,467 (£ 52,200)	
			Sensitivity analysis One-way SA (risk of progression is changed according to risk factors) DSA (costs are changed by + or -10%)	Intervention 2 is cost-effective in one of the following situations: - vertical cup to disc ratio plus 0.7 or more - corneal thickness plus 80µm No change in results	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Bernard 2003[10] France **Economic analysis:** cost-effectiveness **Study design** Decision analysis* **Time horizon:** 2 years and 3 years **Discount rates:** Costs: 3% Effects: 0%	**Patient group:** patients newly diagnosed with open angle glaucoma or ocular hypertension (IOP>21 mmHg and no optic nerve damage).	**Intervention 1:** First-line treatment with a beta-blocker followed by usual care for patients who switch therapy. **Intervention 2:** First-line treatment with latanoprost 0.005% followed by usual care for patients who switch therapy.	Proportion of patients remaining on first-line treatment (after 1 year; after 2 years)	**Int 1:** 46%; 29% **Int 2:** 82%; 73% **p value:** NR	**Funding:** Pharmacia Corporation, Peapack, USA **Limitations:** Clinical outcomes were not compared to other studies. Limited time horizon. **Additional outcomes:** Proportion of patients undergoing surgery (7% for Int 1and 3% for Int 2 over 3 years) **Notes:** * Model inputs were taken from chart reviews. ** Calculated by NCC-AC from incremental cost per IOP-controlled day gained.
			Mean time spent on the initial therapy (months)	**Int 1:** 13.4 **Int 2:** 20.5 **p value:** <0.0001	
			Mean number of therapies used over 2 years (CI)	**Int 1:** 2.08 (± 0.94) **Int 2:** 1.38 (± 0.74) **p value:** <0.0001	
			Mean IOP-controlled days (days) (over 2 years; over 3 years)	**Int 1:** 653; 973 **Int 2:** 703; 1047 **p value:** <0.0001	
			Mean cost per patient (over 2 years; over 3 years) (2002 Euro Cost of management, treatment, surgery)	**Int 1:** € 539 (£ 366); € 817 (£ 556) **Int 2:** € 580 (£ 394); € 844 (£ 574) **p value:** <0.0001	
			Cost-effectiveness Incremental cost per IOP-controlled year gained per patient** (over 2 years; over 3 years)	**Int 2 vs Int 1:** € 299 (£ 204); € 131 (£ 88)	
			Sensitivity analysis One-way sensitivity analysis	The results were sensitive to time to therapy failure, bottle duration, assessment visit schedule for patients who switched treatments, surgical rates, and cost of surgery.	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Day 2004[31] USA **Economic analysis:** Cost consequences **Study design** Retrospective cohort study **Duration of follow-up:** 6 months **Discount rates:** Costs: NA Effects: NA	**Patient group:** adult patients with COAG or OHT in at least one eye whose records were stored in large glaucoma practices in the USA. **<u>All patients</u>** **N:** 1182 (1 eye randomly chosen evaluated) **N with glaucoma:** 922 **M/F:** 510/672 **Drop outs:** 0 **<u>Group 1</u>** **N:** 487 **N with glaucoma:** 361 **Age (mean±SD):** 64.4±14.3 **M/F:** 219/268 **Ethnic origin:** Caucasian 325, African-American 82, Asian 6, Hispanic 12, Other and Unknown 62 **<u>Group 2</u>** **N:** 490 **N with glaucoma:** 401 **Age (mean±SD):** 67±13.9 **M/F:** 207/283 **Ethnic origin:** Caucasian 303, African-American 109, Asian 1, Hispanic 8, other and unknown 69 **<u>Group 3</u>** **N:** 205 **N with glaucoma:** 160 **Age (mean±SD):** 68.9±12.8 **M/F:** 84/121 **Ethnic origin:** Caucasian 114, African-American 30, Asian 1, Hispanic 5, Other and Unknown 55	**Group 1:** Beta-blockers monotherapy as first or second line (71% with Timolol). **Group 2:** Latanoprost monotherapy as first or second line. **Group 3:** Bimatoprost monotherapy as first or second line.	Risk ratio to discontinue therapy compared to group2	**Group 1:** 1.15 (95% CI: 1.03, 1.27) **Group 2:** 1 **Group 3:** 1.08 (95% CI: 1.01, 1.16) **p value:** 0.02	**Funding:** Pfizer, Inc. **Limitations:** No differentiation between treatments used as a first- or second-choice. The short follow-up does not allow including the costs associated with disease progression (e.g. surgery). Mean IOP at baseline not reported. **Additional outcomes:** Main reasons for changing or adding to current medication before 6 months of therapy were IOP not controlled and adverse events. Patient visits were fewer with latanoprost (p=0.01). The number of ocular adverse events was fewer with beta-blockers.
			IOP at the last visit before the therapy is changed (mmHg±SD)	**Group 1:** 17.9±3.7 **Group 2:** 17.3±3.9 **Group 3:** 18.0±3.6 **p value:** <0.0001	
			Mean cost per patient per 6months of therapy 2004 US$ Direct costs only: cost of drugs (average wholesale price) + visits and procedures resulting from adverse events as well. Cost of drug based on both eyes receiving treatment and assuming perfect compliance	**Group 1:** $ 119 (76+43) (£ 74) **Group 2:** $ 154 (116+38) (£ 95) **Group 3:** $ 164 (124+40) (£ 101) **p value:** <0.0001 (drugs), p=0.07 (visits and procedures)	
			Cost-effectiveness	NR	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Goldberg 2006[48] USA **Economic analysis:** cost-effectiveness **Study design** Decision analysis based on RCT* **Time-horizon:** 1 year **Discount rates:** Costs: NA Effects: NA	**Patient group:** patients with POAG or OHT (IOP 22-34 mmHg) in at least one eye. **<u>All patients</u>*** **N:** 715 **M/F:** 307/408 **Drop outs:** 86 **Ethnic origin:** 583 non-black, 132 black **<u>Group 1</u>** **N:** 241 **Age (mean):** 61 **M/F:** 101/140 **Drop outs:** 27 **Mean IOP at baseline:** NR **Ethnic origin:** 195 non-black, 46 black **<u>Group 2</u>** **N:** 474 **Age (mean):** 61.7 **M/F:** 206/268 **Drop outs:** 59 **Mean IOP at baseline:** NR **Ethnic origin:** 388 non-black, 86 black	**Group 1:** Timolol twice daily morning and evening as first-line. **Group 2:** One drop of Bimatoprost 0.03% once-daily in the evening as first-line.	Percentage of patients achieving target pressure (17mmHg) after 12 months.	**Group 1:** 37%, 27%, 16%, 9%, 5% **Group 2:** 58%, 47%, 31%, 21%, 12% **p value:** <0.05	**Funding:** Allergan, Inc. **Limitations:** The study assumes success is achieved after dual therapy and patients are perfectly compliant. The study does not consider surgical treatment, adverse events or endpoints other than IOP (e.g. blindness). Limited time horizon. **Notes:** *Higginbotham 2002[62]. Data from another RTC excluded because it has a 3-month follow-up. ** calculated by NCC-AC according to costs and algorithm reported in the study.
			Mean annual cost per patient** 2003 US$, (cost of initial and adjunctive medication based on average wholesale prices + cost of visits, if target pressure 17mmHg)	**Group 1: $**828 (£ 517), $ 896 (£ 559), $964 (£ 601), $1032 (£ 644), $1063 (£ 663). **Group 2:** $1043 (£ 651), $1066 (£665), $1112 (£ 694), $1151 (£ 718), $1183 (£ 738). **p value:** NR	
			Cost-effectiveness** Incremental cost per additional treatment success	**Group 2 vs Group 1:** $1024 (£ 639)	
			Sensitivity analysis one-way sensitivity analysis	ICER was $850 (£ 530), $987 (£ 616), $992 (£ 619), $1714 (£ 1069) if target pressure was respectively16mmHg, 15mmHg, 14mmHg, 13mmHg. Results were sensitive to the average wholesale prices (if branded Timolol was used, bimatoprost would become at least 30% more cost effective at target IOP 17), to changes in treatment success rates, to the adjunctive agent chosen (if brimonidine, bimatoprost would be dominant).	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Halpern 2002[54] USA **Economic analysis:** Cost consequences **Study design** Decision analysis based on a RCT (Netland 2001) **Duration of follow-up:** 1 year **Discount rates:** Costs: NA Effects: NA	**Patient group:** black patients with POAG or OHT. **<u>All patients</u>** **N:** 132 **M/F:** 56/76 **Drop outs:** 19 **<u>Group 1</u>** **N:** 40 **Age (mean):** 62.3 **M/F:** 15/25 **Drop outs:** 7 **Mean IOP at baseline:** 25.8 **<u>Group 2</u>** **N:** 43 **Age (mean):** 58.6 **M/F:** 18/25 **Drop outs:** 3 **Mean IOP at baseline:** 26.2 **<u>Group 3</u>** **N:** 49 **Age (mean):** 62.6 **M/F:** 23/26 **Drop outs:** 9 **Mean IOP at baseline:** 25.3	**Group 1**: Timolol 0.5%, one drop at 8 AM and at 8 PM as first-line. **Group 2:** Latanoprost 0.005% One drop at 8PM plus placebo at 8AM as first-line. **Group 3:** Travoprost 0.004% One drop at 8PM plus placebo at 8AM as first-line.	Mean IOP during the 1-year follow-up (mm Hg±SD)	**Group 1:** 20.5±3.4 **Group 2:** 18.7±2.4 **Group 3:** 17.3±2.5 **p value:** <0.05 (group 1 and 2 vs 3)	**Funding:** Alcon Research, Ltd. **Limitations:** It is not clearly stated if the costs of medication have been included. It is not clear when the IOP at follow-up was measured. Limited follow-up. **Notes:** *Calculated by averaging various algorithms that link IOP with visual field defect ** Inpatient costs: increased VFDS x mean number of hospitalisation per year due to severe visual field defect x average length of stay x cost per day as reimbursed by Medicare. Outpatient costs: Medicare 2000 reimbursement values x increased VFDS
			Mean increase in visual field progression rates*	**Group 2 vs Group 3:** 19% **Group 1 vs Group 3:** 27.5% **p value:** Sig	
			Mean increase in annual cost per patient 2000 US$, inpatient and outpatient costs, based on the likelihood of increased Visual Field Defect Score (VFDS)**	**Group 2 vs Group 3: $**170 (£ 108) **Group 1 vs Group 3:** $ 247 (£ 156) **p value:** NR	
			Cost-effectiveness	NR	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rouland 2003 [125] France **Economic analysis:** Cost-effectiveness **Study design** decision analysis based on retrospective cohort study **Duration of follow up:** one year **Discount rates:** Costs: NA Effects: NA	**Patient group:** second-line adult patients with COAG or OHT (IOP>21 mmHg and no optic nerve damage) in at least one eye for whom treatment was changed or stopped, presenting in 37 centres in France. **<u>All patients</u>** **N:** 283 (549 eyes)* **N eyes with glaucoma:** 425 **Age (mean):** 65±1.5 **M/F:** 155/128 **Mean IOP at baseline:** 20.0±4.3 **<u>Group 1</u>** **N:** 209 eyes **Mean IOP at baseline:** 19.5±3.9 **<u>Group 2</u>** **N:** 90 eyes **Mean IOP at baseline:** 19.3±4.7 **<u>Group 3</u>** **N:** 39 eyes **Mean IOP at baseline:** 20.9±3.7	**Group 1:** Beta-blocker as a second-line treatment **Group 2:** Latanoprost as a second line treatment **Group 3:** Unfixed combination of Latanoprost+Timolol as a second line treatment	Mean IOP reduction per treated eye (mmHg)	**Group 1:** 2.1 **Group 2:** 3.0 **Group 3:** 5.3 **p value:** 0.02 (group 1 vs group 2 only)	**Funding:** Pharmacia corporation, Peapack, NJ, USA **Limitations:** Short follow-up Clinical outcomes were not compared to other studies and RCTs. **Additional outcomes:** average number of days remaining on the same treatment (longer for Group 2 and 3) **Notes:** * other groups treated with CAI and other combinations not reported here as a CEA was not performed ** calculated by NCC-AC from data reported in the study *** calculated by NCC-AC (different figures reported by authors)
			Proportion of eyes remaining on the same second-line treatment after 1 year	**Group 1:** 69% **Group 2:** 84% **Group 3:** 80% **p value:** 0.0068 (group 1 vs group 2 only)	
			Mean annual cost per patient** (2001, Euros direct costs: visits, medical procedures, drugs, surgery including trabeculectomy, trabeculoplasty, combined cataract-trabeculectomy, iridotomy, and 10% of cataract surgery) estimated from National Sources.	**Group 1:** € 179 (£ 124) **Group 2:** € 273 (£ 189) **Group 3:** € 329 (£ 228) **p value:** <0.0001 (group 1 vs group 2 only)	
			Cost-effectiveness*** additional cost per 1 mmHg of control gained after 1 year of treatment	Group 2 vs Group 1: £ 72 Group 3 vs Group 1: £33 Group 3 vs Group 2: £24	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rouland 2005[126] France **Economic analysis:** cost-effectiveness **Study design:** decision analysis based on cohort study **Duration of follow-up:** 2 years **Discount rates:** Costs: NR Effects: NR	**Patient group:** second-line adult patients with COAG or OHT (IOP>21 mmHg and no optic nerve damage) in at least one eye presenting in 37 centres in France. **<u>All patients (eyes)</u>** **N:** 498 (672 eyes) **N eyes with glaucoma:** 511 **Age (mean±SD):** 64.8±12.9 **M/F:** 159/187 **Drop outs:** 152 **Mean IOP at baseline ±SD:** 20.1±4.1 **<u>Group 1</u>** **N eyes:** 248 eyes **Mean IOP:** 19.7 **<u>Group 2</u>** **N eyes:** 112 eyes **Mean IOP:** 19.9 **<u>Group 3</u>** **N eyes:** 39 eyes **Mean IOP:** 20.5	**Group 1:** Beta-blocker as a second-line treatment **Group 2:** Latanoprost as a second line treatment **Group 3:** Unfixed combination of Latanoprost+Timolol as a second line treatment	Frequency of episodes of adverse events	**Group 1:** 116 **Group 2:** 21 **Group 3:** 3 **p value:** NR	**Funding:** Pfizer **Limitations:** Short follow-up. Clinical outcomes were not compared to other studies and RCTs. **Additional outcomes:** average number of days remaining on the same treatment (longer for Group 2) **Notes:** * other groups include combinations, not reported here ** calculated by NCC-AC from data reported in the study *** calculated by NCC-AC
			Relative risk of adverse events vs group 1 (95% CI)	**Group 1:** 1.00 (0.996-1.004) **Group 2:** 0.40 (0.16-0.64) **Group 3:** NR **p value:** NR	
			Proportion of eyes remaining on the same second-line treatment after 2 years	**Group 1:** 41% **Group 2:** 62% **Group 3:** 44% **p value:** NR	
			Mean IOP reduction after 2 years per treated eye (mm Hg)	**Group 1**: 2.6 **Group 2**: 3.3 **Group 3**: 4.4 **p value**: NR	
			Mean 2-year cost per eye** (2003, Euros, direct costs: visits, medical procedures, drugs, surgery, 10% of cataract surgery)	**Group 1:** € 388 (£ 260) **Group 2:** € 556 (£ 373) **Group 3:** € 731 (£ 490) **p value:** NR	
			Cost-effectiveness*** additional cost per 1 mmHg of control gained after 2 years of treatment	Group 2 vs Group 1: £162 Group 3 vs Group 1: £128 Group 3 vs Group 2: £106	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Le Pen et al., 2005[82] France **Economic analysis:** Cost-utility **Study design** Decision analysis based on a Markov model **Time horizon:** 5 years **Discount rates:** Costs: 5% Effects: NR	**Patient group:** patients with advanced POAG in five European countries.	**Intervention 1:** Timolol 0.5% twice daily as first-line. **Intervention 2:** Latanoprost 0.005% once daily as first-line. **Intervention 3:** Travoprost 0.004% once daily as first-line.	Mean daily IOP over all visit days (mmHg)*	**Int 3 - Int 1:** -1.3 **Int 3- Int 2:** -1.0 **p value:** <0.0001	**Funding:** Alcon Laboratories Inc, USA. **Limitations:** Complicated third and fourth line strategies after disease progression were not considered. Limited time horizon. Clinical outcomes were not derived from a systematic search. Calculations of QALYs and ICUR were dubious. **Additional outcomes:** Same outcomes reported for other countries (Austria, France, Germany, and the Netherlands). The results were consistent across countries. **Notes:** * data from Netland 2001[110] ** Calculated from an algorithm that links IOP with VFD *** unclear calculation ****ICUR as reported in the study= €23,828 (£ 15,989)
			Time without a VFD=disease progression over 5 years (years)**	**Int 1:** 2.812 **Int 2:** 3.285 **Int 3:** 3.417 **p value:** NR	
			Patients experiencing a new visual field defect after 5 years of treatment**(%)	**Int 1:** 72.8% **Int 2:** 59.4% **Int 3:** 55.7% **p value:** NR	
			QALYs over 5 years***	**Int 1:** 3.6001 **Int 2:** 3.6164 **Int 3:** 3.6210 **p value:** NR	
			Mean cost per patient over 5 years in the UK 2003 Euro (€ 1.5 = £1). Cost of drugs, visits, surgery, laser, taken from national sources (UK GP Research Database and BNF)	**Int 1:** € 790 (£ 530) **Int 2:** € 1,041 (£ 698) **Int 3:** € 993 (£ 666) **p value:** NR	
			Cost-effectiveness ICUR = incremental cost per QALY gained (2003 €) calculated from difference in costs and QALYs as reported above****	Int 3 vs Int 1: €10,150 (£ 6,767) Latanoprost is dominated by Travoprost	
			Sensitivity analysis Probabilistic SA based on a Monte Carlo simulation (variables included were the cut-off value adopted for defining stability, the utility loss associated with a new VFD and the cost of a stable and progressive patient).	Probability ICUR Int 3 vs Int 1 <45,000€/QALY is 98.8%.	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Cottle & Begg, 1988[27] Canada **Economic analysis:** CEA **Study design** cohort study **Duration of follow-up:** 12 months (mean) **Discount rates:** Costs: NA Effects: NA	**Patient group:** consecutive patients with newly diagnosed, untreated POAG (IOP => 21 mmHg in at least one eye, glaucomatous visual field loss). **<u>All patients</u>** **N:** 71 (130 eyes) **N with glaucoma:** 71 **Age (mean ± SD):** 64 (±13.1) **M/F:** 34/37 **Drop outs:** 0 **Mean IOP at baseline (all eyes):** 28.7 (± 6.13) **Ethnic origin:** all white **<u>Group 1</u>** **N:** 85 eyes* **<u>Group 2</u>** **N:** 20 eyes* **<u>Group 3</u>** **N:** 10 eyes* **<u>Group 4</u>** **N:** 19 eyes* **<u>Group 5</u>** **N:** 8 eyes*	**Group 1:** Timolol 0.25% (Beta-blocker) **Group 2:** Timolol 0.5% (Beta-blocker) **Group 3:** Dipivefrine 0.1% (Sympathomimetic) **Group 4:** Pilocarpine 2.0% **Group 5:** Pilocarpine 1.0%	Number of eyes controlled in terms of satisfactory IOP	**Group 1:** 39 (46%) **Group 2:** 10 (50%) **Group 3:** 8 (80%) **Group 4:** 7 (37%) **Group 5:** 5 (62%) **p value:** NR	**Funding:** IMS, Inc., supplied the costs of the drugs. The study received a Grant 6610-1272-42 from the National Health Research and Development Program, Department of National Health and Welfare, Canada **Limitations:** Very small sample size. Some patients were included in more than 1 group. **Notes:** * the same eye could be included in more than one group when the treatment was changed **calculated by NCC based on monthly costs and on the assumption that treating both eyes has the same cost of treating 1eye (bottle is discarded anyway after 1month).
			Number of severe adverse reactions	**Group 1:** 9 (11%) **Group 2:** 0 (0%) **Group 3:** 2 (20%) **Group 4:** 2 (10%) **Group 5:** 1 (12%) **p value:** NR	
			Usefulness Quotient (number of patients whose condition was controlled with no severe adverse reaction divided by the number of patients who started on the treatment)	**Group 1:** 0.39 **Group 2:** 0.50 **Group 3:** 0.60 **Group 4:** 0.36 **Group 5:** 0.50 **p value:** Not Sig	
			Mean annual cost per eye treated** 1982 Can $, mean wholesale cost per bottle of drug, included the medication discarded during the study and the surplus remaining at the end.	**Group 1:** $42 (£17) **Group 2:** $50 (£21) **Group 3:** $29 (£12) **Group 4:** $13 (£5) **Group 5:** $12 (£5) **p value:** NR	
			Mean annual cost per eye treated if 54 BNF prices are used.	**Group 1:** £44 **Group 2:** £36 **Group 3:** £46 **Group 4:** £30 **Group 5:** £32	
			Cost-effectiveness ** incremental cost per year per additional patient controlled without side effects	Group 1 and 2 dominated by Group 3 and 5. Group 2 vs Group 1: $73 (£30)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			Cost-effectiveness** Incremental cost per year per additional patient controlled without side effects, calculated by NCC-AC using 54 BNF prices.	Group 1 dominated by 2. Group 3 vs Group 2: £10. Group 1 and 2 dominated by Group 5.	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Stewart et al., 2002[143] USA **Economic analysis:** cost-effectiveness **Study design** Retrospective cohort study **Duration of follow-up:** up to 12 months **Discount rates:** Costs: NA Effects: NA	**Patient group:** adult patients diagnosed with POAG or OHT in at least one eye previously prescribed a topical beta-blocker as monotherapy. **<u>All patients</u>** **N:** 148 (one eye from each subject) **<u>Group 1</u>** **N:** 37 **Age (mean):** 72.8 **M/F:** 16/21 **Mean IOP at baseline:** 20.9 **Ethnic origin:** 27 Caucasian, 10 Black **<u>Group 2</u>** **N:** 74 **Age (mean):** 75.2 **M/F:** 31/43 **Mean IOP at baseline:** 20.9 **Ethnic origin:** 42 Caucasian, 30 Black, 2 Hispanic **<u>Group 3</u>** **N:** 37 **Age (mean):** 76.4 **M/F:** 14/23 **Mean IOP at baseline:** 21.7 **Ethnic origin:** 24 Caucasian, 12 Black, 1 Hispanic	**Group 1:** Switch from Beta-blocker to Latanoprost monotherapy **Group 2:** Beta-blocker + adjunctive therapy with Latanoprost once daily **Group 3:** Beta-blocker + adjunctive therapy with Brimonidine twice daily	Number of patients with therapeutic success (IOP decreased by 2 mm Hg or more)	**Group 1:** 54% (20/37) **Group 2:** 70% (52/74) **Group 3:** 49% (18/37) **p value:** 0.056	**Funding:** NR **Limitations:** Short follow-up. Retrospective study: possible selection bias. **Additional outcomes:** Treatment changes; number of visits; adverse events; difference in cost from beta-blockers to post-enrolment treatment. **Notes:** *calculated by NCC based on monthly cost
			Mean IOP change from baseline to final follow-up visit (% change in IOP)	**Group 1:** 2.8 (13.4%) **Group 2:** 4.5 (21.5%) **Group 3:** 4.6 (21.2%) **p value:** 0.23 (on mean IOP change)	
			Mean annual cost per patient* 2001, US$ Average wholesale prices of medicines prescribed and reimbursement cost of visits and tests due to adverse events	**Group 1:** $644 (£401) **Group 2:** $998 (£622) **Group 3:** $1,274 (£794) **p value:** 0.038 (for monthly cost)	
			Cost-effectiveness* additional cost per 1 mmHg of change in IOP after 1 year of treatment	On the basis of %change in IOP Group 3 is dominated by Group 2. Group 2 vs Group 1: $208 (£130)	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ainsworth & Jay, 1991[3] UK **Economic analysis:** cost analysis **Study design** RCT* **Duration of follow-up:** 8 years **Discount rates:** Costs: none Effects: none	**Patient group:** consecutive patients of 8 ophthalmologists in 5 hospitals in Glasgow area newly diagnosed with POAG (untreated IOP of at least 26 mmHg on two occasions and field defect characteristics). **<u>All patients</u>** **N:** 104 **<u>Group 1</u>** **N:** 51 (23 unilateral glaucoma) **<u>Group 2</u>** **N:** 53 (23 unilateral glaucoma)	**Group 1:** Early trabeculectomy (within 4 weeks of diagnosis). Preliminary medical therapy is used if necessary to reduce the IOP to a safe level prior to surgery. **Group 2:** Conventional management: up to a maximum of three different topical or systemic drugs and late trabeculectomy if medical therapy has failed.	**Mean cost per patient (unilateral** – bilateral glaucoma)** 1989 GBP, cost of drugs plus 6% pharmacists' prescription fee, outpatient visits, field tests, inpatient stay***, operation. Costs adjusted for mortality.	**Group 1:** £2,139 - £2,560 **Group 2:** £1,920 - £2,569 **p value:** NR	**Funding:** NR **Limitations:** Population description missing. Hospital length of stay after surgery could have decreased since time of study. **Notes:** *From Jay1988[65].In Jay 1988 fewer patients. ** Cost of unilateral glaucoma includes subsequent treatment of the fellow eye if applicable. ***average length of stay=7.6 days
			Cost-effectiveness	NR	
			Sensitivity analysis	When the length of inpatient admission is reduced to 4 days or 1 day, early trabeculectomy becomes the less costly strategy. 4 days: Group 1 £1,780 Group 2 £ 1,875 1 day: Group 1 £ 1,130 Group 2 £ 1,405	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Henson et al., 2003[60] UK **Economic analysis:** cost analysis **Study design** comparative study with historical control **Duration of follow-up:** 3 years **Discount rates:** Costs: NR Effects: NA	**Patient group:** suspect of having glaucoma **Group 1** **N:** 194 **Group 2** **N:** 93	**Group 1:** Patients referred to a group of accredited optometrists working within their own practices and subsequently referred to Manchester Royal Eye Hospital if meeting referral criteria. **Group 2:** Patients referred to the GP and then to Manchester Royal Eye Hospital	**3-year cost of overall scheme** 2001 GBP training of optometrists, fees to optometrist, audit, minus cost savings from non-referred cases (40%) to hospital and GP	**Group 2 - Group 1:** 13,426 **p value:** NR	**Funding:** Manchester Health Authority **Limitations:** Cost of false negatives was not accounted for. **Additional outcomes:** if 23 patients per month are enrolled in the scheme of group 1, the cost saving is approximately £16 per patient.

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Coast 1997[23] UK **Economic analysis:** Cost Analysis **Study design** RCT[52,140,142] **Perspective:** NHS and patients **Duration of follow-up:** 1 year **Discount rates:** Costs: NA Effects: NA	**Patient group:** patients with glaucoma whose IOP was satisfactorily controlled with treatment; Snellen VA of 6/18 or better in both eyes, aged 50 or above **<u>All patients</u>** **N:** 405 **Drop-outs:** 2 **<u>Group 1</u>** **N:** 204 **Drop-outs:** 9 **<u>Group 2</u>** **N:** 201 **Drop-outs:** 4	**Group 1:** Monitoring by ophthalmologists with a 10-month interval **Group 2:** Monitoring by optometrists, with a 6-month interval and referral to hospital when necessary.	**Cost per glaucoma visit** 1994 GBP Cost of staff, consumables, overheads.	**Group 1:** 50 **Group 2:** 29 **p value:** NR	**Funding:** South and West Research and Development Directorate, Avon Health and the International Glaucoma Association. **Limitations:** Optometrists were volunteers, therefore the findings cannot be generalised. Effectiveness was not estimated. Data on patients are missing. **Additional outcomes:** 46 clinics per annum could be saved from a total of 1200 clinics. Time and costs to the patients were lower in Group 2.
			Annual full cost per patient 1994 GBP Cost of staff, training of optometrists, consumables, referrals from optometrists (19% patients), and overheads.	**Group 1:** 60 **Group 2:** *77* **p value:** NR	
			Marginal annual opportunity cost per patient 1994 GBP. Cost of staff time.	**Group 1:** £15 **Group 2:** £25 **p value:** NR	
			Cost-effectiveness	NA	
			Sensitivity analysis	When time spent by optometrists with patients was 60 minutes rather than 35 minutes, the annual cost per patient was £124 When rate of referrals in group 2 was 50% lower or higher than baseline annual cost per patient in group 2 was respectively £68 and £87. When follow up interval in group 2 was similar to group 1, the annual cost per patient in group 2 was £46. If the caseload optometrists are willing to accept is 100 patients, the marginal opportunity cost per patient becomes £45.	

Appendix E

Forest plots

Figure 1 Any treatment vs. no treatment – OHT conversion to COAG & COAG progression

Review: Glaucoma - Treatments
Comparison: 61 Any and all treatments v NT/Placebo
Outcome: 05 Number of patients with conversion to or progression of glaucoma - subgrouped by condition

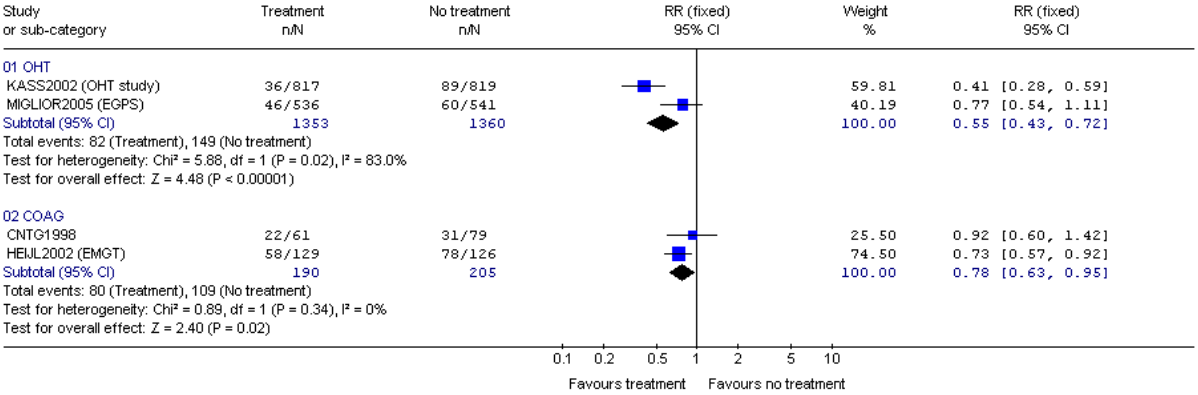


Figure 2 Any treatment vs. no treatment – visual field progression in OHT and COAG patients

Review: Glaucoma - Treatments
Comparison: 61 Any and all treatments v NT/Placebo
Outcome: 07 Number of patients with visual field progression subgrouped by condition

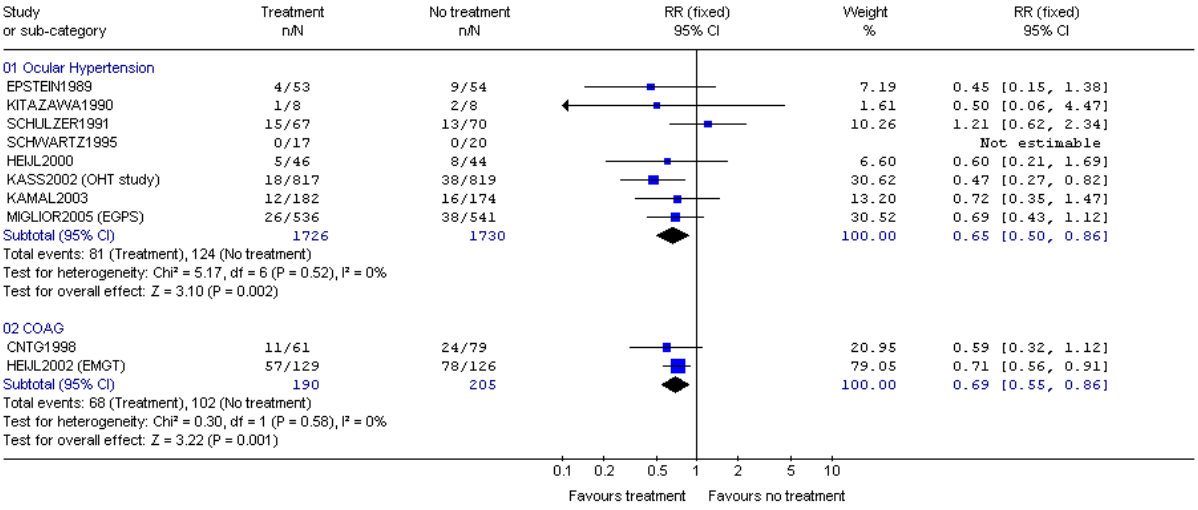


Figure 3 Any treatment vs. no treatment – change in IOP from baseline

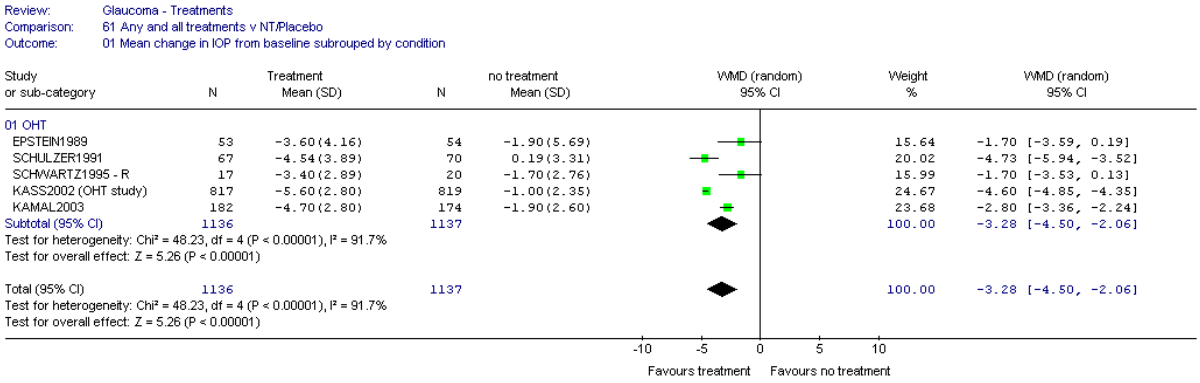


Figure 4 Beta-blockers vs. no treatment – visual field progression

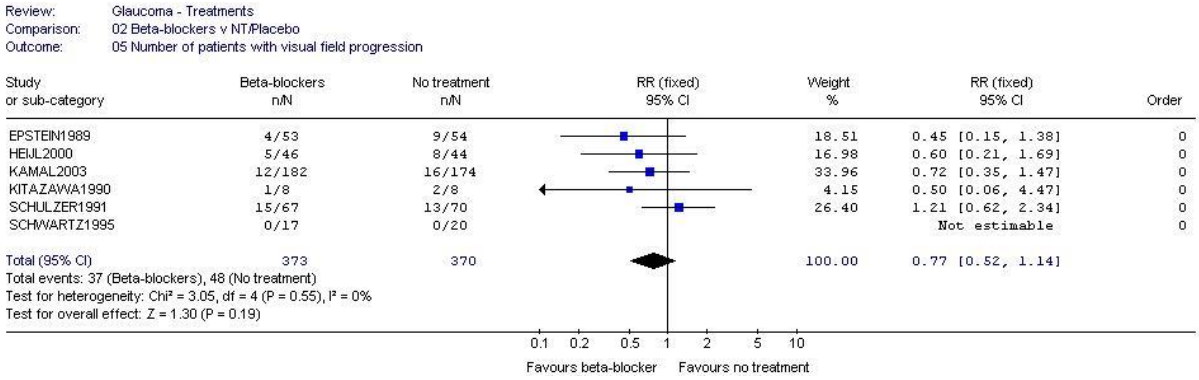


Figure 5 Beta-blockers vs. no treatment – change in IOP from baseline

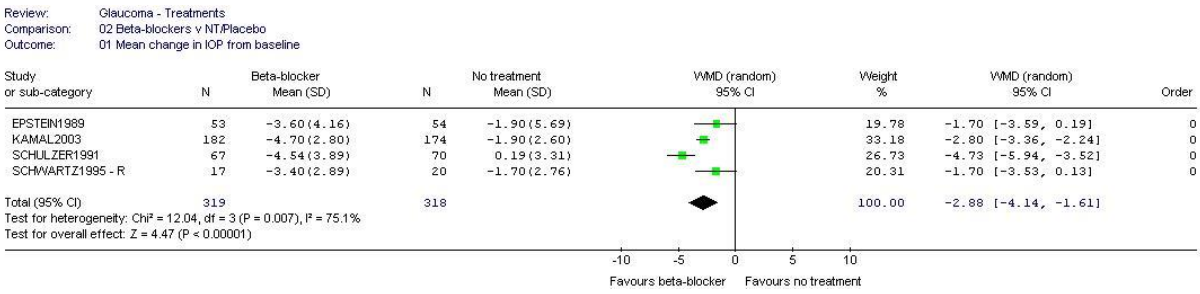


Figure 6 Beta-blockers vs. no treatment – number of patients with an IOP > 30mmHg

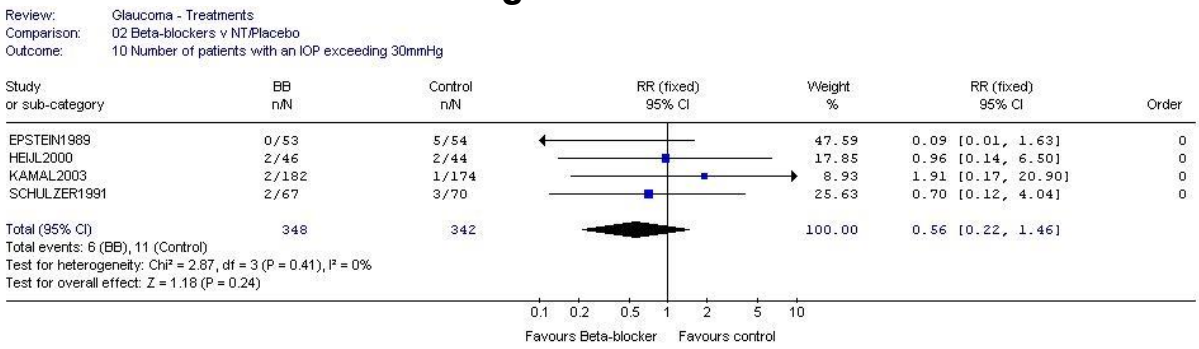


Figure 7 Beta-blockers vs. no treatment – adverse events: respiratory

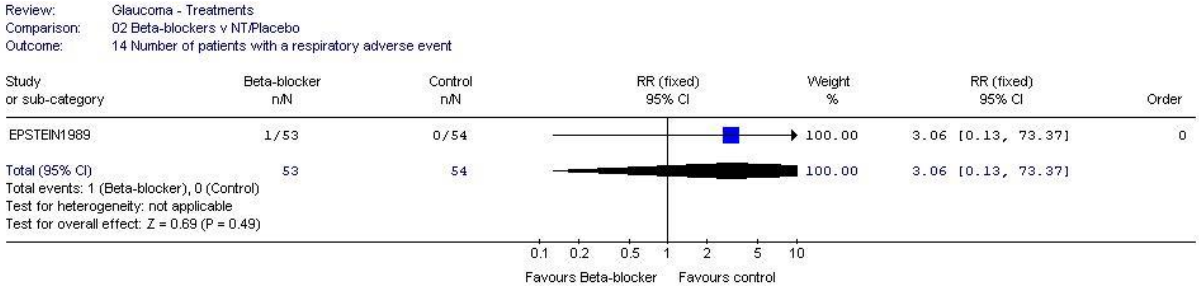


Figure 8 Beta-blockers vs. no treatment – adverse events: cardiovascular

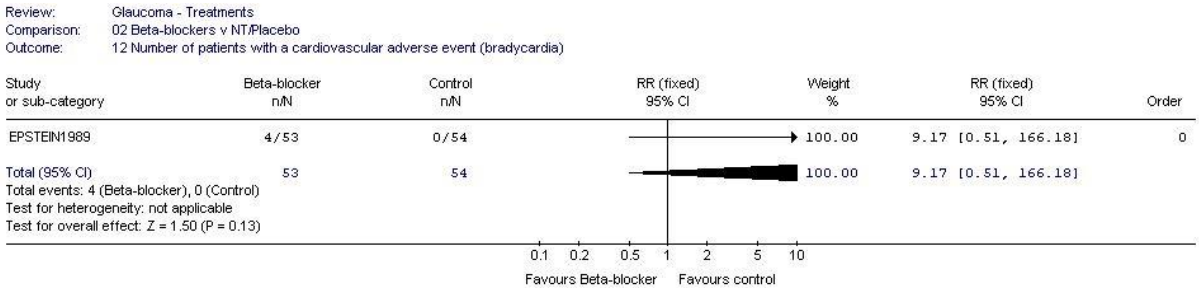


Figure 9 Beta-blockers dosage – timolol 0.5% vs. timolol 0.25% – change in IOP from baseline

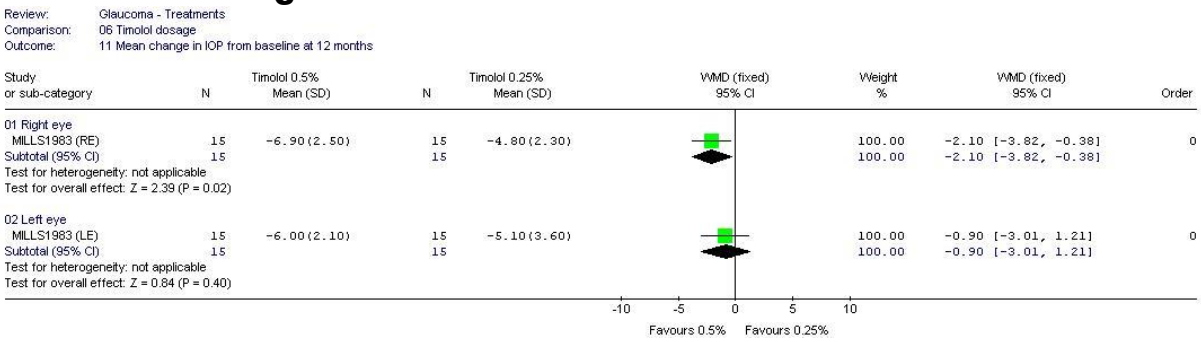


Figure 10 Prostaglandins vs. beta-blockers – change in IOP from baseline

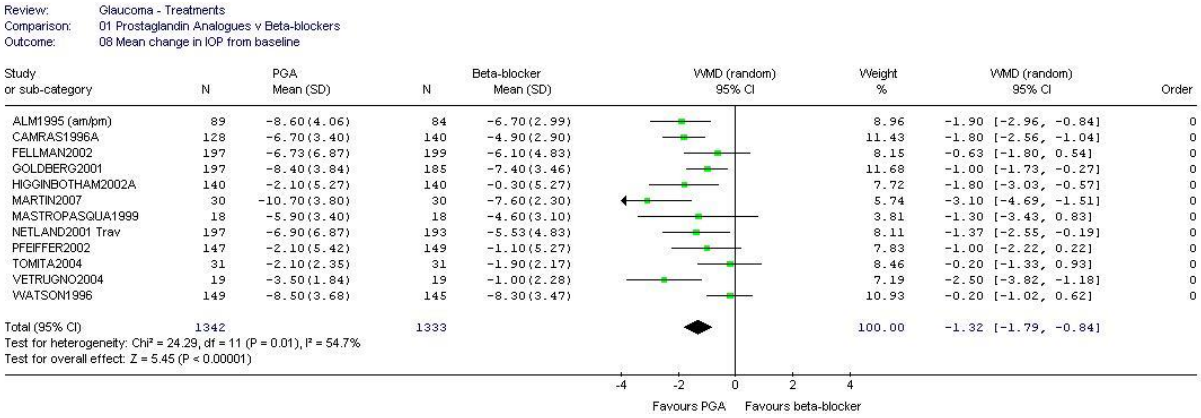


Figure 11 Prostaglandins vs. beta-blockers – number of patients with acceptable IOP

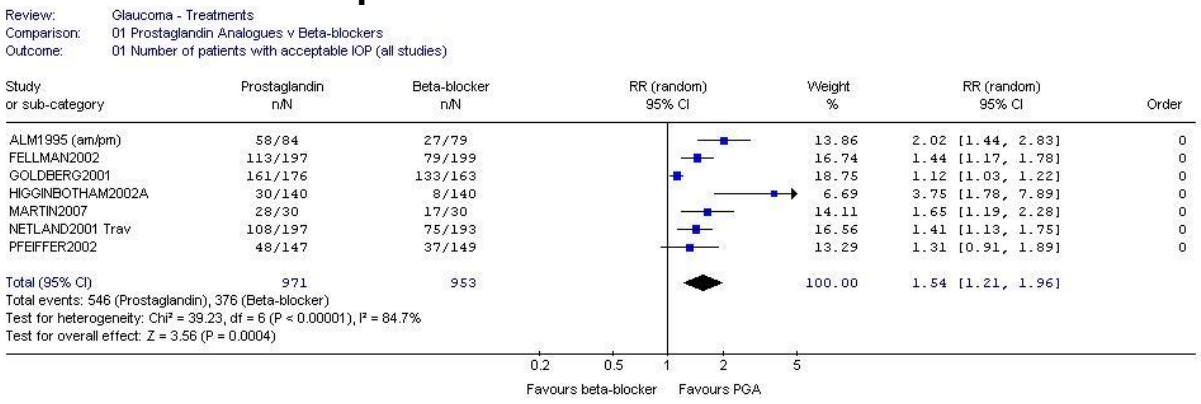


Figure 12 Prostaglandins vs. beta-blockers – adverse events: respiratory

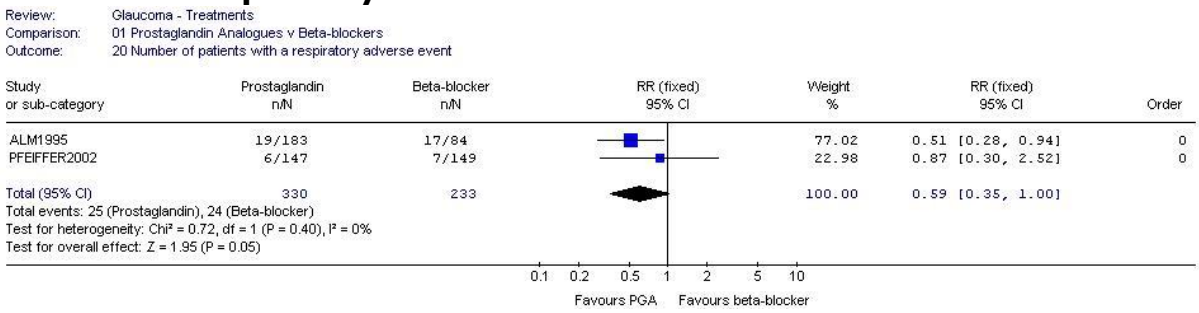


Figure 13 Prostaglandins vs. beta-blockers – adverse events: cardiovascular

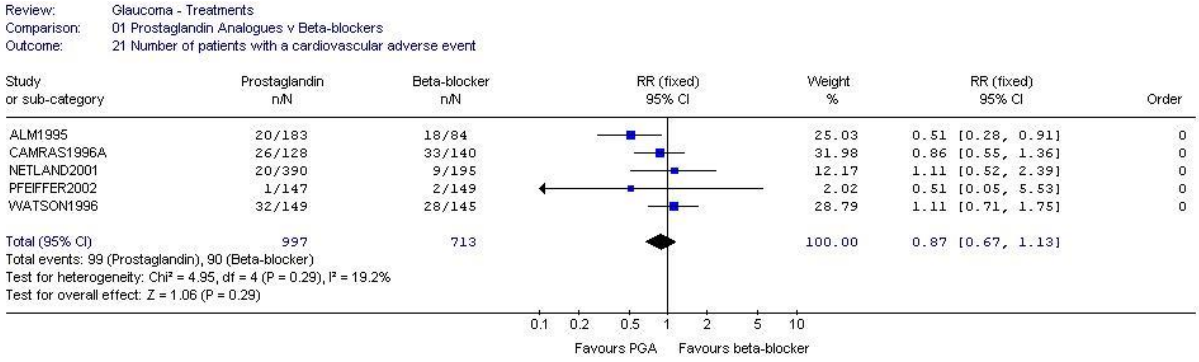


Figure 14 Prostaglandins vs. beta-blockers – adverse events: allergic reaction

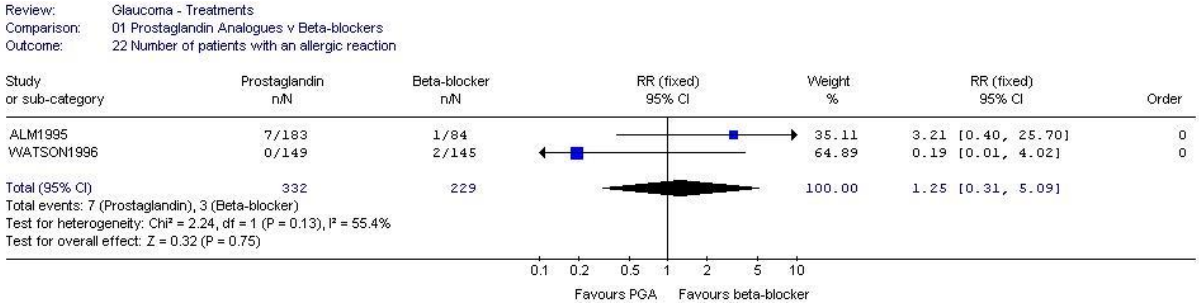


Figure 15 Prostaglandins vs. beta-blockers – adverse events: hyperaemia

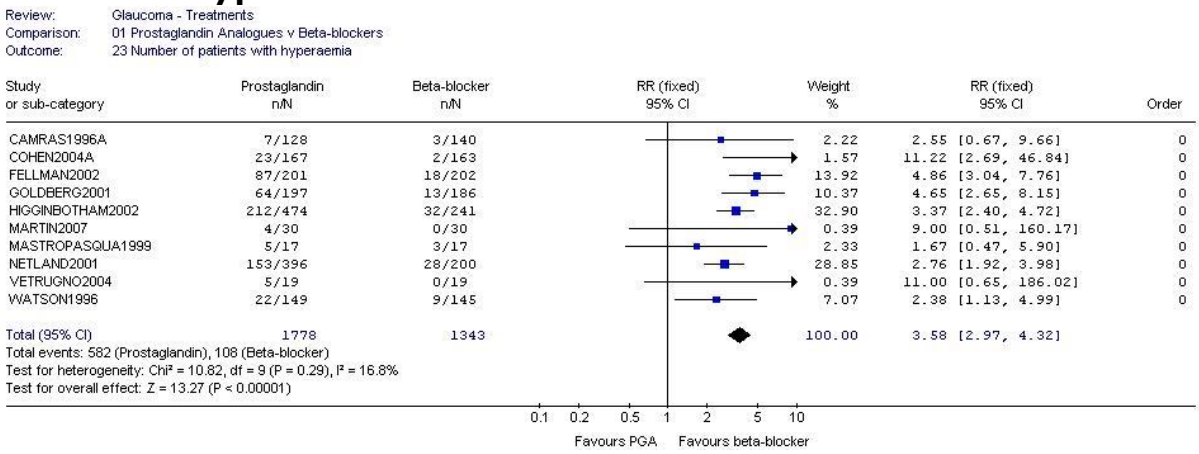


Figure 16 Prostaglandins vs. sympathomimetics – change in IOP from baseline

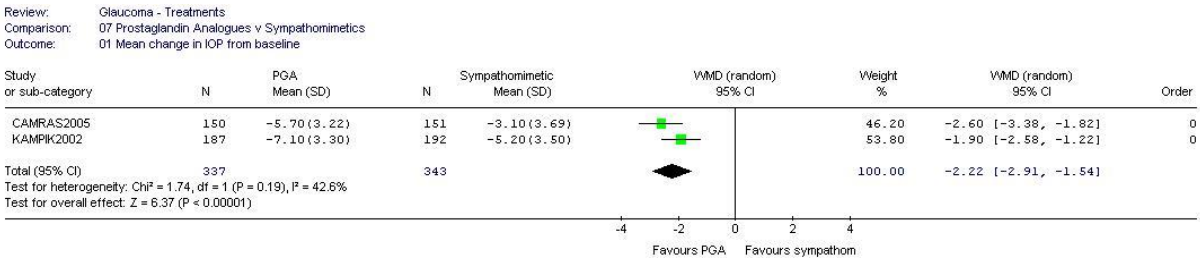


Figure 17 Prostaglandins vs. sympathomimetics – adverse events: allergic reaction

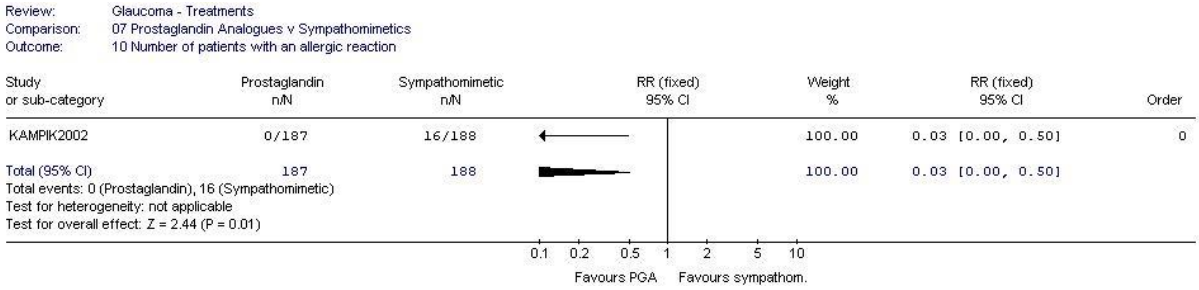


Figure 18 Prostaglandins vs. sympathomimetics – adverse events: hyperaemia

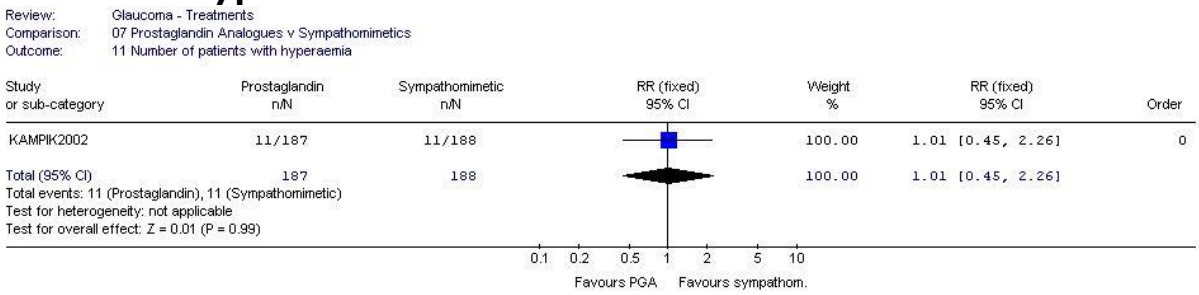


Figure 19 Carbonic anhydrase inhibitors vs. no treatment – conversion to COAG

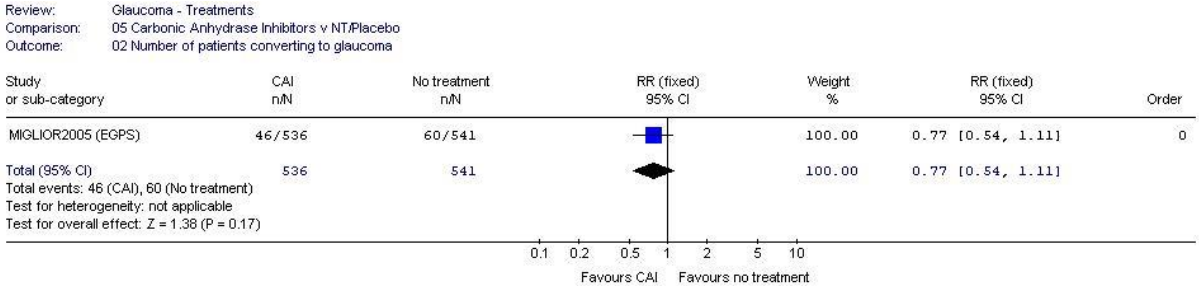


Figure 20 Carbonic anhydrase inhibitors vs. no treatment – visual field progression

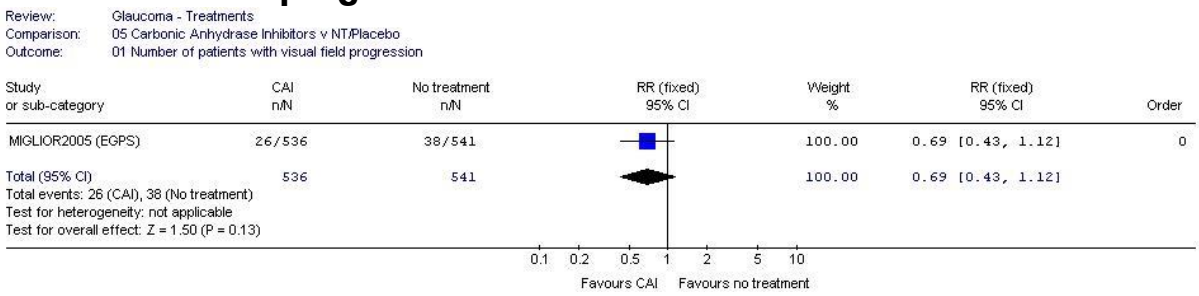


Figure 21 Carbonic anhydrase inhibitors vs. no treatment – number of patients with an IOP > 35mmHg

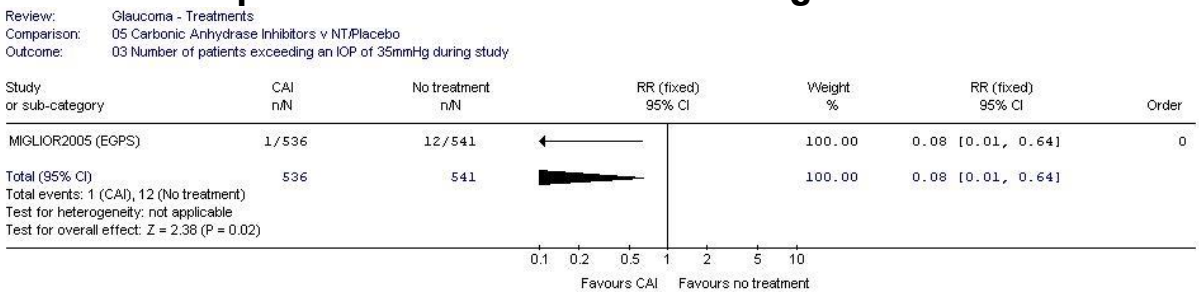


Figure 22 Carbonic anhydrase inhibitors vs. beta-blockers – adverse events: hyperaemia

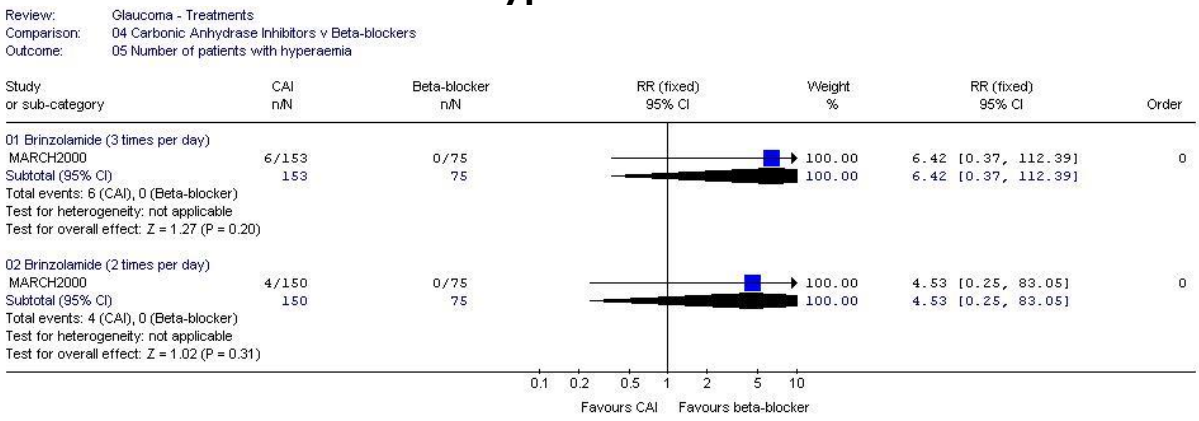


Figure 23 Sympathomimetics vs. beta-blockers – visual field progression

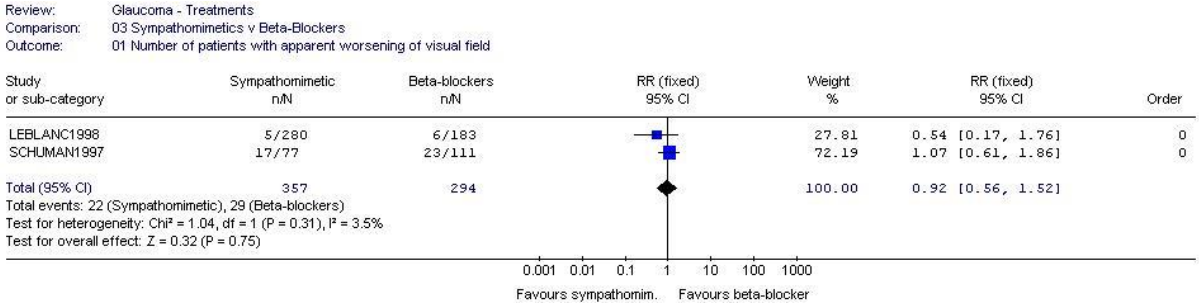


Figure 24 Sympathomimetics vs. beta-blockers – change in IOP from baseline

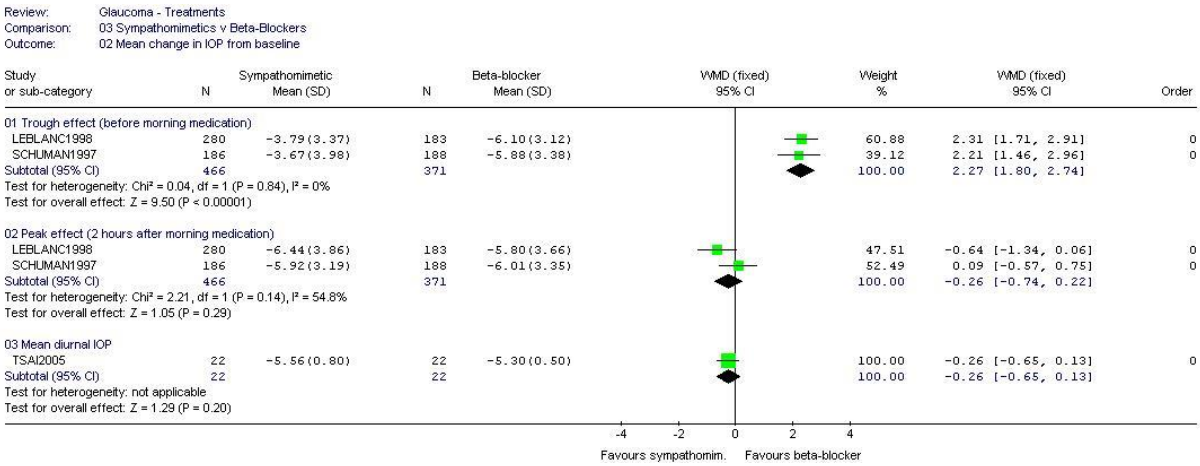


Figure 25 Sympathomimetics vs. beta-blockers – adverse events: allergic reaction

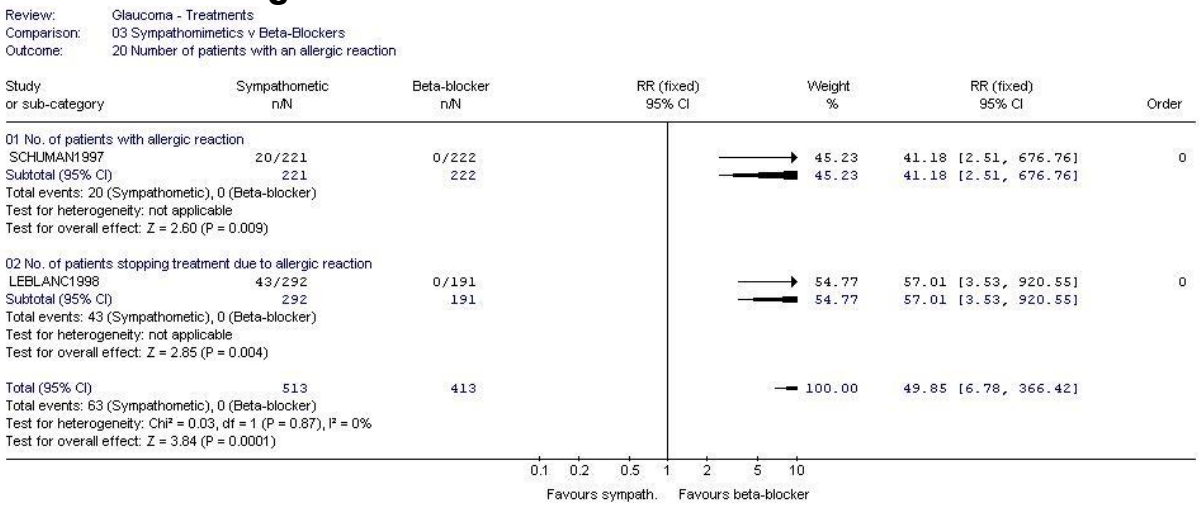


Figure 26 Sympathomimetics vs. beta-blockers – adverse events: fatigue/drowsiness

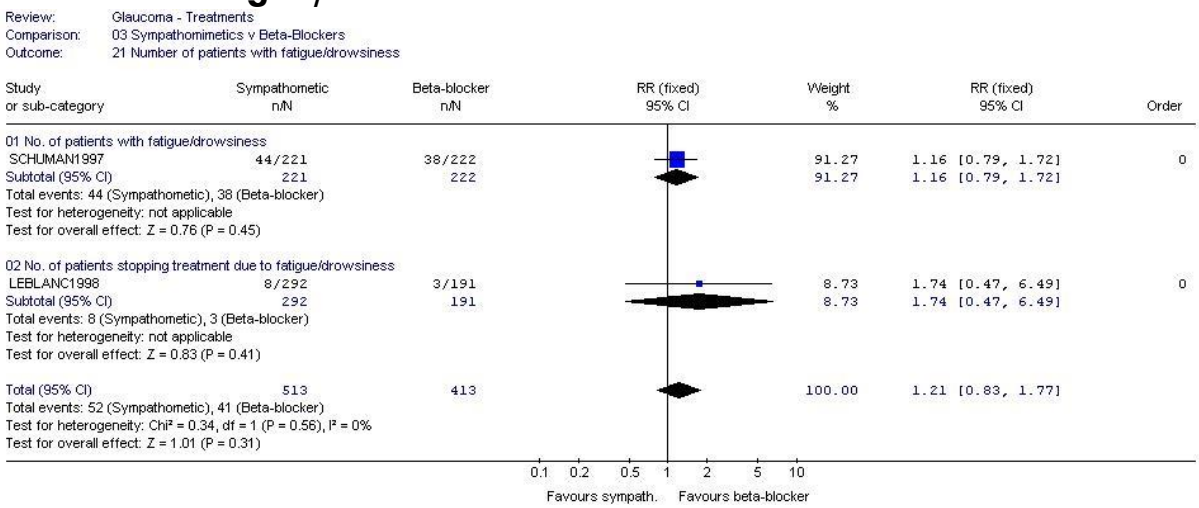
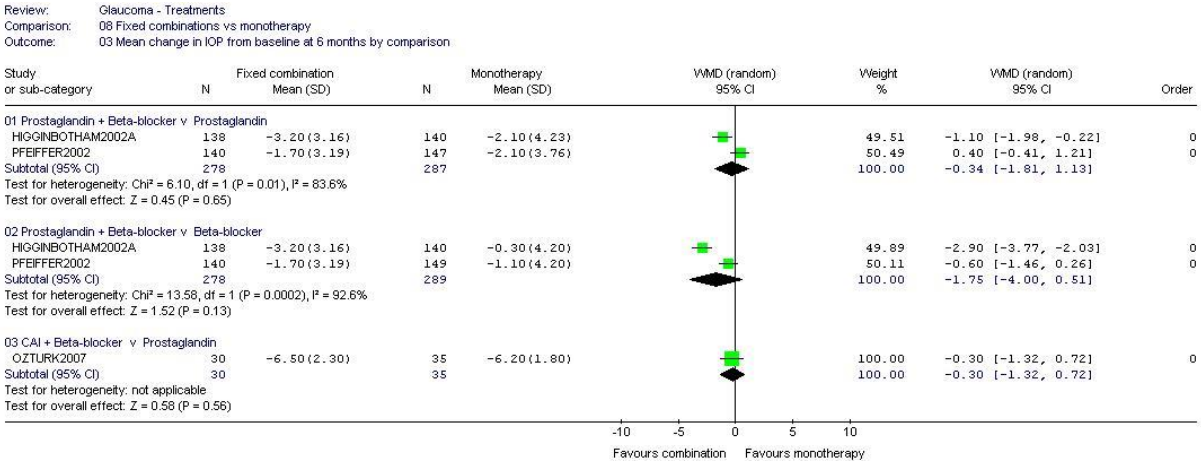
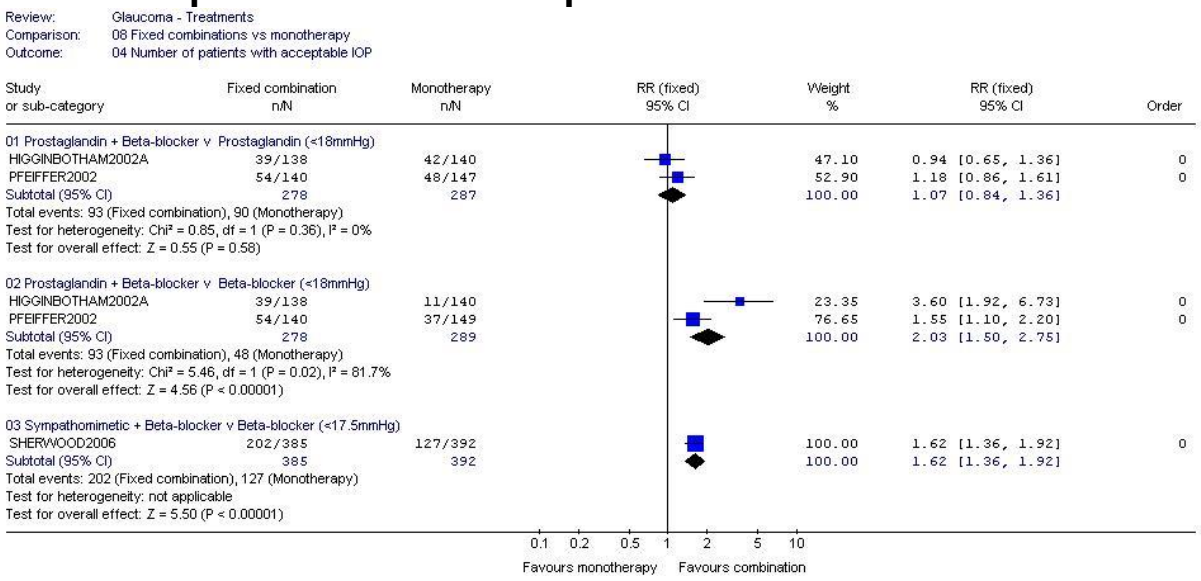


Figure 27 Fixed combination vs. single medications – change in IOP from baseline *



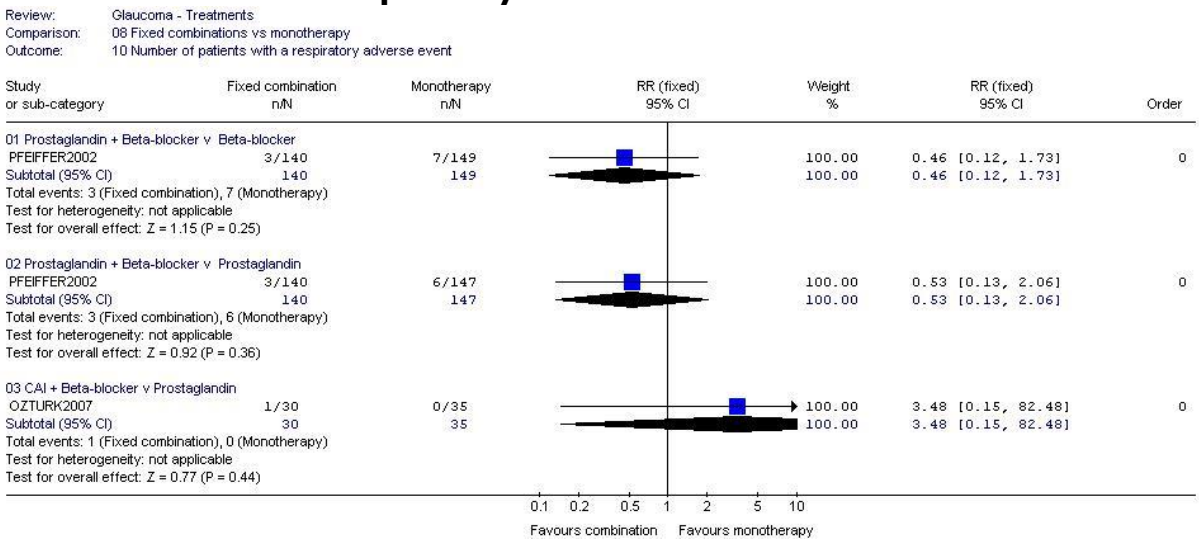
*Although all drug combinations for fixed preparations are presented in one forest plot the effect size is not totaled and each comparison is considered separately

Figure 28 Fixed combination vs. single medications – number of patients with an acceptable IOP *



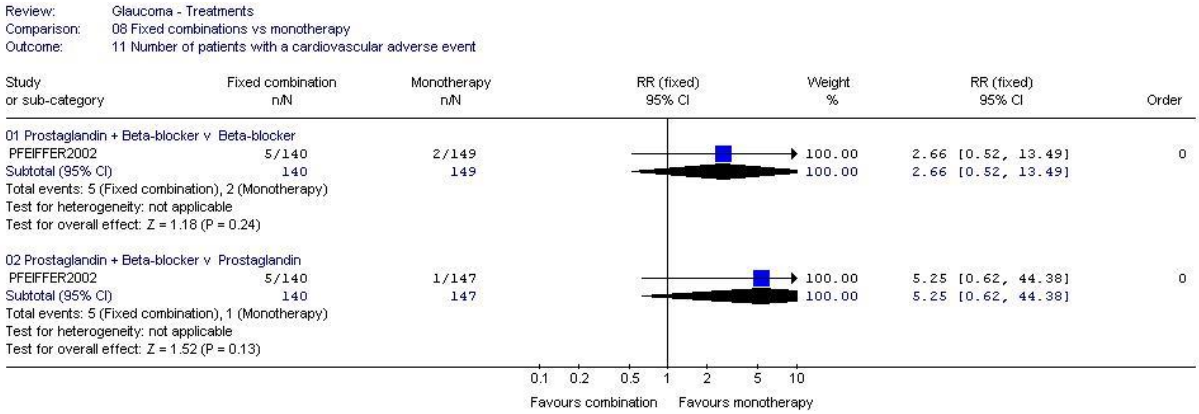
**Although all drug combinations for fixed preparations are presented in one forest plot the effect size is not totaled and each comparison is considered separately*

Figure 29 Fixed combination vs. single medications – adverse events: respiratory *



**Although all drug combinations for fixed preparations are presented in one forest plot the effect size is not totaled and each comparison is considered separately*

Figure 30 Fixed combination vs. single medications – adverse events: cardiovascular *



**Although all drug combinations for fixed preparations are presented in one forest plot the effect size is not totaled and each comparison is considered separately*

Figure 31 Fixed combination vs. single medications – adverse events: allergic reaction *

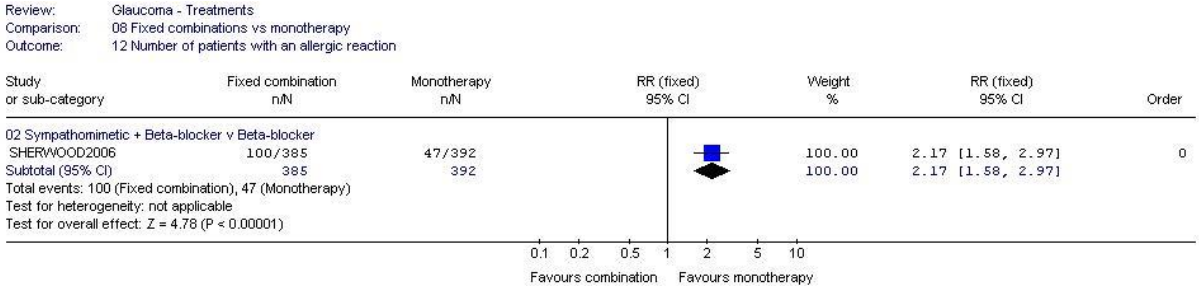
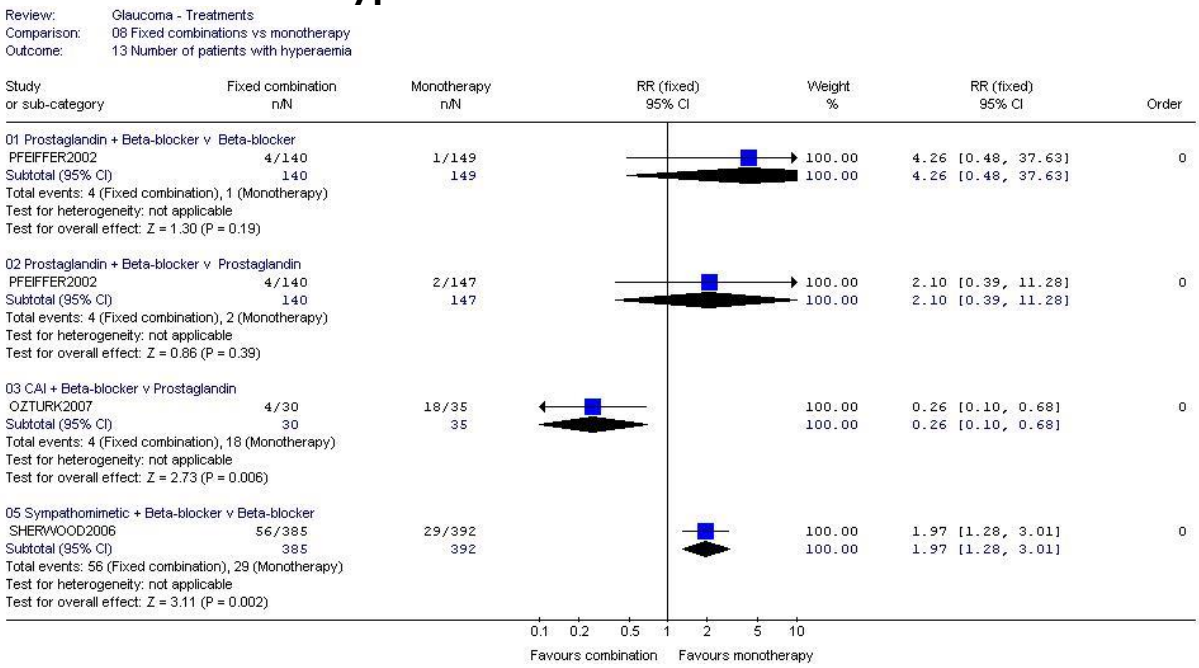


Figure 32 Fixed combination vs. single medications – adverse events: hyperaemia



**Although all drug combinations for fixed preparations are presented in one forest plot the effect size is not totaled and each comparison is considered separately*

Figure 33 Separate combination vs. single medications – change in IOP from baseline

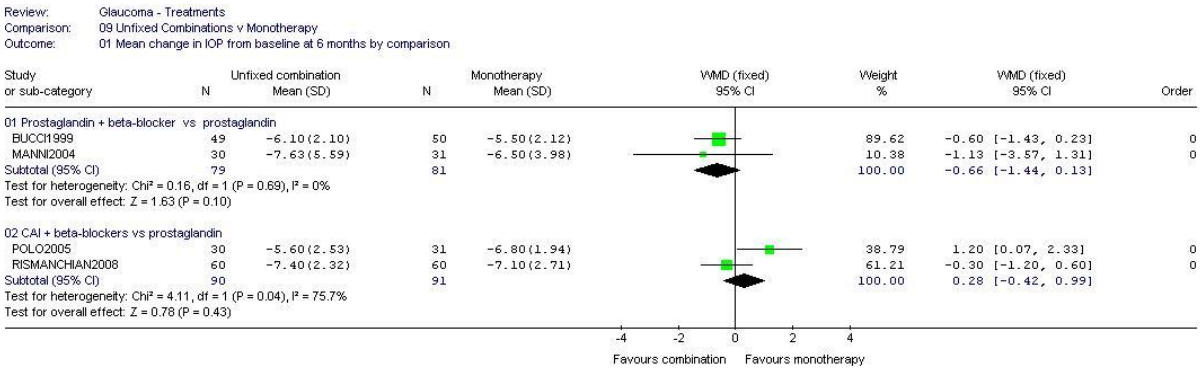


Figure 34 Separate combination vs. single medications – number of patients with an acceptable IOP

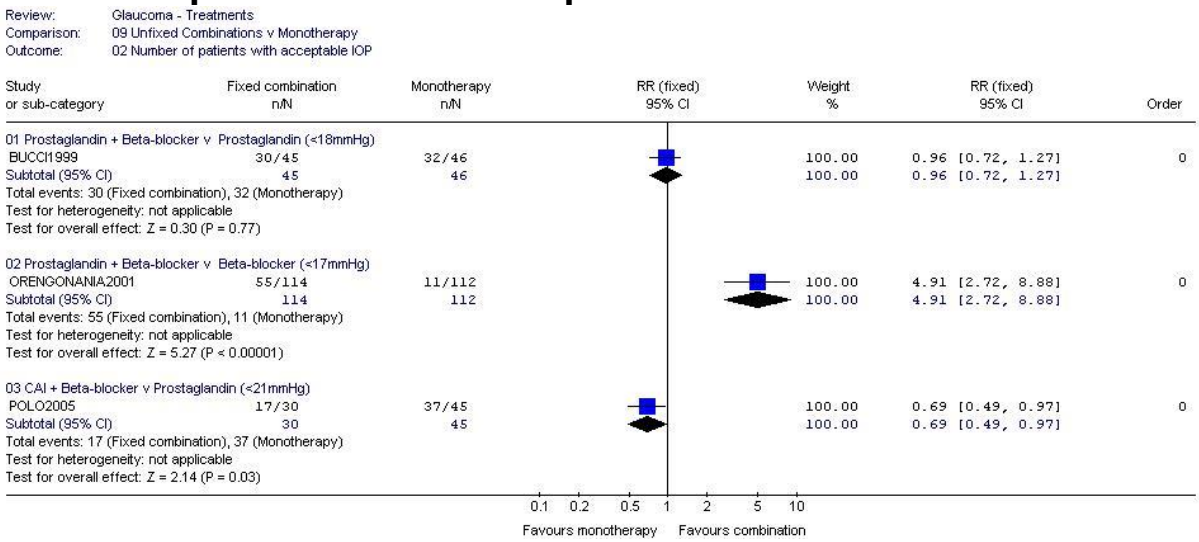


Figure 35 Separate combination vs. single medications – adverse events: respiratory

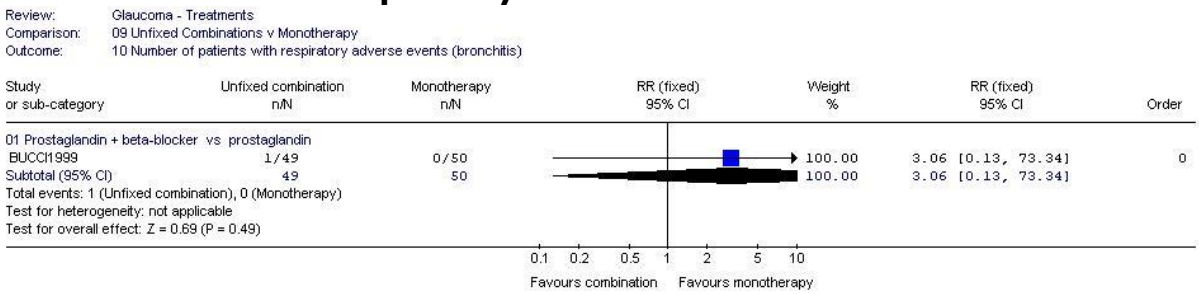


Figure 36 Separate combination vs. single medications – adverse events: hyperaemia

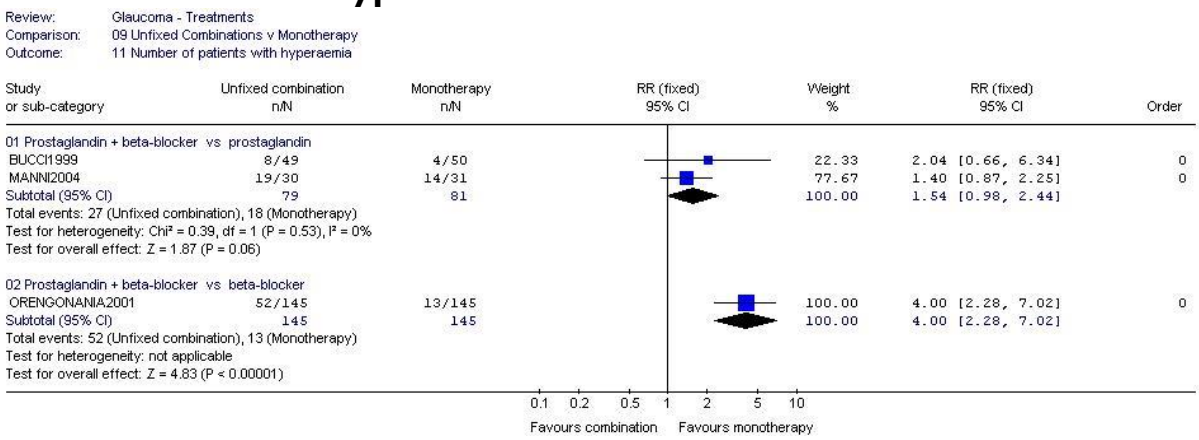


Figure 37 Selective laser trabeculoplasty vs. argon laser trabeculoplasty – change in IOP from baseline

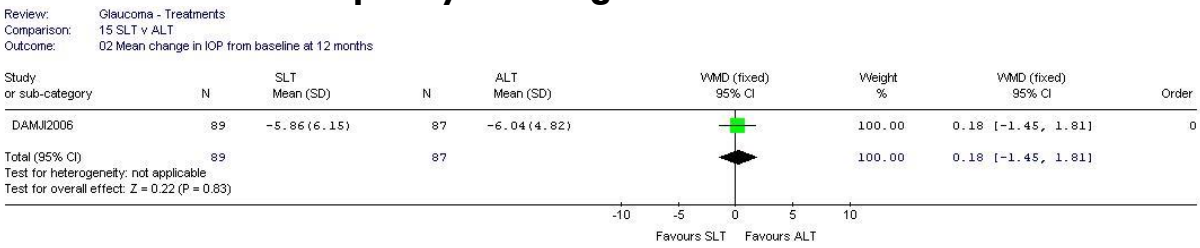


Figure 38 Selective laser trabeculoplasty vs. argon laser trabeculoplasty – unacceptable IOP

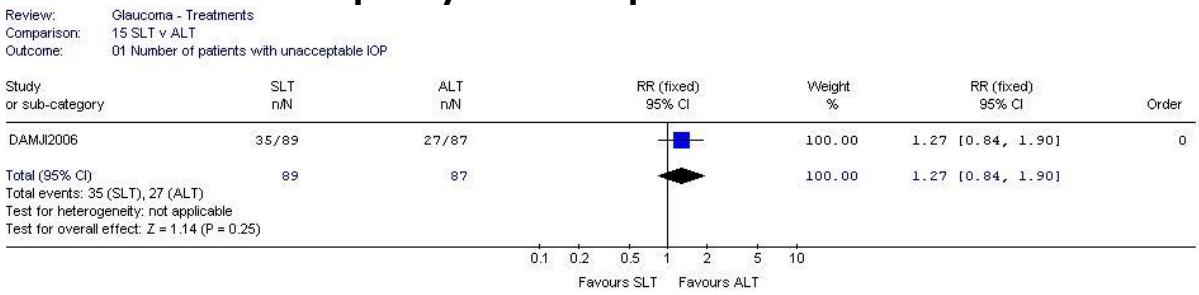


Figure 39 Selective laser trabeculoplasty vs. argon laser trabeculoplasty – complications: PAS formation

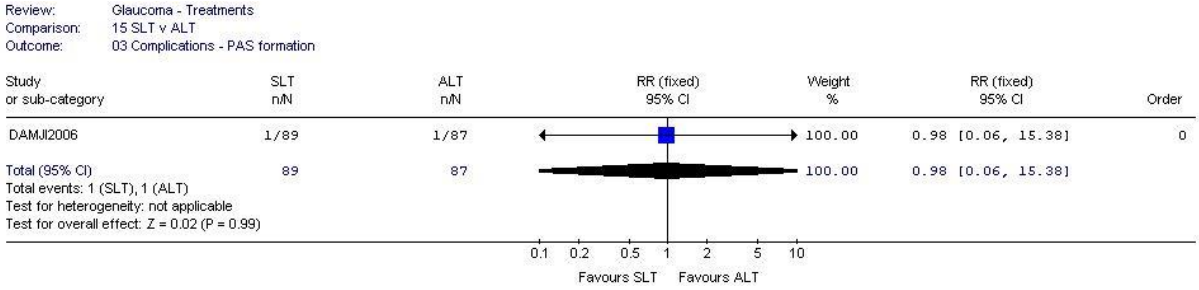


Figure 40 Laser vs. pharmacological treatment – unacceptable IOP

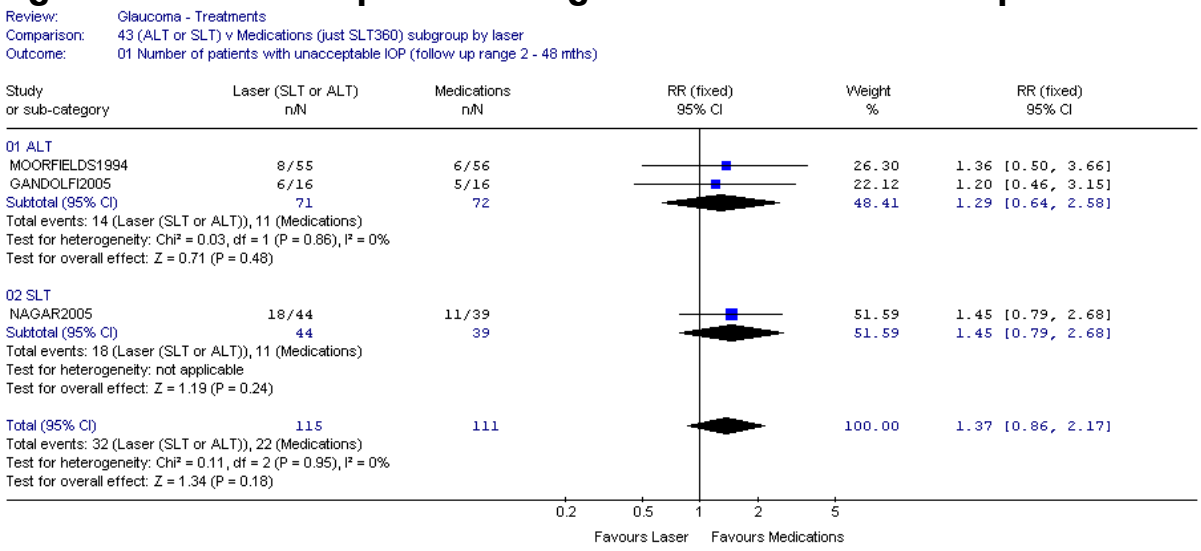


Figure 41 Laser plus pharmacological treatment vs. pharmacological treatment – unacceptable IOP

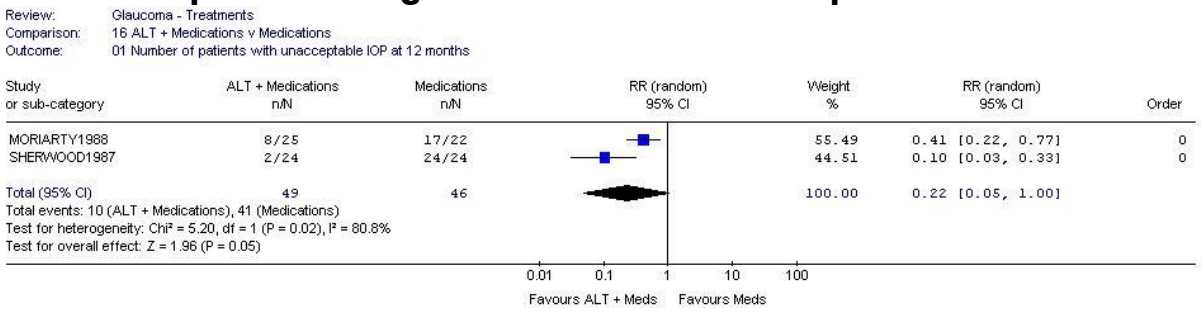


Figure 42 Laser vs. trabeculectomy – unacceptable IOP

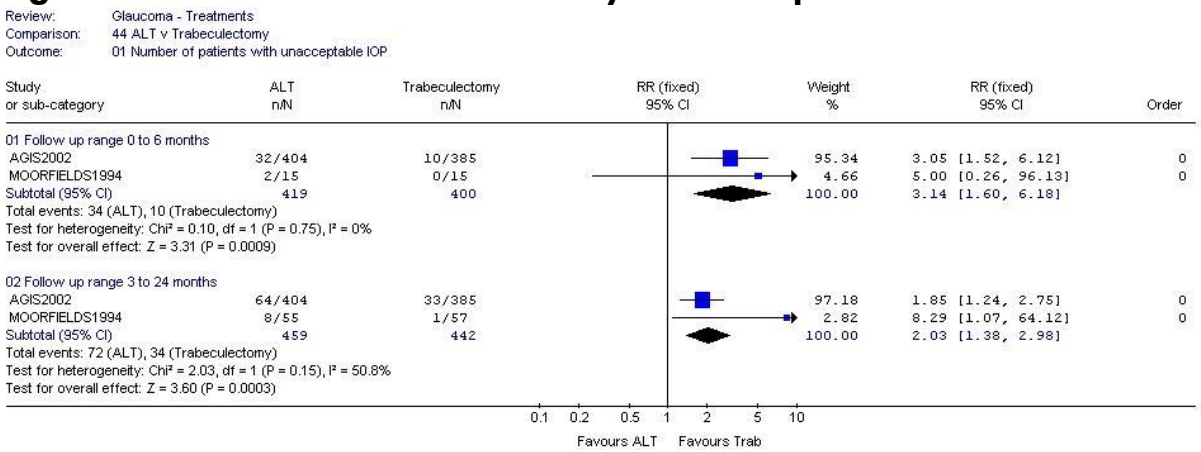


Figure 43 Trabeculectomy vs. pharmacological treatment – visual field progression at 1-5 yrs

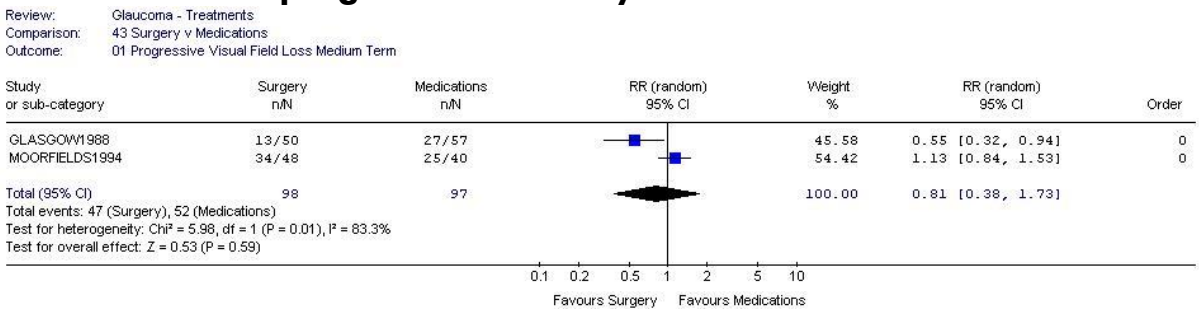


Figure 44 Trabeculectomy vs. pharmacological treatment – change in IOP from baseline at 12 mths

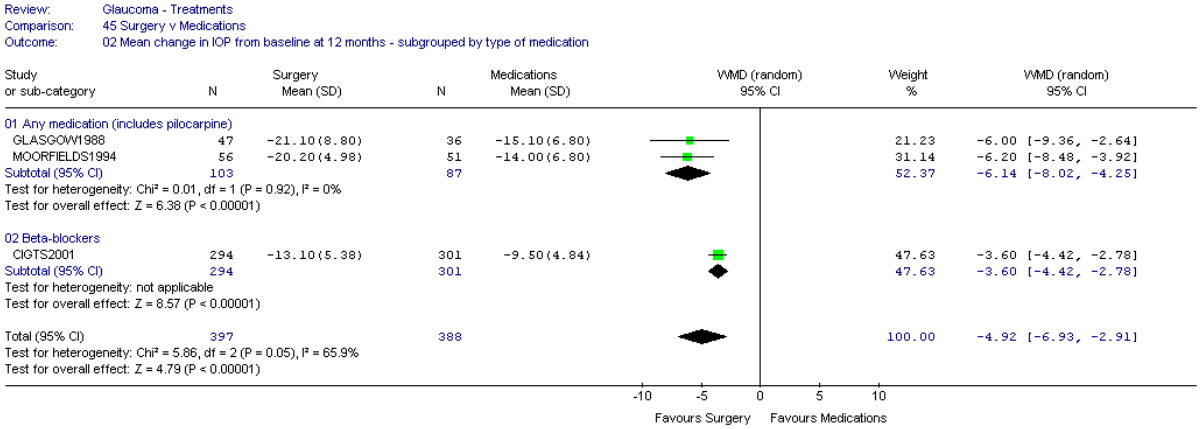


Figure 45 Trabeculectomy vs. pharmacological treatment – change in IOP from baseline at 1-5 yrs

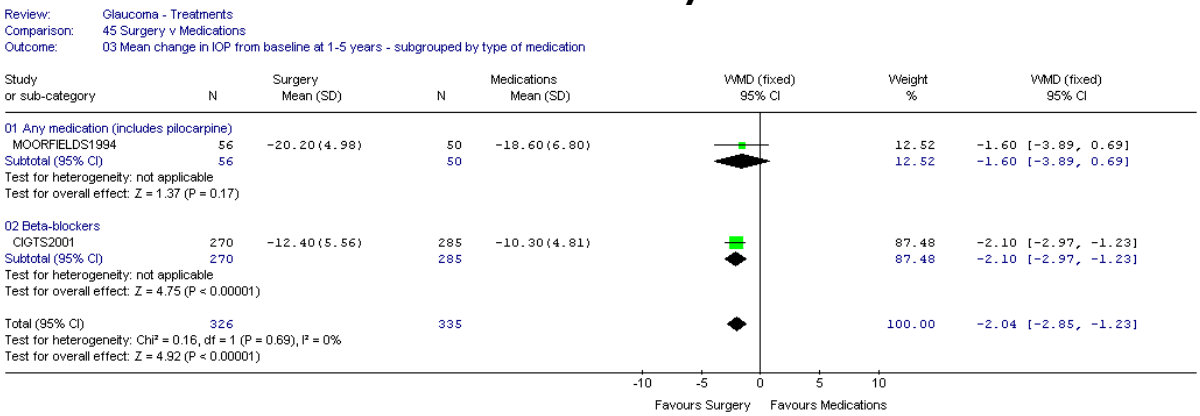


Figure 46 Trabeculectomy vs. pharmacological treatment – change in IOP from baseline at >5 yrs

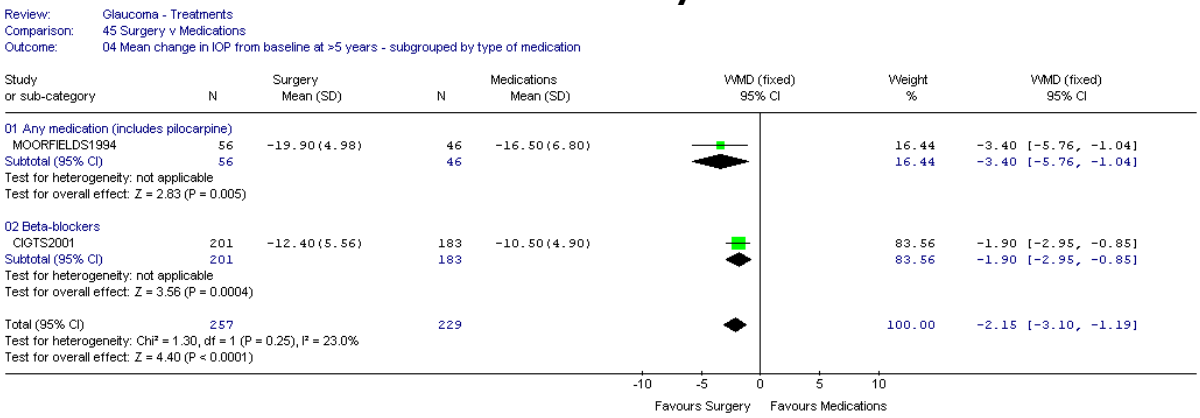


Figure 47 Trabeculectomy vs. pharmacological treatment – unacceptable IOP at 12 months

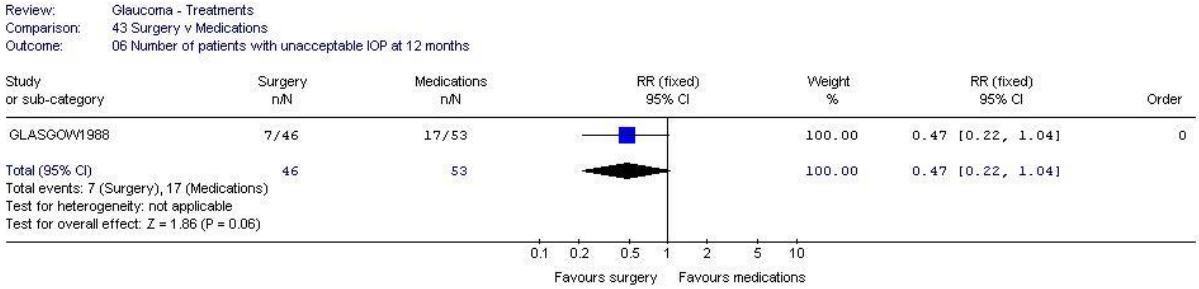


Figure 48 Trabeculectomy plus augmentation vs. trabeculectomy – unacceptable IOP

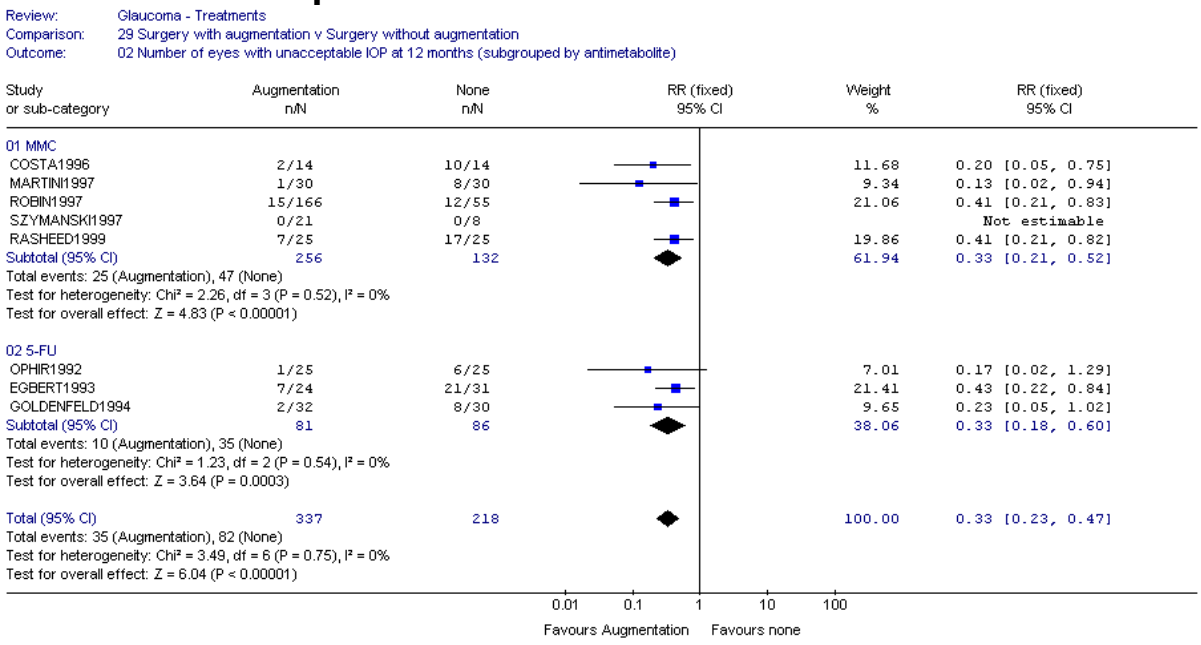


Figure 49 Trabeculectomy plus augmentation vs. trabeculectomy – complications: cataract formation

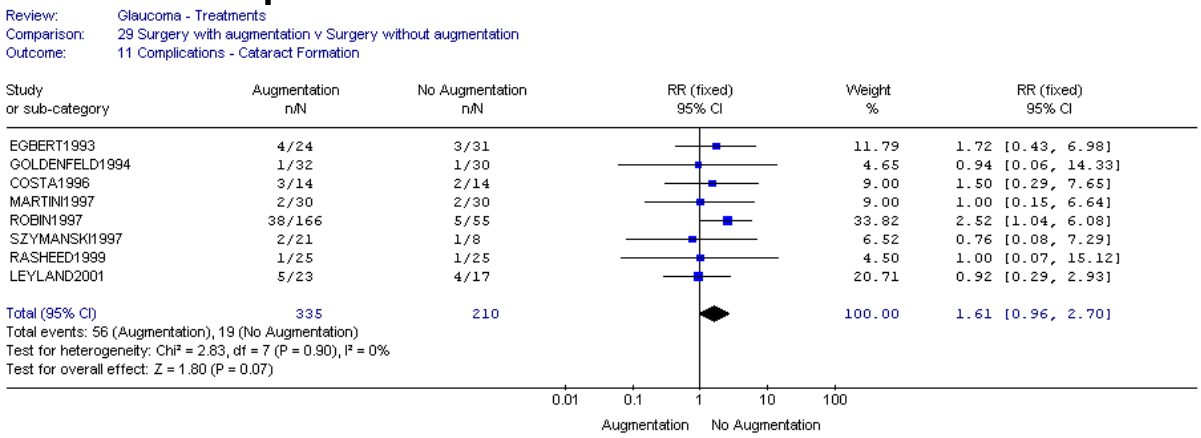


Figure 50 Trabeculectomy plus augmentation vs. trabeculectomy – complications: persistent hypotony

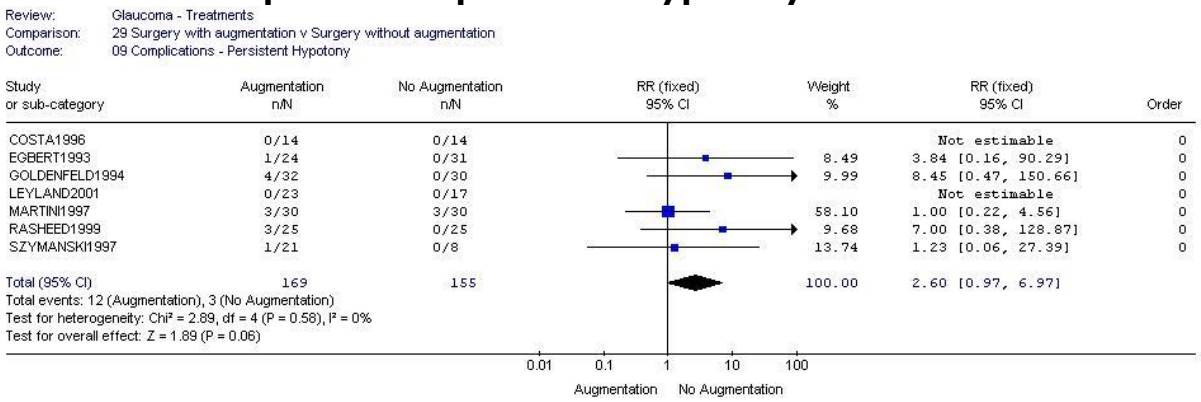


Figure 51 Trabeculectomy plus augmentation vs. trabeculectomy – complications: wound leaks

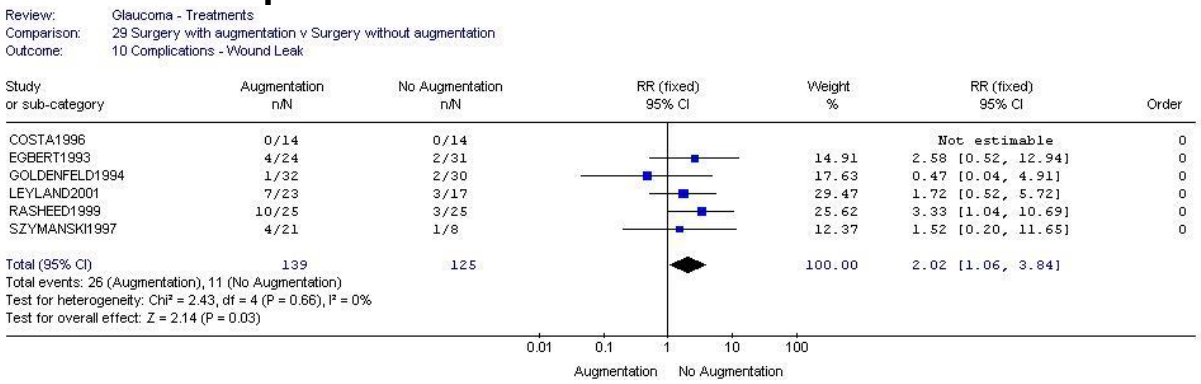


Figure 52 Trabeculectomy plus augmentation vs. trabeculectomy – complications: corneal epithelial defects

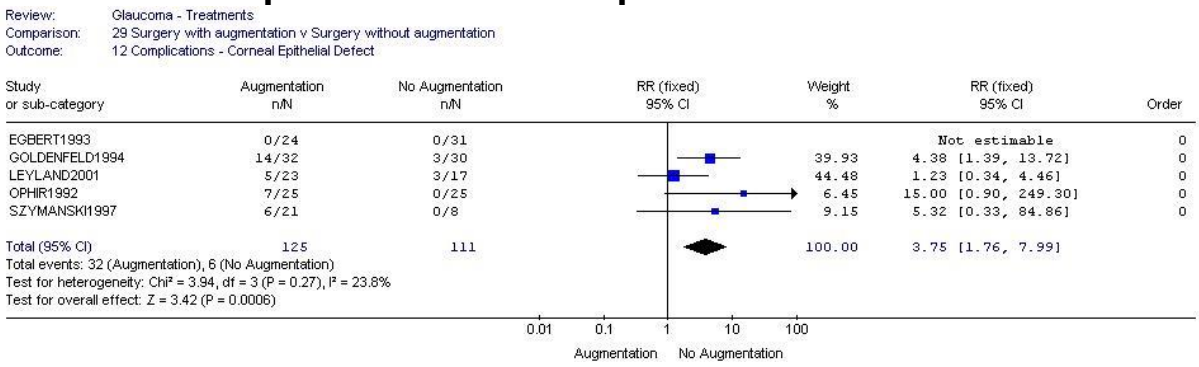


Figure 53 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – unacceptable IOP

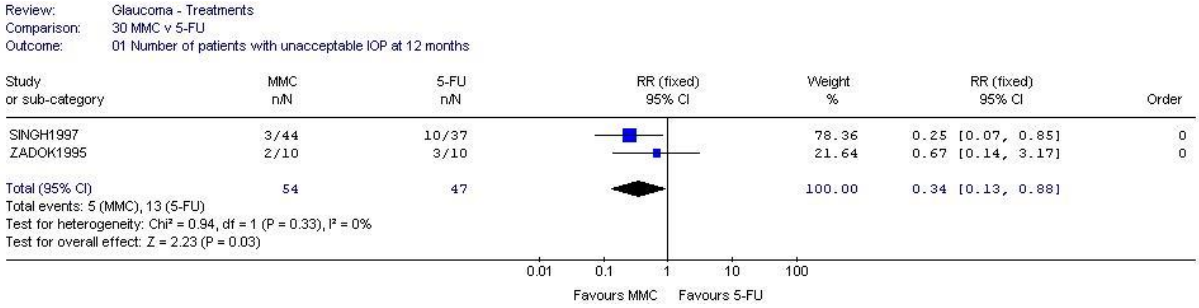


Figure 54 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: cataract formation

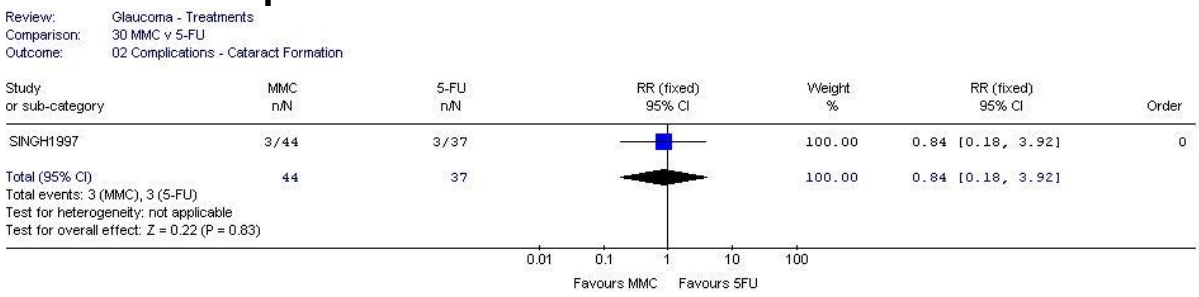


Figure 55 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: persistent hypotony

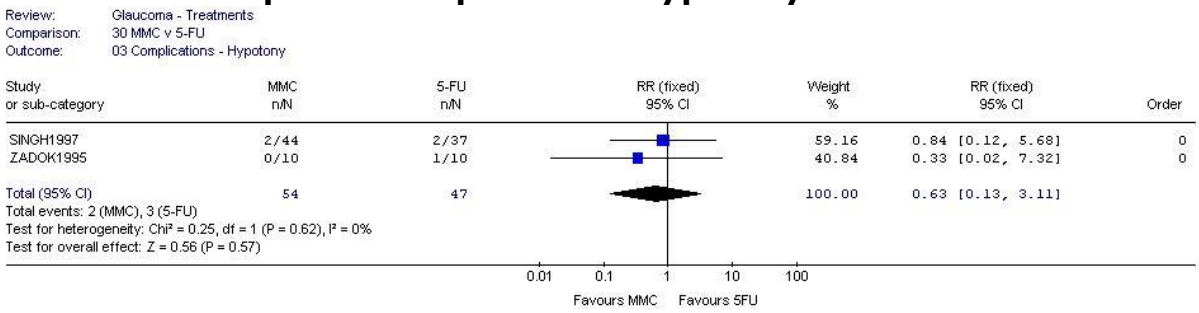


Figure 56 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: wound leaks

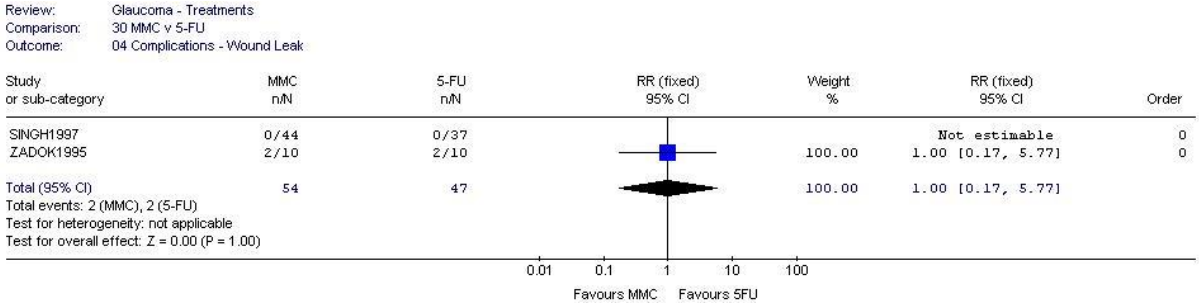


Figure 57 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: corneal defects

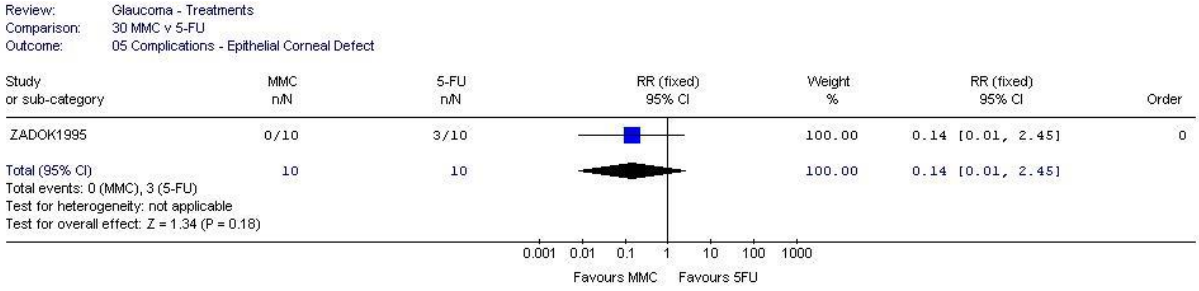


Figure 58 Viscocanalostomy vs. deep sclerectomy – change in IOP from baseline at 6 months

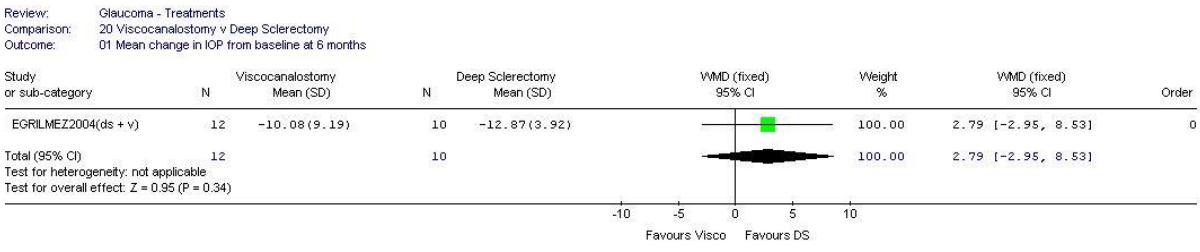


Figure 59 Non-penetrating surgery vs. trabeculectomy – change in IOP from baseline at 6 months

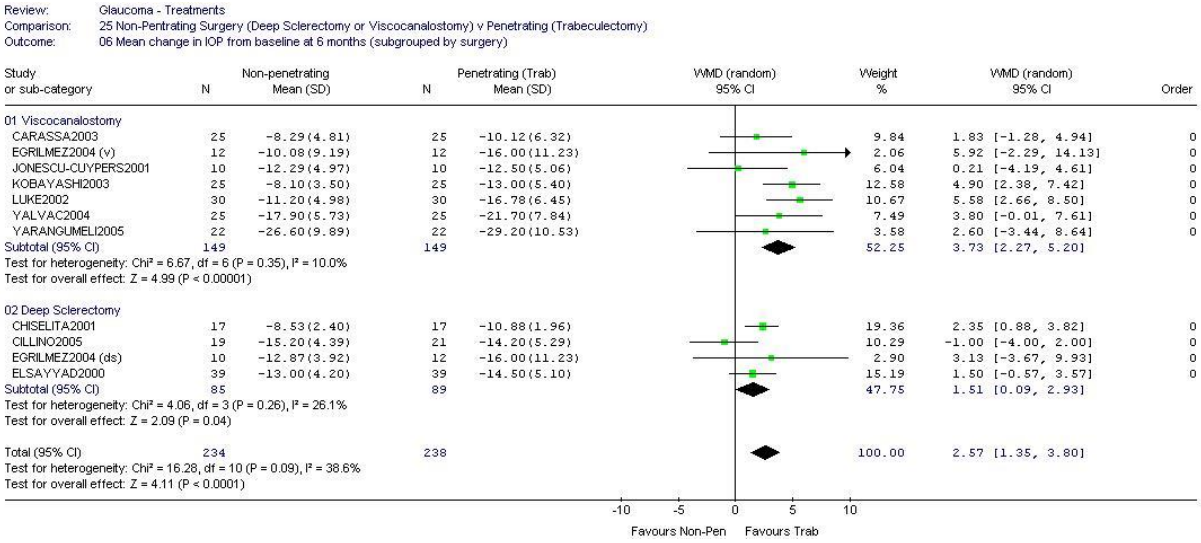


Figure 60 Non-penetrating surgery vs. trabeculectomy – change in IOP from baseline at 12 months

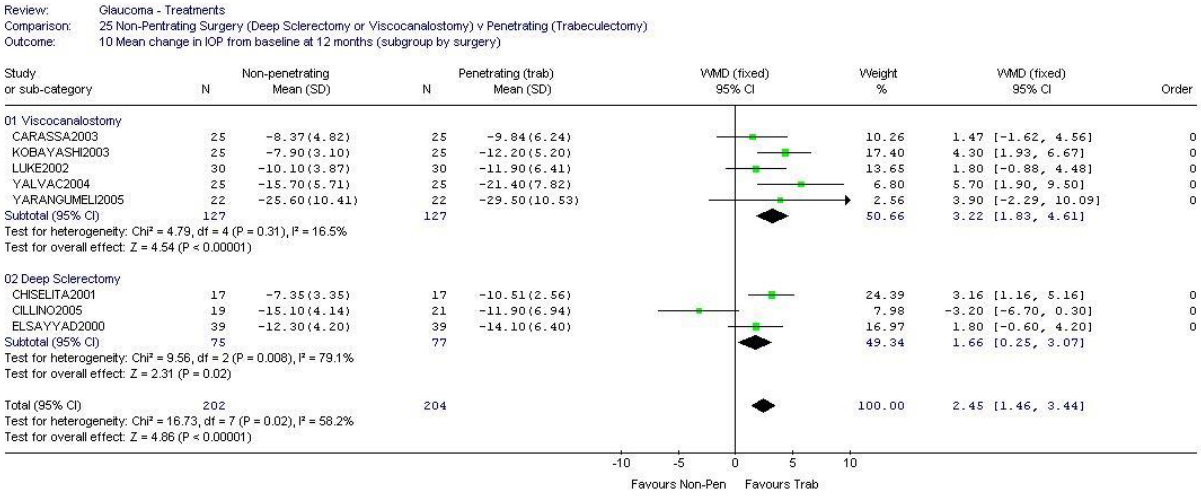


Figure 61 Non-penetrating surgery vs. trabeculectomy - unacceptable IOP

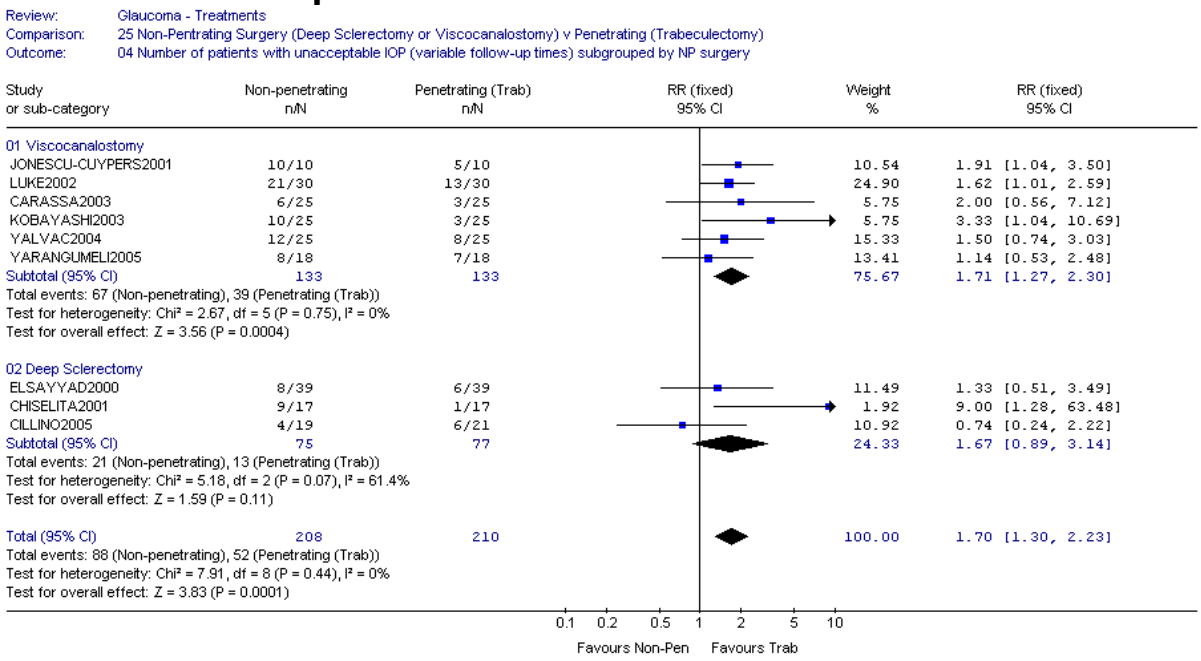


Figure 62 Non-penetrating surgery vs. trabeculectomy – complications: cataract formation

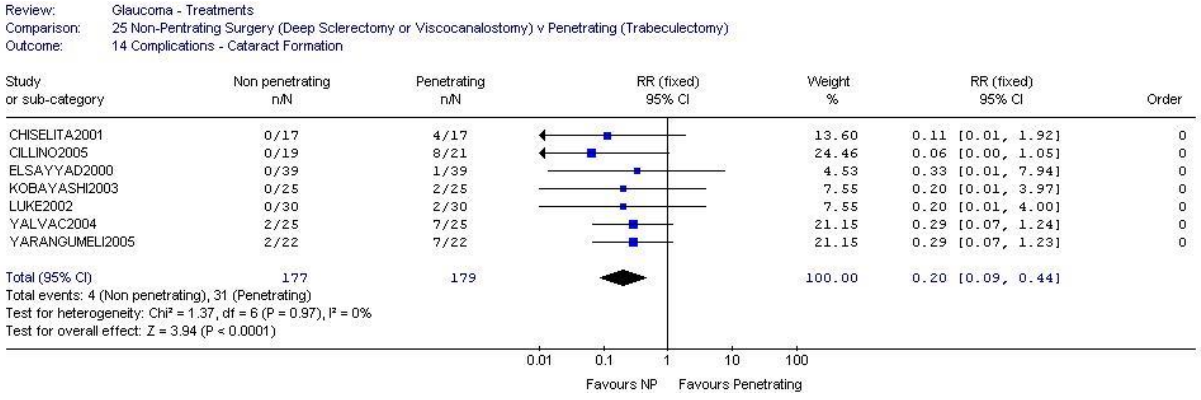


Figure 63 Non-penetrating surgery vs. trabeculectomy – complications: persistent hypotony

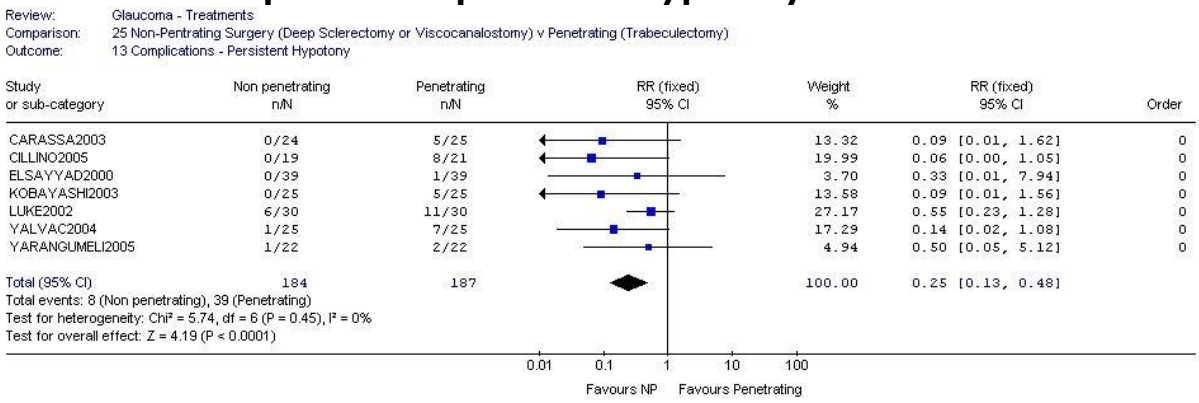


Figure 64 Non-penetrating surgery vs. trabeculectomy – complications: wound leaks

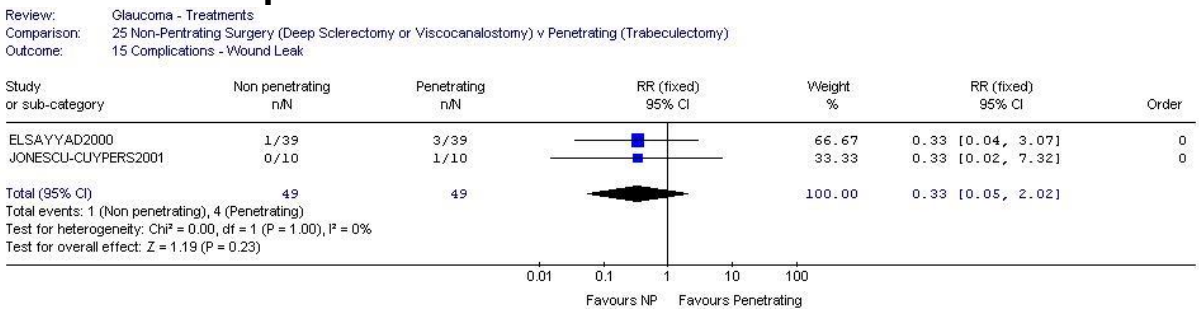
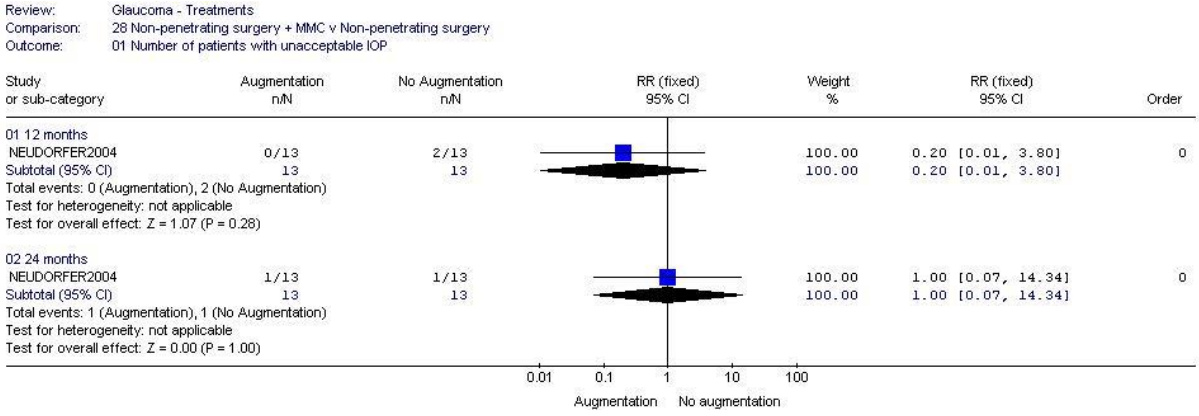


Figure 65 Non-penetrating surgery plus augmentation vs. non-penetrating surgery – unacceptable IOP



Appendix F

1 Cost-effectiveness analysis

1.1 Introduction

Most of the economic evidence of this guideline derives from original cost-effectiveness analyses carried out by the NCC-AC. The main cost-effectiveness analysis was carried out to answer the clinical questions on treatment of patients with OHT and COAG suspects (Chapter 7), and the clinical question on treatment of patients with COAG (Chapter 8). Throughout the guideline we refer to this analysis as 'NCC-AC model'.

A further cost analysis was carried out to answer the clinical questions on diagnosis and monitoring measurements (Chapters 4 and 5). Throughout the guideline we refer to this analysis as 'NCC-AC cost analysis'.

1.2 Methods

The GDG identified the initial treatment strategy for both COAG and OHT patients as a high priority area for economic analysis. Specifically, the aim was to determine the most cost-effective strategy for patients who have not been treated before. Therefore, the priority for economic evaluation was limited to the following interventions according to the availability of good data on their clinical effectiveness, current use and licensing as a first-choice treatment:

- no treatment
- medical treatment with prostaglandin analogues (PGA)
- medical treatment with beta-blockers (BB)
- trabeculectomy (for COAG patients only)

For this area a review of the literature was conducted followed by economic modelling of the cost-effectiveness of the listed interventions in England and Wales (1.3). The literature search and review methods can be found in 2.4 and 2.6.

The questions on clinical measurements at diagnosis and monitoring were assigned a medium priority for economic analysis and so only a simple cost-analysis (1.4) was performed.

1.3 NCC-AC model: Cost-effectiveness of treatment

Our aim in constructing the model was to determine the most cost-effective strategy in managing OHT and COAG patients from the point of diagnosis.

We found a number of economic evaluations in the published literature (Chapters 7 and 8) but still it was necessary to develop our own analysis to determine the most cost-effective treatment strategy for different subgroups of patients. We took this approach because we found limited applicability in the published economic evaluations, mainly because the important long-term consequences (i.e. development of blindness) were ignored[3], drugs were lumped together in a single medical treatment group[3,80,144], or important alternatives such as surgery were not considered[82]. Furthermore most of the published studies did not evaluate cost-effectiveness using the NICE reference case[3,82].

The medical interventions we compared in the model are those which are licensed to be used as first-line treatments (beta-blockers and prostaglandin analogues). For COAG patients, trabeculectomy was compared to beta-blockers and prostaglandin analogues.

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.
- When published data was not available we used expert opinion to populate the model.
- Model assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- We followed the methods of the NICE reference case[108]. Therefore costs were calculated from a health services perspective. Health gain was measured in terms of quality-adjusted life-years (QALYs) gained. Both future costs and QALYs were discounted at 3.5%.
- The model employed a cost-effectiveness threshold of £20,000 per QALY gained.

1.3.1 General method

Glaucoma is a progressive disease where a patient's sight can deteriorate and never recover. The model is thus represented by a Markov model where patients cannot go back to previous stages. The cycle length was set at 2 months as this was thought to be the minimum time after which a change in treatment could occur. All the probabilities, costs and health utilities were converted in order to reflect the two-month values.

When defining the COAG stages we have used an adapted version of the Hodapp, Parrish and Anderson classification (Table 168). We have opted for this staging system as it allows us to use costs and utility values associated with different severity levels of COAG already present in the literature (see 1.3.11 and 1.3.14).

It was also used in previous glaucoma economic models[14,80] and in the selected sources of probability of progression[14].

Compared to the original staging system, we have collapsed the last two stages (severe COAG and blindness) as there was an overlap of their definitions and a lack of data of progression in the absence of treatment from severe COAG to blindness.

Table 168 - Staging classification in the model

COAG STAGE	*MEAN DEFECT SCORE*
No COAG (a)	No visual field defect
Early	-0.01 to -6.00 dB
Moderate	-6.01 to -12.00 dB
Advanced	-12.01 to -20.00
Severe Visual Impairment	-20.01 or worse

(a) *Includes OHT patients*

Patients diagnosed with OHT could be initially treated with a beta-blocker or a prostaglandin analogue or could be offered no treatment until they develop COAG (Figure 66).

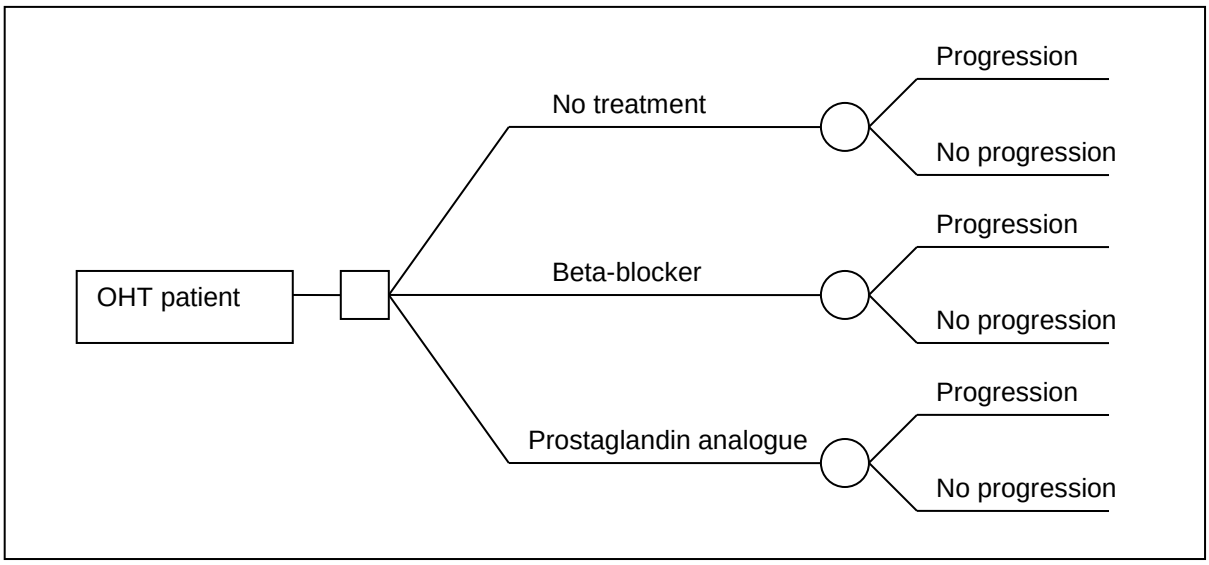


Figure 66 - Treatment strategies for OHT patients

Patients diagnosed with COAG could be treated either with a beta-blocker, a prostaglandin analogue, or trabeculectomy or could be offered no treatment until they progress to the following COAG stage (Figure 67). In the base case scenario patients were diagnosed with early COAG but in the sensitivity analysis we varied this assumption.

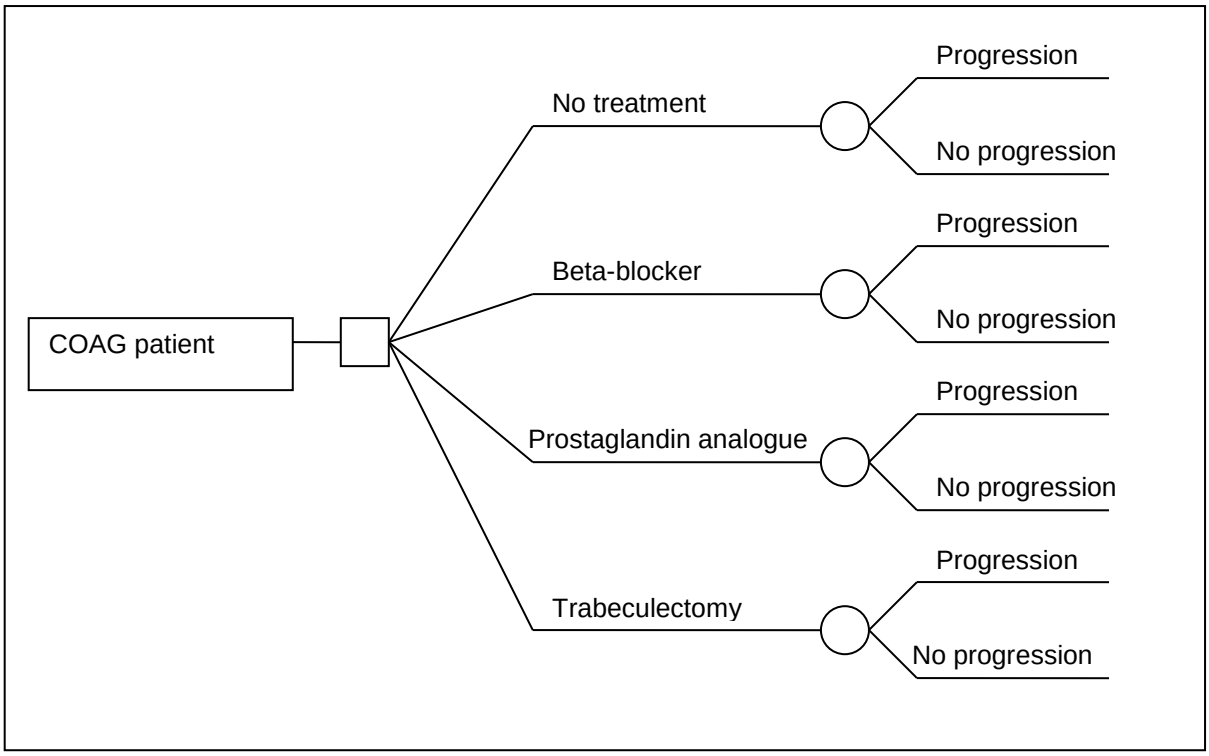


Figure 67 - Treatment strategies for COAG patients

The main effect of each strategy was considered to be the increase/decrease in risk of progression to the following COAG stages. However, in the literature the most commonly reported treatment outcome is the change in intraocular pressure (IOP). Two further systematic searches were conducted: one to find the Relative Risk (RR) of progression in OHT and in patients with COAG for each unit of IOP reduction (1.3.7), and the other one to find data on probability of progression from one stage to the next in both untreated and treated patients (1.3.5).

Each strategy is associated with upstream and downstream costs: the former are costs associated with the specific treatment while the latter are costs associated with the severity of the disease and thus dependent on the progression to later stages.

Some treatments could cause adverse events (see Chapters 7 and 8). Nevertheless not all of them result in important increased costs or reduced quality of life. We selected those more likely to occur and with a considerable impact on costs and quality of life using national sources[37] and expert opinion. Cataract and flat anterior chamber were the complications associated with trabeculectomy, while asthma was the only complication associated with beta-blockers for which incidence and annual cost per patient could be estimated. Other minor adverse events not requiring medical treatment are accounted for in the case of a change of COAG therapy.

For each strategy the expected healthcare costs and expected QALYs were calculated by estimating the costs and QALYs for each COAG stage and then multiplying them by the proportion of patients who would be in that stage as determined by the strategy taken.

We performed a probabilistic sensitivity analysis (PSA) to test the robustness of the results against the imprecision of these estimates and the other model parameters, and to obtain more accurate estimates of expected costs and QALYs.

In the base case of the OHT model, patients are 60 years old. However, from the review on risk of progression (see 1.3.5) we know that age is a significant risk factor for development of COAG. For this reason, we conducted a one-way sensitivity analysis on the age at decision point.

1.3.2 Time horizon

We considered the cost of treatment and health effects during a lifetime.

1.3.3 Key assumptions

In both COAG and OHT models the following assumptions were made:

a) In the absence of treatment, the change in IOP is equal to 0.

b) The change in IOP due to a treatment does not depend on whether the patient has COAG or OHT.

c) A patient starting with a prostaglandin analogue who demonstrates intolerance to this drug is switched to a beta-blocker.

d) A patient starting with a beta-blocker who demonstrates intolerance to this drug (including development of asthma) is switched to a prostaglandin analogue.

e) After a first switch in treatment, a second one can occur only after progression and thus its cost is included in the downstream cost of the stage.

f) When used after a treatment switch, beta-blockers and prostaglandin analogues have the same IOP lowering effect as when they are used as a first-choice treatment.

g) The severity of the condition is similar in both eyes of a patient.

In the COAG model the following assumptions were made:

a) In the base case the average age of patients at the beginning of the model is 72 years, as this was the mean age of COAG patients in the UK[154].

b) Patients are reviewed every three months.

c) The surgical procedure is trabeculectomy with or without enhancement.

d) Trabeculectomy is performed first in one eye then in the other after 2 months.

e) If post-surgery complications occur, the patient is treated appropriately and trabeculectomy is performed on the second eye if this has not already been done.

In the OHT model the following assumptions were made:

a) In the base case the average age of patients at the beginning of the model is 60 years, being the mid-point of the range 40-80 for which data on progression is available.

b) Untreated patients are reviewed on average every six months.

c) Treated patients are reviewed on average every three months.

1.3.4 Software

The cost-effectiveness analysis was conducted using TreeAge Pro 2007.

1.3.5 Baseline probability of progression

A search was conducted to identify papers looking at progression in OHT and COAG. We selected papers which reported the probability for one or more of the following progressions:

- from OHT to COAG in untreated patients
- from Early to Moderate COAG in treated and untreated patients
- from Moderate to Advanced COAG in treated and untreated patients
- from Advanced COAG to Severe Visual Impairment in treated and untreated patients

Only studies using a definite staging system and published after 1998 were included since it was GDG opinion that before that time the detection of COAG was not accurate. We found three studies in total matching our inclusion criteria:

Lee et al (2006)[85] is a retrospective cohort study where patients in OHT and COAG stages were followed up for 5 years to detect progression. It was excluded due to its small sample size (on average 25 patients in each stage) and short follow-up.

A cost-effectiveness study[80] reported the annual risk of developing COAG in untreated OHT patients based on the results of the Ocular Hypertension Treatment Study[50], a multicentre RCT with 1636 participants randomised to either treatment or no treatment and followed-up for a mean of 6 years. In addition to the estimate of probability of progression in the absence of treatment, the study[50] calculated the hazard ratio of each clinical parameter for developing COAG through a multivariate Cox proportional hazards model.

A Health Technology Assessment (HTA)[14] estimated the progression rates by COAG stage defined as mild, moderate and severe COAG, corresponding to our definitions of early, moderate and advanced COAG. The approach adopted was to use RCTs of treatment compared to control to calculate the progression rate by visual field mean defect. Since no RCT was found for the severe stage, its progression was projected from the previous stages.

Table 169 summarises the studies selected and their results.

Table 169 – Baseline probability of progressions

	Annual Probability Of Progression In Treated Patients	Annual Probability Of Progression In Untreated Patients	Source
OHT to COAG	-	2.2% (a)	Ocular Hypertension Treatment Study[50,80]
Early to Moderate COAG	20%	25%	HTA – Burr (2007)[14]
Moderate to Advanced COAG	7%	11%	HTA – Burr (2007)[14]
Advanced COAG to Severe Visual Impairment	6%	10%	HTA – Burr (2007)[14]

(a) Average value. See Table 170 and Table 171 for all the combinations of risk factors.

The calculation of the probability of conversion from OHT to COAG was based on different combinations of those parameters that resulted in significant risk factors for the progression from OHT to COAG. Following the exclusion of pattern standard deviation and cup-disc ratio since they are already clinical signs of COAG, the significant risk factors identified were age, IOP and central corneal thickness (CCT). First we inputted the probability of progression for each age group in the model (Table 170), and then we multiplied this by the RR resulting from the combination of IOP and CCT (Table 171) as follows:

- pCOAG = pCOAG[age] x RR

Table 170 - Probability of developing COAG in OHT patients (a)

Age group	Annual probability of progression in untreated patients
40-49 years	1.50%
50-59 years	1.90%
60-69 years	2.27%
70-80 years	2.69%

(a) Source: Kymes et al (2006)[80]

Table 171 - Relative risk for progression to COAG in OHT patients (a)

IOP	CCT	RR

>21 – 25 mmHg	>590 µm	0.16
>25 – 32 mmHg	>590 µm	0.49
>21 – 25 mmHg	555-590 µm	0.73
>25 – 32 mmHg	555-590 µm	1.06
>21 – 25 mmHg	≤555 µm	1.39
>25 – 32 mmHg	≤555 µm	2.93

(a) *Source: Gordon et al (2002)*[50]

The original IOP categories reported in the study[50] were IOP >21- 23.75 mmHg, IOP 23.75-25.75 mmHg, and IOP 25.75 - 32 mmHg. The GDG felt that keeping the middle group was clinically meaningless as the range limits are so close; therefore we incorporated this group into the two remaining groups IOP >21 – 25 mmHg and IOP >25 – 32 mmHg. The CCT categories in the study were CCT>588µm, CCT 555-588 µm, and CCT≤555 µm, which for clinical simplicity were rounded to CCT>590 µm, CCT 555-590 µm, and CCT ≤555 µm.

1.3.6 IOP reduction

Data on change in IOP from baseline due to each treatment was derived from the systematic review of clinical effectiveness of treatments in OHT and COAG patients (Chapter 7 and 8). No studies comparing prostaglandin analogues to no treatment and trabeculectomy to no treatment met the inclusion criteria. The data used in the model is summarised in Table 172 and correspond to the results of the forest plots in Figure 5, Figure 10, and Figure 44 in Appendix E. Among the comparisons of trabeculectomy with any medical treatment, the Collaborative Initial Glaucoma Treatment Study (2001)[89] was the only study comparing beta-blockers to trabeculectomy and thus the only trial included for this specific comparison (Figure 44 – subgroup 2).

Table 172 – Mean difference in change in IOP from baseline

	Mean difference
Beta-blockers vs No treatment	- 2.88 mmHg
Prostaglandin analogues vs Beta-blockers	- 1.32 mmHg
Trabeculectomy vs Beta-blockers	- 3.6 mmHg

1.3.7 IOP reduction and progression

We conducted a search in order to find a measure of the link between IOP reduction and protection against progression. Two scenarios were considered:

- a link between IOP reduction and reduced conversion from OHT to COAG,

- a link between IOP reduction and reduced progression of established COAG.

We included only studies reporting the RR of each mmHg reduction in IOP for progression or conversion, defined by deterioration in visual field or optic nerve appearance or both.

We found a study reporting the RR of developing COAG from OHT per unit of IOP reduction[50] and two studies reporting the RR of progression in COAG patients per unit of IOP reduction[86,87]. Leske et al (2007)[87], an update of Leske et al (2003)[86], is more up to date, and more conservative and so we used this in the base-case model.

In OHT patients, the percentage reduction in the probability of developing COAG was 10% per mmHg of IOP reduction. In COAG patients, the percentage reduction in the probability of progressing was 8% per mmHg of IOP reduction.

The overall effectiveness of each intervention was calculated by multiplying the mean difference in IOP reduction with the percentage reduction in progression per mmHg of IOP reduction.

Table 173 – Overall Effectiveness of interventions

INTERVENTION	MEAN CHANGE IN IOP (mmHg)	PROGRESSION REDUCTION per mmHg change in IOP		PROGRESSION REDUCTION (overall effectiveness) Mean change in IOP * Progression Reduction/mmHg for each treatment option	
		OHT	COAG	OHT	COAG
No treatment	0	10%	8%	0	0
Beta-blockers	2.88	10%	8%	29%	23%
Prostaglandin analogues	4.2	10%	8%	42%	34%
Trabeculectomy	6.48	NA	8%	NA	52%

1.3.8 Probability of progression after treatment

In each branch of the model where patients received a treatment, the baseline probability of progression in the absence of treatment was adjusted by the overall effectiveness of the respective treatment:

II Baseline probability * (1-overall effectiveness)

For example, a patient with Early COAG would have an annual probability of progression to Moderate COAG of 25% if untreated, and 25%*(100%-34%) = 16.5% if treated with a prostaglandin analogue.

The probability thus calculated was used for the time during which the patients received that treatment in the model. Once a switch in treatment occurred without progression this probability was recalculated according to the new drug used. Once a patient has progressed to the following stage, the new probability is the baseline probability in treated patients for that stage (Table 169). The rationale is that after progression any new treatment could be introduced, for which we cannot estimate the effectiveness. As a consequence, we used progression estimates for nonspecific treatments.

1.3.9 Other probabilities

Other probabilities used in the model were:

- Probability of developing asthma after use of beta-blockers: it was estimated from a prospective cohort study[74] comparing the difference in respiratory disease in 2,645 patients treated with beta-blockers to 9,094 unexposed patients. The difference between the proportions of patients given a new prescription of drug for reversible airways obstruction in 12 months after treatment was 3.3%. The same study[74] reports that the risk of respiratory problems ceases to be significant after the first year of exposure; therefore the probability of developing asthma is kept in the model only within the first year.

- Probability of discontinuation due to reasons other than treatment failure: we found one UK study[166] reporting the proportion of patients discontinuing treatment for reasons other than treatment failure (i.e. adverse events, intolerance). In this study, 19 out of 149 patients (13%) treated with prostaglandin analogues and 158 out of 632 patients (25%) treated with beta-blockers discontinued within 1 year. From the latter figure we subtracted 3.3% which was the proportion of patients developing asthma that would have been included in the discontinuation of beta-blockers; the remaining annual probability for this group is 21.7%. Data for later years were not available; thus these probabilities were used only during the first year of treatment.

- Probability of post-surgery complications: the GDG identified those complications that require further treatment and are therefore associated with extra costs. Rare (with an incidence of1% or less) and promptly resolving complications were excluded. Cataract and flat anterior chamber were the two complications identified. There was overall agreement between experts' estimates and national sources on the incidence of cataract. The probability was obtained from the National Survey of Trabeculectomy[37] considering only the cases that required cataract extraction (2.5%). The incidence of flat anterior chamber requiring treatment was estimated by experts as 0.75%, reported in the National Survey[37] as 0.2%, and in the Moorfields Glaucoma service annual audits 2001-2007 as 4%. We decided to use an average of these figures (1.65%) to estimate the probability of reformation of anterior chamber. Cataract extraction and reformation of anterior chamber were assumed to occur in the model only in the two months (1cycle) following surgery for both the first eye and the second eye operation.

- Probability of needing medication after surgery: the probability of adding a medication because of poor IOP control after trabeculectomy was obtained from the National Survey of Trabeculectomy[38]. Patients requiring post-operative anti-glaucoma medications were 147/1105 (13.3%) after 1 year. This probability was also used in the following years.

1.3.10 Life expectancy

Life expectancy in patients with COAG or OHT was assumed to be the same as the general population in England and Wales. Life expectancy was estimated for each age by calculating the mean of the figures for men and women reported in the Life Tables for the general population of England and Wales in the year 2004-2006 in the Government Actuary Department (http://www.gad.gov.uk/Demography_Data/Life_Tables/Interim_life_tables.asp)

1.3.11 Quality of life

The utility scores in Table 174 are a measure of the quality of life associated with each of the COAG stage on a scale from 0 (death) to 1 (perfect health). A systematic search for quality of life in OHT and COAG patients was performed. Studies were included if health state utility values were reported or obtainable for stages separately and they were based on visual field defect.

One study[119], using data obtained from Brown et al (2003)[12], was selected that applied utilities for visual acuity to each category of visual field loss. Two functions to calculate health utilities for each continuous dB increment of visual field defect were developed. In order not to favour the most effective treatment, we adopted the formula that resulted in the most conservative estimate of quality of life detriment resulting from visual field defects:

III Health utility = $0.98991+0.0022*dBs - 0.00080518*dBs^2$

where dBs are expressed as an absolute numbers and is therefore a positive number.

Since the stages in the model were defined as ranges of visual field defect (Table 168), it was possible to calculate the upper and lower limits and the central utility score for each stage by substituting the range limits and the central value of the stage definition. The central value of the severe visual impairment stage was assumed to be -26dB following the World Health Organization definition of blindness as reported in Rein et al (2007)[119], while the upper limit was assumed to be -30dB. The quality of life in OHT patients was assumed to be equal to perfect health as there was no visual field defect.

Table 174 - Health Utilities by COAG stage

STAGE	LOWER LIMIT	UPPER LIMIT	CENTRAL VALUE
OHT	-	-	1
Early COAG	0.974	0.990	0.989
Moderate COAG	0.900	0.974	0.944
Advanced COAG	0.712	0.900	0.819
Severe Visual Impairment	0.331	0.712	0.503

When we compared our estimates with other published studies[16,53,78,84] we found that overall we had been more conservative.

Adverse events were assumed to be negligible in terms of quality of life because they could be promptly treated, with the exception of asthma. A search for quality of life measures in the CEA Registry (https://research.tufts-nemc.org/cear/default.aspx) retrieved a study[130] where the health utility in treated asthma patients was 0.84. Hence it was assumed that treated asthma symptoms produce a decrease in quality of life of 0.16 over one year. This is probably an overestimation because the treatment with beta-blockers should be immediately discontinued with the consequent reduction of symptoms. On the other hand, beta-blockers are known to have other important adverse events for which incidence, costs and quality of life detriment could not be estimated.

1.3.12 Calculating QALYs gained

For each strategy, the expected QALYs per cohort of patients in each cycle are calculated as follows:

IV Expected QALYs = $U_{OHT} \times P_{OHT} + U_e \times P_e + U_m \times P_m + U_a \times P_a + U_b \times P_b + P_{ast} \times U_{ast}$ where

U_{OHT} , U_e , U_m , U_a , U_b = the utility score for each stage

U_{ast} = the utility detriment due to asthma (negative number)

P_{OHT} , P_e , P_m , P_a , P_b = the proportion of patients in each of the COAG stage at the end of each cycle

P_{ast} = the proportion of patients developing asthma in each cycle

The proportion of patients in each COAG stage depends on the progression reduction of the treatment and on the proportion of patients still alive according to the mortality rate for the general population of England and Wales.

The overall lifetime expected QALYs are given by the sum of QALYs calculated for each cycle. The incremental QALYs gained associated with a treatment strategy are calculated as the difference between the expected QALYs with that strategy and the expected QALYs with the comparator.

1.3.13 Upstream treatment costs

Upstream treatment costs are those directly associated with the treatment strategy considered and so those arising before a progression. The resources used in each cycle for the different strategies are summarised in Table 175. These resources are used only until the patient remains in the treatment strategy assigned at the beginning of the model. Patients in the beta-blocker and prostaglandin analogue arms can interchange treatment in which case the cost of an additional visit is added and the cycle cost is calculated according to the new treatment.

Table 175 - Resources used

	No Treatment	Beta-blockers	Prostaglandin analogues	Surgery	Source

Drugs	-	2 bottles of Timolol	2 bottles of either Latanprost, Travoprost, Bimatoprost	Used post-operatively: 1 bottle Chloramphenicol + 4 bottles Predforte + 1bottle Cyclopentolate 1bottle of either a prostaglandin or a beta-blocker in the two months between surgery in first eye and second eye	Expert opinion
Trabeculectomy inpatient	-	-	-	34% in both first and second cycle (first and second eye)	Hospital Episode Statistics for 2006/07
Trabeculectomy daycase	-	-	-	66% in both first and second cycle (first and second eye)	Hospital Episode Statistics for 2006/07
Monitoring visits - OHT	0.33 (a)	0.33 (a) + 1 if treatment switch	0.33 (a) + 1 if treatment switch	0.33 (a)	Expert opinion and recommendation in the Guideline
Monitoring visits - COAG	0.67 (b)	0.67 b + 1 if treatment switch	0.67 b + 1 if treatment switch	0.67 (b)	Expert opinion and recommendation in the Guideline

(a) .One visit every 6 months
(b) One visit every 3 months

The costs of the resources used are reported in Table 176. All the cost figures are expressed in 2006 Pound Sterling.

Table 176 - Cost per unit of resource used

	COST	SOURCE
Bottle of beta-blocker	£3.12	BNF 56
Bottle of prostaglandin analogue	£11.70 (a)	BNF 56
Post-operative drug treatment	£9.7 (b)	BNF 56
Trabeculectomy – inpatient	£1,316	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined (HRG code BZ18Z)
Trabeculectomy – daycase	£789	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined (HRG code BZ18Z)

Trabeculectomy – weighted average cost	£968 (c)	NCC-AC calculation
Cost of monitoring visit	£62	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined – Consultant led follow up attendance outpatient face to face - specialty code 130 Ophthalmology

(a) Mean cost of Travoprost, Latanoprost and Bimatoprost
(b) Cost of 1 Chloramphenicol + 4 Predforte + 1Cyclopentolate (£2.72 + 4 x £1.50 + £0.97)
(c) Proportion of inpatient x cost inpatient + proportion daycase x cost daycase

1.3.14 Downstream treatment costs

While a calculation of the resources used was made for the upstream costs, it would have been inaccurate if not impossible to do that for the costs arising after a disease progression. We conducted a systematic search on the cost of glaucoma stages and we selected a cost-of-illness study[151] reporting the direct healthcare cost per patient associated with each COAG stage. We chose this study because the staging system was the same that we adopted (Hodapp, Parrish and Anderson classification, 1.2), and it contained UK data. The figures in Table 177 were obtained by converting the 2004 Euros into GBP by a conversion factor of 0.67, which was the reciprocal of the one used by the author to convert GBP into Euros.

Table 177 – Annual cost of COAG stage per patient

Stage	Cost year per patient (£)	Source
Early COAG	399	Traverso et al (2006)[151]
Moderate COAG	449	Traverso et al (2006)[151]
Advanced COAG	357	Traverso et al (2006)[151]

In the paper, the costs of severe COAGand blindness did not account for social costs, thus leading to an underestimation of the true costs. Therefore for the last stage (Severe Visual Impairment) we based our cost analysis on the services provided to patients with blindness as described in Meads and Hyde (2003)[96]. Table 178 illustrates the services considered in our analysis, the calculation of their costs, and the proportion of patients receving each service as reported in Meads and Hyde (2003)[96]. The same study includes the cost of depression and hip replacement in individuals with visual impairment. We did not use these data as they were not controlled for incidence in the general population.

Table 178 - Cost of severe visual impairment

Service	Cost (£)	Source	Proportion of patients receiving the service
Blind registration	122.78 (one-off)	Pay Circular 3/2008 – Annex A Section 5 http://www.nhsemployers.org/pay-conditions/pay-conditions-	95%

		2339.cfm%20Pay%20circular%20M&D%20(3/2008)	
Low vision aids	150 (one-off)	Meads and Hyde (2003)[96] – figures uplifted to year 2008	33%
Low vision rehabilitation	207 (one-off)	Curtis (2007)[28] - NHS community occupational therapist cost of episode of care including qualification	11%
Community care	8,216	Curtis (2007)[28] - Annual cost for a local authority home care worker	6%
Residential care	16,344	Curtis (2007)[28] - Annual cost of private residential care assuming that 30% of residents pay themselves	30%

The cost of OHT was not used in the model because it is always dependent on the treatment strategy adopted (upstream cost).

For each strategy, the expected cost per cohort of patients in each cycle is calculated as follows:

$$\textbf{V} \quad \text{Expected cost} = UC_a \times P_a + \Sigma\, DC_i \times P_i$$

where

UC_a = upstream cost of the initial treatment strategy

P_a = proportion of patients in the initial treatment strategy

DC_i = downstream cost of stage i

P_i = proportion of patients in the stage i

and where stage i could be any later stage

The proportion of patients in each COAG stage depends on the magnitude of the progression reduction of the treatment and on the proportion of patients still alive according to the mortality rate for the general population of England and Wales.

The overall lifetime expected costs are given by the sum of costs calculated for each cycle. The incremental cost associated with a treatment strategy is calculated as the difference between the expected cost with that strategy and the expected cost with the comparator.

1.3.15 Adverse events and complications costs

Three main adverse events and complications were identified (1.3.9) and their costs estimated as shown in Table 179.

We searched for UK cost of illness studies on asthma. We found one study [160] but being too old we opted for a bottom-up approach. We estimated the cost of an annual treatment with beta-agonist and corticosteroids from a NICE Technology Appraisal[11].

The cost of treating the two post-operative complications, cataract and anterior flat chamber, corresponds to the cost of cataract extraction and anterior chamber reformation.

Table 179 - Cost of adverse events and complications

	COST	SOURCE
Annual cost of asthma treatment	£147 (a)	Brocklebank et al (2001)[11]
Cataract extraction	£977 (b)	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined – HRG code BZ03Z
Reformation of anterior chamber of eye	£974 (c)	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined – HRG code BZ19Z

(a) *annual cost of beta-agonist + corticosteroids = 105+42 = £147*
(b) *all daycase*
(c) *weighted cost - £556 x 46%(daycase) + £1,330 x 54%(inpatient)*

In addition, a treatment change following asthma is always associated with the one-off cost of an extra visit (£62).

1.3.16 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed to assess the robustness of the OHT and COAG models results to plausible variations in the model parameters.

Probability distributions were assigned to each model parameter, where there was some measure of parameter variability (Table 180). We then re-calculated the main results 10000 times, and each time all the model parameters were set simultaneously, selecting from the respective parameter distribution at random. When some distributions were used in either the OHT model or in the COAG model only, this is specified in Table 180.

Table 180 - Parameters used in the probabilistic sensitivity analysis (a)

Description of variable	Mean value	Probability distribution	Parameters	Source	Model
Mean difference in change in IOP from baseline – BB vs No Treatment	- 2.88 mmHg	Normal	SD = 0.643	Systematic review of clinical effectiveness	COAG and OHT models
Mean difference in change in IOP from baseline – PGA vs BB	-1.32 mmHg	Normal	SD = 0.24	Systematic review of clinical effectiveness	COAG and OHT models
Mean difference in change in IOP from baseline – trabeculectomy vs BB	-3.6 mmHg	Normal	SD = 0.418	Systematic review of clinical effectiveness	COAG model
Age at diagnosis of OHT	60 years	none		assumption	OHT model

Age at diagnosis of COAG	72 years	Custom distribution	age range/probability: 40-44 1.6% 45-49 2.3% 50-54 3.5% 55-59 5.4% 60-64 8.8% 65-69 13.4% 70-74 16.3% 75-79 18.5% 80-84 16.3% 85-89 13.9%	Tuck et al (1998)[154]	COAG model
Cost of Early COAG	£399	Gamma	α = 61.46 λ = 0.154 based on +/-25% for upper and lower bounds	Traverso et al (2006)[151]	OHT model
Cost of Moderate COAG	£449	Gamma	α = 61.46 λ = 0.137 based on +/-25% for upper and lower bounds	Traverso et al (2006)[151]	COAG and OHT models
Cost of Advanced COAG	£357	Gamma	α = 61.46 λ = 0.172 based on +/-25% for upper and lower bounds	Traverso et al (2006)[151]	COAG and OHT models
Cost of Severe Visual Impairment	see 1.3.14	none		NCC-AC calculation of cost of Severe Visual Impairment	COAG and OHT models
Cost of Blindness Registration	£122.78	Gamma	α = 61.46 λ = 0.500 based on +/-25% for upper and lower bounds	Pay Circular 3/2008 – Annex A Section 5 http://www.nhsemployers.org/pay-conditions/pay-conditions-2339.cfm%20Pay%20circular%20M&D%20(3/2008)	COAG and OHT models
Cost of low-vision aids	£150	Gamma	α = 61.46 λ = 0.410 based on +/-25% for upper and lower bounds	Meads and Hyde (2003)[96]	COAG and OHT models

Cost of low-vision rehabilitation	£207	Gamma	α = 61.46 λ = 0.297 based on +/-25% for upper and lower bounds	Curtis (2007)[28]	COAG and OHT models
Cost of community care for blindness	8,216	Gamma	α = 61.46 λ = 0.007 based on +/-25% for upper and lower bounds	Curtis (2007)[28]	COAG and OHT models
Cost of residential care for blindness	16,344	Gamma	α = 61.46 λ = 0.004 based on +/-25% for upper and lower bounds	Curtis (2007)[28]	COAG and OHT models
Cost of beta-blockers	see Table 176	none		BNF 56	COAG and OHT models
Cost of prostaglandin analogues	see Table 176	none		BNF 56	COAG and OHT models
Cost of trabeculectomy	see 1.3.13	none		National Schedule of Reference Costs 2006-07 – Glaucoma category 2 (HRG BZ18Z)	COAG model
Cost of trabeculectomy – inpatient	£1,316	Gamma	α = 7.55 λ = 0.0057 based on IQR	National Schedule of Reference Costs 2006-07	COAG model
Cost of trabeculectomy – daycase	£789	Gamma	α = 12.03 λ = 0.015 based on IQR	National Schedule of Reference Costs 2006-07	COAG model
Cost of follow-up visit	£62	Gamma	α = 14.45 λ = 0.233 based on IQR	National Schedule of Reference Costs 2006-07	COAG and OHT models
Cost of asthma	£147	Gamma	α = 61.46 λ = 0.42 based on +/-25% for upper and lower bounds	Broklebank et al (2001)[11]	COAG and OHT models

Cost cataract extraction	£977	Gamma	α = 11.77 λ = 0.014 based on IQR	National Schedule of Reference Costs 2006-07 non-phacoemulsification cataract surgery (HRG code BZ03Z)	COAG model
Cost anterior chamber reformation	See 1.3.15	none		National Schedule of Reference Costs 2006-07 – Glaucoma – category 1 (HRG code BZ19Z)	COAG model
Cost anterior chamber reformation – daycase	£556	Gamma	α = 12.03 λ = 0.015 based on IQR	National Schedule of Reference Costs 2006-07	COAG model
Cost anterior chamber reformation – inpatient	£1,776	Gamma	α = 4.41 λ = 0.0025 based on IQR	National Schedule of Reference Costs 2006-07	COAG model
Proportion of trabeculectomy daycase: inpatient	66%: 34%	none		Hospital Episode Statistics 2006/07	COAG model
Proportion of anterior chamber reformation – daycase: inpatient	46%: 54%	none		Hospital Episode Statistics 2006/07	COAG model
Discount rate (cost and QALYs)	3.5%	none		NICE reference case[107]	COAG and OHT models
Number of follow-up visits per year – COAG and treated OHT patients	4	Triangular	Min = 2 Likeliest = 4 Max = 6	Experts opinion	COAG and OHT models
Number of follow-up visits per year – OHT untreated patients	2	Triangular	Min = 1 Likeliest = 2 Max = 3	Experts opinion	OHT model
Annual probability of developing COAG – untreated	see 1.3.5	none		Gordon et al (2002)[50]	OHT model
Relative Risk for progression to COAG – IOP >21-25 mmHg; CCT >590µm	0.16	Beta	α = 2 β = 88	Gordon et al (2002)[50]	OHT model
Relative Risk for progression to COAG – IOP >25 – 32 mmHg; CCT >590µm	0.49	Beta	α = 5 β = 75	Gordon et al (2002)[50]	OHT model

Relative Risk for progression to COAG – IOP >21-25mmHg; CCT 555-590µm	0.73	Beta	α = 7 β = 70	Gordon et al (2002)[50]	OHT model
Relative Risk for progression to COAG – IOP >25-32mmHg; CCT 555-590µm	1.06	Beta	α = 10 β = 69	Gordon et al (2002)[50]	OHT model
Relative Risk for progression to COAG – IOP >21-25mmHg; CCT ≤555µm	1.39	Beta	α = 13 β = 65	Gordon et al (2002)[50]	OHT model
Relative Risk for progression to COAG – IOP >25-32mmHg; CCT ≤555µm	2.93	Beta	α = 28 β = 50	Gordon et al (2002)[50]	OHT model
Annual probability of progression Early to Moderate – untreated	25%	Triangular	Min = 12.5% Likeliest = 25% Max = 37.5% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007)[14]	COAG model
Annual probability of progression Early to Moderate – treated	20%	Triangular	Min = 10% Likeliest = 20% Max = 30% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007)[14]	OHT model
Annual probability of progression Moderate to Advanced – treated	7%	Triangular	Min = 3.5% Likeliest = 7% Max = 10.5% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007)[14]	COAG and OHT models

Annual probability of progression Advanced to Severe Visual Impairment – treated	6%	Triangular	Min = 3% Likeliest = 6% Max = 9% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007)[14]	COAG and OHT models
Annual probability of developing asthma in patients treated with BB	3.3%	Beta	α = 21 β = 611	Kirwan et al (2002)[74]	COAG and OHT models
Annual probability of adding a medication after surgery	13.3%	Beta	α = 147 β = 958	Edmunds et al (2001)[38]	COAG model
Probability of cataract extraction after trabeculectomy	2.3%	Beta	α = 29 β = 1211	Edmunds et al (2002)[37]	COAG model
Probability of anterior chamber reformation after trabeculectomy	1.65%	none		Edmunds et al (2002){EDMUNDS 2002 and experts opinion	COAG model
Probability of natural death	function of age	none		Life Tables England and Wales	OHT and COAG models
Probability of switching treatment with BB including asthma	25%	Beta	α = 158 β = 474	Zhou et al (2004)[166]	COAG and OHT models
Probability of switching treatment with BB excluding asthma	see 1.3.9	none		Assumption	COAG and OHT models
Probability of switching treatment with PGA	13%	Beta	α = 19 β = 130	Zhou et al (2004)[166]	COAG and OHT models
Health utility OHT	1	none		Assumption	OHT model
Health utility Early	0.989	Triangular	Min = 0.974 Likeliest = 0.989 Max = 0.990 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the central value.	Rein et al (2007)[119]	COAG and OHT models

Health utility Moderate	0.944	Triangular	Min = 0.900 Likeliest = 0.944 Max = 0.974 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the central value.	Rein et al (2007)[119]	COAG and OHT models
Health utility Advanced	0.819	Triangular	Min = 0.712 Likeliest = 0.819 Max = 0.900 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the central value.	Rein et al (2007)[119]	COAG and OHT models
Health utility Severe Visual Impairment	0.503	Triangular	Min = 0.331 Likeliest = 0.503 Max = 0.712 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the WHO definition of blindness	Rein et al (2007)[119]	COAG and OHT models
Health decrement with Asthma	-0.16	none		Schermet et al (2002)[130]	COAG and OHT models
RR of progression per unit of IOP reduction – OHT	0.10	1 – Log-Normal	SE = 0.037	Gordon et al (2002)[50]	OHT model
RR of progression per unit of IOP reduction – COAG	0.08	1 – Log-Normal	SE = 0.02	Leske et al (2007)[87]	COAG model

(a) When the variable is a function, its definition is reported in the referenced paragraph.

1.3.17 Results of the cost-effectiveness analysis

1.3.17.1 OHT

We found that the results of the OHT model were particularly sensitive to the age of patients at the decision point. Age is a risk factor for the development of COAG but it is also important for estimating the likelihood of visual impairment. Table 181 shows the results of the base case analysis and the one-way sensitivity analysis conducted by varying the patient's age between 40 and 80. Beyond these limits we do not have data on the probability of developing COAG.

For patients at an average age of 60, no treatment is the most cost-effective strategy if the CCT >555µm and IOP is within the 21 – 32 mmHg range. If the CCT ≤555 µm, treatment with prostaglandin analogues is the most cost-effective strategy for any IOP.

Table 181 - Results of OHT model – base case

	Mean cost (£)	QALYs	Incremental cost (£) per QALY gained vs No Treatment	Incremental cost (£) per QALY gained vs BB	One-way sensitivity analysis on age
IOP>21 – 25 mmHg, CCT>590 µm					
No Treatment	2,165	14.574	-	-	-
BB	4,748	14.586	213,504	-	Not sensitive to age
PGA	5,665	14.586	296,593	Dominated	Not sensitive to age
IOP >25 – 32 mmHg, CCT>590 µm					
No Treatment	2,872	14.471	-	-	-
BB	5,105	14.513	52,670	-	Not sensitive to age
PGA	5,934	14.522	59,805	94,182	Not sensitive to age
IOP>21 – 25 mmHg, CCT 555-590 µm					
No Treatment	3,344	14.403	-	-	-
BB	5,351	14.464	32,749	-	Not sensitive to age
PGA	6,121	14.478	36,598	52,760	Not sensitive to age
IOP >25 – 32 mmHg, CCT 555-590 µm					
No Treatment	3,940	14.316	-	-	-
BB	5,672	14.399	20,864	-	If age<60 BB is more cost-effective than no treatment.
PGA	6,368	14.421	23,124	31,650	If age<58 PGA is more cost-effective than no treatment. PGA vs BB not sensitive to age.
IOP >21 – 25 mmHg, CCT ≤555 µm					

No Treatment	4,484	14.237	-	-	-
BB	5,974	14.339	14,617	-	If age>67 no treatment is more effective than BB.
PGA	6,603	14.367	16,307	22,464	If age>65, no treatment is more cost-effective than PGA. If age<58 PGA is more cost-effective than BB..
IOP >25 – 32 mmHg, CCT ≤555 µm					
No Treatment	6,475	13.949	-	-	
BB	7,179	14.102	4,605	-	If age>80 no treatment is more effective than BB.
PGA	7,566	14.150	5,429	8,056	If age>77 BB are more cost-effective than PGA. If age >80 no treatment is more cost-effective than PGA.

The cost-effectiveness of treating OHT is strongly interconnected with the patient's risk factors for the development of COAG (age, IOP and CCT) and with the likelihood of becoming visually impaired which depends on the age at diagnosis.

In the absence of risk factors, the probability of developing COAG is so low that the little improvement in the quality of life treatment would bring does not warrant the high costs of a lifetime treatment. Not treating patients with IOP>21-25mmHg and CCT>590µm is significantly cost-effective compared to PGA as reported in Table 182, where the 95% confidence interval (CI) is above the £20,000/QALY threshold. When compared to BB, the cost-effectiveness is not significant as the lower limit crosses the £20,000/QALY threshold.

Medical treatment is cost-effective in patients with CCT≤555 µm with any IOP up to 32 mmHg and in patients with CCT 555-590 µm and IOP >25-32 mmHg. However, the 95% CI limits crossed our cost-effectiveness threshold (Table 182).

Considering only those patients for whom treatment is cost-effective, if both beta-blockers and prostaglandin analogues are available (e.g. they are not contraindicated), beta-blockers are more cost-effective if CCT 555-590 µm and IOP >25-32mmHg or if CCT<555 µm and IOP >21 – 25 mmHg while prostaglandin analogues are more cost-effective if CCT<555 µm and IOP >25 – 32mmHg. The results of the comparison between prostaglandin analogues and beta-blockers are not significant with 95% confidence (Table 182). For these groups of patients, there is an age beyond which treatment does not substantially improve the quality of life, and thus it is not cost-effective (see One-way sensitivity analysis in Table 181). For clinical simplicity, the results can be rearranged in order to round the age threshold and to limit the maximum number of age groups to two for each IOP and CCT combination. In this case after we exclude beta-blockers from the comparison, prostaglandin analogues are cost-effective up to the age

of 65 in the IOP >21 – 25 mmHg and CCT<555 µm group and up to the age of 80 in the IOP >25 – 32 mmHg and CCT<555 µm group,

Table 182 - Results of PSA – OHT model

	Mean ICER (£/QALY)	95% CI – lower limit (£/QALY)	95% CI – upper limit (£/QALY)	Probability of being cost-effective at £20,000/QALY
IOP>21 – 25 mmHg, CCT>590 µm				
BB vs no treat	149,606	17,713	dominated	No Treat 97%
PGA vs No treat	649,300	64,402	dominated	BB 3%
PGA vs BB	193,576	32,110	dominated	PGA 0%
IOP >25 – 32 mmHg, CCT>590 µm				
BB vs no treat	42,773	2,801	423,141	No Treat 81%
PGA vs No treat	82,141	23,334	dominated	BB 18%
PGA vs BB	50,144	10,141	665,186	PGA 1%
IOP>21 – 25 mmHg, CCT 555-590 µm				
BB vs No Treat	28,280	942	224,519	No Treat 67%
PGA vs No Treat	50,626	15,892	11,180,850	BB 28%
PGA vs BB	32,791	6,154	271,632	PGA 5%
IOP >25 – 32 mmHg, CCT 555-590 µm				
BB vs No Treat	18,647	cost saving	138,698	No Treat 48%
PGA vs No Treat	33,040	11,036	346,902	BB 37%
PGA vs BB	21,638	3,378	152,848	PGA 15%
IOP >21 – 25 mmHg, CCT ≤555 µm				
BB vs No Treat	12,844	cost saving	89,068	No Treat 33%
PGA vs No Treat	23,184	7,466	162,175	BB 35%
PGA vs BB	15,099	1,417	93,199	PGA 32%
IOP >25 – 32 mmHg, CCT ≤555 µm				
BB vs No Treat	3,720	cost saving	38,637	No Treat 8%
PGA vs No Treat	8,277	1,460	52,186	BB 9%
PGA vs BB	4,818	cost saving	39,453	PGA 83%

1.3.17.2 COAG

Table 183 shows the results of the base case COAG model. Trabeculectomy is the most effective and most cost-effective option.

Table 183 - Results of COAG model – base case

	Mean cost (£)	QALYs	Incremental cost (£) per QALY gained vs No Treat	Incremental cost (£) per QALY gained vs BB	Incremental cost (£) per QALY gained vs PGA	Sensitivity analysis
No Treat	6,246	8.635	-	-	-	If annual probability of progression < 6% or surgical intervention costs >£1,455, trabeculectomy is not cost-effective anymore. Results not sensitive to COAG stage.
BB	6,017	8.714	cost saving	-	-	
PGA	6,113	8.745	cost saving	3,100	-	
Trab	7,247	8.849	14,679	9,113	10,906	

When the severity of the disease (COAG stage) was varied, the overall results did not change and trabeculectomy was still the most cost-effective strategy. Sensitive parameters in the model were the annual probability of progression to the following stage and the cost of trabeculectomy. When the probability of progression was lowered from 25% in the base case to 6%, trabeculectomy was not cost-effective anymore. By using the following formula we could calculate the rate in visual field deterioration corresponding to a 7% annual probability of progression:

$$\textbf{VI} \quad \text{rate} = (VF_{mod} - VF_{Early})/\text{years}$$

where

VF_{mod} = absolute value of lower bound of Moderate COAG definition (6.01dB)

VF_{Early} = absolute central value of Early COAG definition (3.00)

years = years necessary to reach Moderate COAG, calculated as

$$\textbf{VII} \quad \text{years} = 1/(\text{probability of progression})$$

The rate thus calculated was

$$\textbf{VIII} \quad \text{rate} = (6.01 - 3.00)/(1/0.06) = 0.18\text{dB/year}$$

If the visual field deteriorates at a rate lower than this value, trabeculectomy is not cost-effective.

The uncertainty over the cost-effectiveness of trabeculectomy was revealed by the results of the PSA as well (Table 184). While beta-blockers and prostaglandin analogues are significantly more cost-effective than no treatment (i.e. the upper limit is below the £20,000/QALY threshold used in our economic evaluation), the upper limit of the ICER of trabeculectomy vs any other intervention always exceeds the £20,000/QALY threshold (Table 184).

Table 184 - Results of PSA - COAG model

	Mean ICER (£/QALY)	95% CI – lower limit (£/QALY)	95% CI – upper limit (£/QALY)	Probability of being cost-effective at £20,000/QALY
BB vs no treatment	cost saving	cost saving	9,461	
PGA vs no treatment	cost saving	cost saving	13,836	No treatment 1%
Trab vs no treatment	3,488	cost saving	57,676	BB 4%
PGA vs BB	3,079	cost saving	23,258	PGA 38%
Trab vs BB	7,483	cost saving	85,631	Trab 57%
Trab vs PGA	11,495	cost saving	122,050	

When the severity of COAG at the point of decision was increased to moderate or advanced, trabeculectomy became more cost-effective and this result less sensitive

to the probability of progression. By applying a formula similar to VI, we estimated the minimum rate of visual field deterioration in order for trabeculectomy to be cost-effective in moderate COAG (0.09dB/year) and advanced COAG (0.08dB/year).

1.3.18 Discussion

The cost-effectiveness of treating OHT patients depends on their risk for development of COAG. We found that age, IOP and CCT are the clinical indicators correlated with this risk (1.3.5). According to the possible combinations of these parameters, different strategies can be cost-effective.

Beta-blockers are cost-effective for patients with IOP >25 – 32 mmHg and CCT *555 – 590* μm up to the age of 60. Prostaglandin analogues are cost-effective for patients with IOP> 21 – 25 mmHg and CCT<*555* μm up to the age of 65 and for patients with IOP>25 – 32 mmHg and CCT≤*555*μm up to the age of 80. All other OHT patients should not receive treatment according to our analysis.

On the other hand, treating all COAG patients from an early stage is cost-effective. Results show that trabeculectomy is the most cost-effective treatment. Nevertheless being an invasive procedure it has drawbacks that we could have failed to capture in our analysis. More generally, some treatments are associated with common adverse events and complications which often require further interventions. In our model we have tried to incorporate the costs and effects of the most common and serious ones but we might have underestimated them since there is no good up to date literature on this topic.

In addition, the cost-effectiveness of trabeculectomy is conditional upon a considerable rate of progression in visual field defect. It could be worthwhile initiating medical treatment while monitoring for progression; only when a progression is detected could the patient be listed for surgery.

For patients in the later stages of COAG trabeculectomy is cost-effective even in the presence of a very low rate of progression (see 1.3.17.2) because the threat to their vision is more imminent.

We have kept some parameters conservative:

- Quality of life estimates from the selected study were generally higher than in other excluded studies.
- Increase in mortality risk due to blindness or visual impairment was not included in the model.
- The probability of developing COAG in OHT patients 70-80 years old was used also for older patients, although it was likely to be higher.
- Normal Tension Glaucoma patients were included in the IOP reduction results as well. However, including data for this population could decrease the effectiveness of treatment in reducing IOP. In fact, the effectiveness corresponds to the difference between IOP at baseline and after treatment

and since their IOP at baseline is already low and drugs could be less effective in decreasing this value further.

Had we modified these assumptions, we would have favoured the most effective interventions.

However, our analysis is limited for a number of reasons:

- The OHT model is based on the findings of an RCT[50] where patients were included only if their age was between 40 and 80 years and IOP between >21and 32 mmHg. Therefore we cannot generalise our results beyond these limits.

- Some probabilities of progression were extrapolated beyond the follow-up periods cited in the literature and for advanced COAG to severe visual impairment there was no RCT data available.

- The methodology adopted by the study[119] used as the source of health utilities in the model has not been validated yet. Also, the original health utilities [12]were estimated for different ocular conditions causing a defect in visual acuity. These utilities might not be applicable to glaucoma patients since the pattern of visual loss differs from other conditions. Furthermore, generic instruments such as the EQ-5D might not completely capture the quality of life decrement caused by small changes in visual ability.

The results of our model are applicable to OHT or COAG patients who have not been treated before. Although we have included data on IOP reduction in NTG patients, we could not find any evidence on the relationship between IOP reduction and progression reduction in this population. The results of our model might not be directly applicable to these patients.

Another assumption in our model was that the severity of OHT or COAG is similar in both eyes. However, in clinical practice a patient could present with unilateral COAG or OHT. We believe that the treatment should be established according to the worse eye if treated with medical therapy. In fact, a single bottle of drops per month is used for treating either both eyes or one eye only as the bottle should be discarded after 28 days from the opening. In addition, since it is the patient who is being treated and not the eye, the cost of follow up visits and adverse events would be the same. Conversely, a surgical approach should be adopted only for the eye that requires it.

If the results of our economic analysis were adopted in the NHS, there would be an increase in surgical treatments with more pressure on Hospital Eye Services. However, if this was accompanied by a change in the referral scheme and monitoring provision, the resources freed up by the implementation of these policies could be used for the care of those patients requiring immediate treatment to prevent further progression. In addition, OHT patients with a low risk of progression would not be treated according to our model, which saves resources in terms of drugs and visits as well as patients not receiving treatment who would be monitored less frequently. On the other hand, OHT patients at a high risk for progression would receive prostaglandin analogues which are the most effective medical treatment. As a consequence, fewer people would develop COAG with less pressure on the Hospital Eye Service and the provision of surgery.

Another consequence of our results is that more emphasis would be given to the assessment of clinical parameters such as IOP and CCT for OHT patients and visual field defect for COAG patients.

Our findings are similar to those of previous studies: Kymes et al (2006)[80] and Stewart et al (2008)[144] found that treating all OHT patients is not cost-effective, while according to Kymes et al (2006)[80] selecting those with an elevated risk of conversion to COAG is a more cost-effective strategy (see Evidence Table – Appendix D). Le Pen et al (2005)[82] explored the cost-effectiveness of prostaglandin analogues compared to beta-blockers in COAG patients through a Markov model reaching conclusions similar to our model (see Evidence Table – Appendix D).

1.3.19 Conclusions

- Treating all patients with OHT is not cost-effective.
- It is cost-effective to treat only OHT patients with IOP> 25 – 32 mmHg and CCT 555 – 590 µm with a beta-blocker until the age of 60 and OHT patients with IOP >21 and CCT ≤555µm with a prostaglandin analogue until the age of 80.

It is always cost-effective to treat COAG patients. However, trabeculectomy is cost-effective only when progression of visual field defect for Early COAG patients is >0.18 dB/per year – which is to say in the presence of any detectable progression. Trabeculectomy becomes more and more cost-effective the more advanced the stage of COAG.

1.4 NCC-AC cost analysis: Cost-effectiveness of tests

There is a wide variety of techniques and tests that are currently available for the assessment of clinical characteristics in order to diagnose and monitor OHT and COAG patients. Table 185 shows the clinical features and the relative tests used for their measurement which were included in our analysis.

Some of the tests are used for both diagnosis of OHT or COAG and monitoring. However, the importance of the result accuracy could vary between the two phases in the provision of care. CCT measurement for example is particularly important when diagnosing OHT in order to identify the relevant treatment strategy (1.3.17.1).

In our analysis, each test was compared only with the reference standard (marked in Table 185) used for the same clinical measurement.

Table 185 - Tests included in the economic analysis

Clinical Feature	Tests
IOP	Goldmann Applanation Tonometry*
	Non-contact tonometry (Pulse Air)
Optic Disc	Slit lamp biomicroscopy*
	Slit lamp biomicroscopy + stereoscopic disc photography
	Heidelberg Retina Tomography (HRT)
	Optical Coherence Tomography (OCT)
	Laser polarimetry
Visual Field	24-2 SITA Humphrey*
	Henson
	Dicon
	Octopus
	Frequency Doubling Technology
	Humphrey non-SITA
Anterior chamber angle	Gonioscopy*
	iris eclipse or shadow test
	Redmond-Smith slit lamp assessment
	Scheimpflug anterior segment photography
	Ultrasound BioMicroscopy (UBM)
	Van Herick
	A-scan
	B-scan
	Optical Coherence Tomography (OCT)

* *Reference standard*

1.4.1 General methodology

We found that the most practical approach for an economic evaluation was a cost analysis. In fact, estimating the consequences of false positives and false negatives

could be unattainable as there is uncertainty around the stage patients would be when undergoing the assessment and above all, around the time when they will be eventually correctly diagnosed. Another parameter that was not accounted for in our analysis is the time necessary to complete the tests. This exclusion is due to the following factors:

- the individual variability of the time to carry out the test,
- the consideration that while a test is being completed, the same healthcare professional could be involved in other activities,
- the variability of the opportunity cost depending on the type of healthcare professional who is performing the test,
- the GDG believed there are no substantial differences in times (with the exception of the 24-2 SITA standard Humphrey Visual Field test which we believe to be quicker than its comparators – see 1.4.5).

Consequently, we restricted our cost analysis to the calculation of capital costs, life span of the machines used, and the consumables.

We conducted a systematic search in order to identify published studies from the UK reporting cost data on the tests in Table 185 but we also relied on expert opinion and data provided by national suppliers (Haag-Streit). A study[66] was excluded because it was published in 1990 and so cost data were considered obsolete. Similarly, a decision model on screening[153] was excluded in which details of the tests which the costs refer to were not given. A HTA Kwartz et al (2005)[79] was selected as a possible source for the costs of HRT, Laser polarimetry, and Humphrey Visual Field Analyser.

Each clinical GDG member estimated the number of patients referred each year to a clinic for a confirmation of diagnosis and the number of follow-up visits. The mean of both the number of diagnostic visits and the number of follow-up visits were calculated.

Finally, we calculated the difference in cost per patient between tests measuring the same clinical feature.

Throughout the cost analysis, expert opinion was gathered from the GDG members.

1.4.2 Assumptions

The following assumptions were used in the cost analysis:

- The same test would be used for both diagnosis and monitoring
- Life span of machines is 5 years unless available data state differently
- Reference standard tests are the most accurate within the same group
- Interest rate for calculating the annual cost of machines is 3.5%
- Drugs used specifically for the test were the only consumables

1.4.3 Population

The number of patients referred every year to a clinic for confirmation/exclusion of COAG was estimated by averaging the estimates provided by the GDG (Table 186). The same method was applied to estimate the number of follow-up visits per year (Table 186). In other words, on average 3 patients per day undergo tests for the diagnosis of COAG and 33 patients per day are followed-up.

Table 186 - Population for tests

Diagnosis Population	Monitoring Population
1,000	12,000

In the cost analysis, the population for each test was the sum of diagnosis and monitoring population.

1.4.4 Resource use and costs

We could not find the capital cost of the machines used in all the tests compared. Those that were found were then used to calculate the annual cost based on the life span and the interest rate according to the formula:

$$\text{IX} \quad E = K/\{[1-(1+r)^{\wedge -n}/r]+ 1\}$$

where E = annual cost of the machine

K = capital outlay (cost of purchasing the machine)

r = interest rate 3.5%

n = life span

The capital cost of a Goldmann Tonometer is composed of the cost of the actual tonometer, the slit lamp on which it is mounted, and the lenses. Experts estimated the overall cost which was later confirmed by data provided by the UK supplier (personal communication). The latter also provided the average life span of the machine. The cost of a non-contact tonometer was obtained from the website of the UK distributor of Keeler Pulsair tonometer. The average life span was not available and therefore subject to assumption.

The same capital cost of the slit lamp as that which was estimated for the Goldmann Tonometer was used to calculate the cost of the slit lamp biomicroscopy test for the optic disc assessment. The cost of the HRT was found in the HTA[79] and confirmed by the UK supplier who gave us estimates of the life span as well. For the OCT we relied solely on supplier data while for the Laser Polarimetry the HTA[79] was the only available source and its life span was assumed to be 5 years. The cost of adding stereoscopic disc photography to the slit lamp examination was based on the cost of Monoscopic photography provided by the UK supplier (Haag-Streit).

No cost data were found on Visual Field tests with the exception of the Humphrey Visual Analyser. Therefore a cost analysis was not performed for this group of tests.

We obtained cost and life span data for Gonioscopy, A-scan, B-scan and OCT from the supplier. Van Herick's test is performed by means of a slit lamp, so only its cost was accounted for. Unfortunately, no cost data were obtained for the other tests.

Table 187 reports the parameters and the results of the calculation of annual costs of equipment according to the formula IX.

Table 187 - Annual cost of equipment

Machine/test	Capital outlay (K)	Life span (n)	interest rate (r)	ANNUAL COST (£)
IOP measurement				
Goldmann tonometry	10,000	15	3.5%	799
Non-contact tonometry	5,000	5	3.5%	907
Optic disc assessment				
Slit lamp biomicroscopy	10,000	30	3.5%	516
Slit lamp biomicroscopy + stereoscopic disc photography	10,000 (a)	7	3.5%	1,406
HRT	30,000	7	3.5%	4,271
OCT	45,000	7	3.5%	6,325
Laser polarimetry	30,000	5	3.5%	5,325
Anterior chamber angle assessment				
Gonioscopy	200 (b) + 10,000 (c)	3 (b) / 30 (c)	3.5%	569 (d)
A-scan	15,000	7	3.5%	2,108
B-scan	20,000	7	3.5%	2,811
OCT	28,000	7	3.5%	3,936
Van Herick	10,000 (c)	30	3.5%	516

(a) Only cost of monoscopic photography without slit lamp
(b) Gonioscope
(c) Slit lamp
(d) Total of gonioscope (£53) + slit lamp (£516)

Other resources considered in the cost analysis were drugs used in order to perform the test. One unit of Proxymetacaine and Fluorescein was used before Goldmann tonometry and Gonioscopy; whereas one unit of Tropicamide was used before Slit lamp biomicroscopy, HRT and OCT. The cost of a unit is calculated by dividing the cost of the pack by the number of units contained, as illustrated in Table 188 - Cost of drugs for tests

Table 188 - Cost of drugs for tests

Drugs	Cost Per Packa	Units	Cost Per Unit (£)
Proxymetacaine and Fluorescein	£7.95	20	0.4
Tropicamide	£5.75	20	0.3

(a) Source BNF 54

For each test, the total cost per patient was calculated as follows:

X TC = ac/p + d

where

TC = total cost per patient

ac = annual cost of equipment

p = diagnosis and monitoring population

d = cost of drug unit (if applicable)

The incremental cost per patient of a test compared to the reference standard was calculated as follows:

$$IC = TC_c - TC_{rs}$$

where

IC = incremental cost

TC_c= total cost of the comparator

TC_{rs}= total cost of the reference standard

An exception was the estimation of the incremental cost of adding stereoscopic disc photography to sit-lamp biomicroscopy which is equivalent to the cost of the photography only as the slit lamp is present in both strategies.

1.4.5 Results of the cost analysis

The incremental cost of the reference standard compared to other tests was given by the difference in the total cost per patient, as reported in Table 189.

Results for the comparison between visual field tests could not be reported since we found cost data on tests other than Humphrey.

Non-contact tonometry is cost saving compared to the more accurate Goldmann tonometry, and similarly non-gonioscopic methods are less costly than Gonioscopy (Table 189). In contrast, tests for assessing optic disc are associated with increased costs (Table 189) without adding valuable or more accurate information on the clinical picture of the patient (expert opinion) when compared to the Slit lamp

biomicroscopic examination. On the other hand, adding stereoscopic disc photography to the slit lamp examination generates an additional cost per patient of 0.11 but could also provide useful information.

Table 189 - Results of cost analysis of tests

Test	Cost per patient (£)	Cost of test – cost reference standard (£)
IOP measurement		
Goldmann tonometry*	0.46	-
Non-contact tonometry	0.07	- 0.39 (cost saving)
Optic disc assessment		
Slit lamp biomicroscopy*	0.33	
Slit lamp biomicroscopy + stereoscopic disc photography	0.44	0.11
HRT	0.62	0.29
OCT	0.77	0.44
Laser polarimetry	0.41	0.08
Anterior chamber angle assessment		
Gonioscopy*	0.44	-
A-scan	0.16	-0.28 (cost saving)
B-scan	0.22	-0.22 (cost saving)
OCT	0.30	-0.14 (cost saving)
Van Herick	0.04	-0.40 (cost saving)

* *Reference standard*

1.4.6 Discussion

The first test that a patient receives at a diagnosis or monitoring visit is tonometry, which is a measurement of IOP. The Goldmann contact-tonometer is considered the reference standard. Whereas other non-contact tonometers are less costly (1.4.5) they are also less accurate. The consequences of obtaining a correct IOP measurement are closely connected to the identification of the most cost-effective treatment strategy (see 1.3). Therefore, despite its higher direct costs, Goldmann tonometry could be cost-effective compared to non-contact tonometry.

Anterior chamber angle assessment is fundamental at diagnosis in order to differentiate between open angle and angle closure glaucoma. It becomes less important at follow-up visits. Our analysis shows that gonioscopy is more costly than non-gonioscopic methods including Van Herick's test when omitting the cost of false referral and incorrect therapy initiation. Because of its elevated accuracy, it was the GDG's opinion that the reference standard cannot be substituted at diagnosis. However, for monitoring purposes van Herick's test could be sufficient. Gonioscopy is not extensively used in current practice and many optometrist practices in the community are not equipped to perform this test. Community Optometrists could

choose between purchasing a gonioscopy contact lens themselves and participating in a Hospital Eye Service (HES) scheme where this equipment would be provided.

Among the methods which are practical for routine use in the NHS, stereoscopic slit lamp biomicroscopy is considered the most reliable investigation to identify optic nerve damage from its appearance. In our cost analysis stereoscopic slit lamp examination turned out to be less costly than HRT, OCT and Laser Polarimetry. When this result is combined with its reputed greater accuracy, stereoscopic slit lamp biomicroscopy dominates the other tests. A further comparison in the analysis was made between the reference standard alone and the reference standard plus stereoscopic disc photography. This technology is not available in the current practice and to date it is only used in clinical trial settings. The additional costs that were found in the cost analysis (1.4.5) could be even higher since they correspond to the costs of monoscopic photography. Identifying optic disc damage is important for the correct diagnosis of COAG; if the damage is not identified the patient risks being discharged at serious risk of delayed diagnosis and treatment.

Our cost analysis has several limitations:

- We were not able to evaluate any estimate of effectiveness associated with each strategy; therefore a cost-effectiveness analysis could not be conducted.
- The cost of misdiagnosing OHT or COAG could be significant but was omitted because it would be very hard to estimate with reasonable precision. (The costs associated with correct diagnoses were also omitted).
- The harms caused by some tests (e.g. infections from Goldmann tonometer) and their costs were not included in the analysis.
- The final consideration on the accuracy of the tests (i.e. the reference standards are the most accurate) was largely based on expert opinion rather than on solid clinical evidence.

Unfortunately we did not find any study that carried out a similar economic analysis, thus we could not compare our findings with previous data.

1.4.7 Conclusions

- Goldmann tonometry and gonioscopy are considered the most accurate for the assessment of IOP and anterior chamber angle respectively. However they also generate more costs compared to non-contact tonometry and to non-gonioscopic methods.
- Stereoscopic slit lamp biomicroscopic assessment is considered the most accurate test for identifying optic nerve damage and it is also associated with less costs compared to HRT, OCT and Laser Polarimetry.
- These results should be treated with caution since the analysis has several limitations.

Appendix G

Recommendations for research

1.1 Recommendations for research on monitoring patients with OHT, COAG and suspected COAG

PICO question	Question: What is the clinical and cost effectiveness of different monitoring intervals for detection of disease progression in COAG patients at risk of progression?
Importance to patients or the population	Detection of progression of visual field damage in COAG is essential if treatments to prevent progression are to be instituted in time to avoid eventual deterioration to permanent severe visual impairment.
Relevance to NICE	The answer to this question is key to guidance on chronic disease monitoring intervals in this guideline. Once diagnosed COAG patients face lifelong monitoring and treatment. Monitoring intervals tailored to the risk of progression for varying risk strata would allow more efficient use of available resources. Risk guided intervals would allow those at high risk of progression to receive more intensive monitoring and relieve the burden of unnecessary monitoring visits on those with slowly progressive disease. Resources would be more appropriately focused on those at greatest risk and with more effective early detection of progression, damage to vision over time may be minimised. With this information available NICE would be in a position to recommend risk guided monitoring intervals resulting in both better use of resources and better outcomes.
Relevance to the NHS	The NHS would be in a better position to focus resources on those in most need. Early detection of progression followed by effective intervention would ultimately result in better visual outcomes and less costs associated with supporting visually impaired people (glaucoma currently accounts for ~10% of blind / partial sight registrations in England).
National priorities	Improving chronic disease management is currently an NHS priority[33]. This DH policy document specifically identifies "Stratifying patients by risk" and "Aiming to minimise unnecessary visits" as 2 of its key priorities, each of which is relevant to this research question.

Current evidence base	No trial evidence was identified
Study design	*Design*: A randomised comparative trial of 3 perceived risk strata (rapid, medium, slow) for progression to be randomised to 2, 3 and 2 alternative monitoring intervals respectively. *Outcome*: Progression events detected.
Feasibility	The research would be ethically and technically feasible. The research costs would need to be considered in the context that participants would still need monitoring if outside a trial.
Other comments	The National Institute for Health Research (NIHR) might be a suitable funding source.
Importance	High. The research is essential to inform future updates of key recommendations in the guideline.

1.2 Recommendations for research on treatment for patients with COAG

1.2.1 Update of National survey of trabeculectomy

PICO question	What are the current NHS national benchmarks for surgical success and complications in patients with COAG undergoing trabeculectomy drainage surgery with and without pharmacological augmentation?
Importance to patients or the population	This would inform patients of what to expect from their surgery in terms of the chances of success and complications. It would provide more accurate and up to date evidence for surgical treatment in glaucoma.
Relevance to NICE	Changes in surgical technique, and therefore success and complication rates, could alter the economic model for glaucoma treatment resulting in potential changes in the NICE recommendations
Relevance to the NHS	Up to date information on surgical success and complication rates will provide benchmarks for clinical audit and assist in planning service provision.
National priorities	Not a national priority in term of NSF or white paper
Current evidence base	Current evidence base is the National Audit of Trabeculectomy. This is now 10 years old and techniques have changed. Some surgeons are advocating the use of other surgical techniques such as deep sclerectomy and drainage tube implants. The audit would set a standard against which newer techniques could be evaluated.
Study design	The study design should be the same as the Audit of 10 years ago so we can compare the outcomes now in the light of changes in technique and the recommendations made by that audit.
Feasibility	Technically, ethically and financially feasible
Other comments	The research could be facilitated by the Royal College of Ophthalmologists. The National Institute for Health Research (NIHR) might be a suitable funding source. The Connecting for Health Information Centre may be a further source of support.
Importance	High. The research is essential to inform future updates of key recommendations in the guideline.

1.2.2 Laser treatment

PICO question	What is the effectiveness and cost-effectiveness of initial argon, diode or selective laser trabeculoplasty treatment compared to PGA alone or laser + PGA in combination in COAG patients?
Importance to patients or the population	The comparative effectiveness and cost effectiveness of laser treatment compared to modern ocular hypotensive agents particularly PGAs are unknown but may offer a period of pressure control without the need for topical medications in some patients. In others, it may offer additional benefit to topical medications and in both cases there may be cost efficiencies and improved prevention of progression of the disease
Relevance to NICE	Because of the lack of evidence, the role of laser trabeculoplasty in COAG management cannot be clearly defined.
Relevance to the NHS	Knowledge of comparative effectiveness to modern medications may offer a significant gain in cost benefit and might lead to a major change in guidance for a significant proportion of newly diagnosed COAG patients
National priorities	Treatment of long term conditions
Current evidence base	A completed Cochrane systematic review clearly points to the need for up to date evidence as indicated above. Existing trials of laser trabeculoplasty compared to medical treatment refer to outdated pharmacological agents.
Study design	RCTs in primary research
Feasibility	The research would be ethically and technically feasible.
Other comments	MRC or NIHR would be suitable sources of funding as opposed to manufacturers of medicines or lasers. To enable double masking or at least single masking, some form of sham laser treatment will be needed.
Importance	High. The research is essential to inform future updates of key recommendations in the guideline.

1.3 Recommendations for research on service provision

PICO question	In patients identified on primary examination as exhibiting possible COAG, OHT or glaucoma suspect status, what is the comparative effectiveness of diagnosis by different healthcare professions?
Importance to patients or the population	High. Further involvement of non-medical healthcare professions in care of patients within the scope of this guideline has potential to increase available staff resource with the potential to improve access to care, both in terms of number of available clinicians and locations.
Relevance to NICE	An answer to this question might potentially alter the service deliver recommendations of the current guideline. This is important in the context of access to care.
Relevance to the NHS	High. The initial guideline recommends that patients within its scope receive care following diagnosis as well as the setting of a management plan, supervised by an NHS consultant ophthalmologist. This research recommendation aims to determine whether alternative options exist. Dependent on findings, it is possible that provision of care by non-medical professionals may impact the NHS in terms of cost and quantity of care available, and may require strategic service planning to determine future staffing requirements.
National priorities	Improving chronic disease management is currently an NHS priority[33]. This DH policy document specifically identifies "Stratifying patients by risk" and "Aiming to minimise unnecessary visits" as 2 of its key priorities, each of which is relevant to this research question.
Current evidence base	The current available evidence base in the area is weak. One RCT exists, but is of limited generalisability due to its design.
Study design	A number of randomized controlled trials will be required.
Feasibility	The research would be ethically and technically feasible. However, due to the nature of the question, it is likely that projects in question will be large scale, require large sample sizes over extended time periods (years) and as such the research will be costly.
Other comments	No large scale service provision primary research on this subject area has been executed in over 10 years although the DH did pilot alternative glaucoma care pathways, demonstrating central government interest in this subject area.
importance	High: the research is essential to inform future updates of key recommendations in the guideline.

1.4 Recommendations for research on information for patients

PICO question	What is the clinical and cost effectiveness of providing glaucoma patients with a 'glaucoma card' or individual record of care compared to standard treatment?
Importance to patients or the population	Patient involvement in and understanding of management of glaucoma could reduce stress and uncertainty for patients and potentially improve compliance with medical treatment requirements, with resultant improved outcome i.e. prolonged sighted lifetime.
Relevance to NICE	This could provide evidence of better care in terms of outcome and patient experience. As such future NICE guidance would be in a position to recommend this more patient focused approach to care.
Relevance to the NHS	This could enable a significant increase in cost effectiveness by improving glaucoma management e.g. maximising the effectiveness of topical medical treatment across more patients.
National priorities	Improving chronic disease management is currently an NHS priority[33]. This DH policy document specifically identifies "Stratifying patients by risk" and "Aiming to minimise unnecessary visits" as 2 of its key priorities, each of which is relevant to this research question.
Current evidence base	No RCTs or systematic reviews were identified in our literature review addressing this question.
Study design	Randomised controlled trial design with a qualitative component. The latter would be needed to develop both an appropriate intervention and patient focused outcome measure to assess patient experience. A standard visual function (field of vision) test would be appropriate for evaluation of visual outcome.
Feasibility	Ethically and technically feasible. The proposed studies would require significant simple size and duration to determine visual outcome with associated cost implications.
Other comments	Time scale to assess useful outcomes would be long, probably 5 years or more.
Importance	Medium. The research is relevant to the recommendations in the guideline but the research recommendations are not key to future updates. Anything that improves concordance with medications could help prolong a person's sight.

Bibliography

1. The Advanced Glaucoma Intervention Study (AGIS): 11. Risk factors for failure of trabeculectomy and argon laser trabeculoplasty. *Am J Ophthalmol* 2002, **134**(4):481-98. *(Guideline Ref ID: AGIS2002A)*

2. The Advanced Glaucoma Intervention Study (AGIS): 12. Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. *Am J Ophthalmol* 2002, **134**(4):499-512. *(Guideline Ref ID: AGIS2002)*

3. Ainsworth JR, Jay JL. Cost analysis of early trabeculectomy versus conventional management in primary open angle glaucoma. *Eye* 1991, **5**(3):322-8. *(Guideline Ref ID: AINSWORTH1991)*

4. Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Scandinavian Latanoprost Study Group. *Ophthalmology* 1995, **102**(12):1743-52. *(Guideline Ref ID: ALM1995)*

5. Atkinson PL, Wishart PK, James JN, Vernon SA, Reid F. Deterioration in the accuracy of the pulsair non-contact tonometer with use: need for regular calibration. *Eye* 1992, **6**(Pt 5):530-4. *(Guideline Ref ID: ATKINSON1992)*

6. Azuara-Blanco A, Burr J, Thomas R, Maclennan G, McPherson S. The accuracy of accredited glaucoma optometrists in the diagnosis and treatment recommendation for glaucoma. *British Journal of Ophthalmology* 2007, **91**(12):1639-43. *(Guideline Ref ID: AZUARABLANCO2007)*

7. Banes MJ, Culham LE, Bunce C, Xing W, Viswanathan A, Garway-Heath D. Agreement between optometrists and ophthalmologists on clinical management decisions for patients with glaucoma. *British Journal of Ophthalmology* 2006, **90**(5):579-85. *(Guideline Ref ID: BANES2006)*

8. Banes MJ, Culham LE, Crowston JG, Bunce C, Khaw PT. An optometrist's role of co-management in a hospital glaucoma clinic. *Ophthalmic & Physiological Optics* 2000, **20**(5):351-9. *(Guideline Ref ID: BANES2000)*

9. Baskaran M, Oen FT, Chan YH, Hoh ST, Ho CL, Kashiwagi K *et al*. Comparison of the scanning peripheral anterior chamber depth analyzer and the modified van Herick grading system in the assessment of angle closure. *Ophthalmology* 2007, **114**(3):501-6. *(Guideline Ref ID: BASKARAN2007)*

10. Bernard LM, Althin R, Dhawan R, Grima DT, Lam A, Aballea S. Clinical and economic impacts of latanoprost 0.005% in first-line treatment of open-angle glaucoma and ocular hypertension in France. *Eur J Ophthalmol* 2003, **13**(Suppl 4):S30-S43. *(Guideline Ref ID: BERNARD2003)*

11. Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L *et al*. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. *Health Technology Assessment* 2001, **5**(26):1-149. *(Guideline Ref ID: BROCKLEBANK2001)*

12. Brown MM, Brown GC, Sharma S, Landy J. Health care economic analyses and value-based medicine. *Surv Ophthalmol* 2003, **48**(2):204-23. *(Guideline Ref ID: BROWN2003A)*

13. Bucci MG. Intraocular pressure-lowering effects of latanoprost monotherapy versus latanoprost or pilocarpine in combination with timolol: a randomized, observer-masked multicenter study in patients with open-angle glaucoma. Italian Latanoprost Study Group. *Journal of Glaucoma* 1999, **8**(1):24-30. *(Guideline Ref ID: BUCCI1999)*

14. Burr J. The clinical and cost-effectiveness of screening for open angle glaucoma. *Health Technology Assessment* 2007, **11**(41). *(Guideline Ref ID: BURR2007)*

15. Burr J, Azuara-Blanco A, Avenell A. Medical versus surgical interventions for open angle glaucoma. *Cochrane Database of Systematic Reviews* 2004, **Issue 2**:CD004399. *(Guideline Ref ID: BURR2004)*

16. Burr J, Kilonzo M, Vale L, Ryan M. Developing a Preference-Based Glaucoma Utility Index Using a Discrete Choice Experiment. *Optometry and Vision Science* 2007, **84**(8):797-808. *(Guideline Ref ID: BURR2007A)*

17. Camras CB. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a six-month masked, multicenter trial in the United States. The United States Latanoprost Study Group. *Ophthalmology* 1996, **103**(1):138-47. *(Guideline Ref ID: CAMRAS1996A)*

18. Camras CB, Sheu WP, United States Latanoprost-Brimonidine Study Group. Latanoprost or brimonidine as treatment for elevated intraocular pressure: multicenter trial in the United States. *Journal of Glaucoma* 2005, **14**(2):161-7. *(Guideline Ref ID: CAMRAS2005)*

19. Carassa RG, Bettin P, Fiori M, Brancato R. Viscocanalostomy versus trabeculectomy in white adults affected by open-angle glaucoma: a 2-year randomized, controlled trial. *Ophthalmology* 2003, **110**(5):882-7. *(Guideline Ref ID: CARASSA2003)*

20. Chiselita D. Non-penetrating deep sclerectomy versus trabeculectomy in primary open-angle glaucoma surgery. *Eye* 2001, **15**(2):197-201. *(Guideline Ref ID: CHISELITA2001)*

21. Cillino S, Di Pace F, Casuccio A, Cillino G, Lodato G. Deep sclerectomy versus trabeculectomy with low-dosage mitomycin C: four-year follow-up. *Ophthalmologica* 2008, **222**(2):81-7. *(Guideline Ref ID: CILLINO2008)*

22. Cillino S, Di Pace F, Casuccio A, Lodato G. Deep sclerectomy versus punch trabeculectomy: effect of low-dosage mitomycin C. *Ophthalmologica* 2005, **219**(5):281-6. *(Guideline Ref ID: CILLINO2005)*

23. Coast J, Spencer IC, Smith L, Spry PG. Comparing costs of monitoring glaucoma patients: hospital ophthalmologists versus community optometrists. *J Health Serv Res Policy* 1997, **2**(1):19-25. *(Guideline Ref ID: COAST1997)*

24. 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, **126**(4):487-97. *(Guideline Ref ID: CNTG1998A)*

25. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *Am J Ophthalmol* 1998, **126**(4):498-505. *(Guideline Ref ID: CNTG1998)*

26. Costa VP, Comegno PE, Vasconcelos JP, Malta RF, Jose NK. Low-dose mitomycin C trabeculectomy in patients with advanced glaucoma. *Journal of Glaucoma* 1996, **5**(3):193-9. *(Guideline Ref ID: COSTA1996)*

27. Cottle RW, Begg IS. Effectiveness and costs of antiglaucoma medications. *Journal of Toxicology-Cutaneous & Ocular Toxicology* 1988, **7**(4):283-93. *(Guideline Ref ID: COTTLE1988)*

28. Curtis L. Unit costs of health and social care http://www.pssru.ac.uk/pdf/uc/uc2007/uc2007.pdf [accessed 19-12-2008]. *(Guideline Ref ID: CURTIS2007)*

29. Dallas NL, Sponsel WE, Hobley AJ. A comparative evaluation of timolol maleate and pilocarpine in the treatment of chronic open angle glaucoma. *Eye* 1988, **2**(3):243-9. *(Guideline Ref ID: DALLAS1988)*

30. Damji KF, Bovell AM, Hodge WG, Rock W, Shah K, Buhrmann R *et al*. Selective laser trabeculoplasty versus argon laser trabeculoplasty: results from a 1-year randomised clinical trial. *British Journal of Ophthalmology* 2006, **90**(12):1490-4. *(Guideline Ref ID: DAMJI2006)*

31. Day DG, Schacknow PN, Sharpe ED, Ellyn JC, Kulze JC, III, Threlkeld AB *et al*. A persistency and economic analysis of latanoprost, bimatoprost, or beta-blockers in patients with open-angle glaucoma or ocular hypertension.[see comment]. *Journal of Ocular Pharmacology & Therapeutics* 2004, **20**(5):383-92. *(Guideline Ref ID: DAY2004)*

32. Day DG, Sharpe ED, Atkinson MJ, Stewart JA, Stewart WC. The clinical validity of the treatment satisfaction survey for intraocular pressure in ocular hypertensive and glaucoma patients. *Eye* 2006, **20**(5):583-90. *(Guideline Ref ID: DAY2006)*

33. Department of Health. Improving chronic disease management http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4075214 [accessed 1-7-2008]. *(Guideline Ref ID: DH2004)*

34. Department of Health. Transmissible spongiform encephalopathy agents: safe working and the prevention of infection http://www.advisorybodies.doh.gov.uk/acdp/tseguidance/ [accessed 15-9-2008]. *(Guideline Ref ID: DH2007A)*

35. Diggory P, Franks W. Medical treatment of glaucoma--a reappraisal of the risks. *Br J Ophthalmol* 1996, **80**(1):85-9. *(Guideline Ref ID: DIGGORY1996)*

36. Drance SM. A comparison of the effects of betaxolol, timolol, and pilocarpine on visual function in patients with open-angle glaucoma. *Journal of Glaucoma* 1998, **7**(4):247-52. *(Guideline Ref ID: DRANCE1998)*

37. Edmunds B, Thompson JR, Salmon JF, Wormald RP. The National Survey of Trabeculectomy. III. Early and late complications. *Eye* 2002, **16**(3):297-303. *(Guideline Ref ID: EDMUNDS2002)*

38. Edmunds B, Thompson JR, Salmon JF, Wormald RP. The National Survey of Trabeculectomy. II. Variations in operative technique and outcome. *Eye* 2001, **15**(Pt 4):441-8. *(Guideline Ref ID: EDMUNDS2001)*

39. Egbert PR, Williams AS, Singh K, Dadzie P, Egbert TB. A prospective trial of intraoperative fluorouracil during trabeculectomy in a black population. *American Journal of Ophthalmology* 1993, **116**(5):612-6. *(Guideline Ref ID: EGBERT1993)*

40. Egrilmez S, Ates H, Nalcaci S, Andac K, Yagci A. Surgically induced corneal refractive change following glaucoma surgery: nonpenetrating trabecular surgeries versus trabeculectomy. *Journal of Cataract & Refractive Surgery* 2004, **30**(6):1232-9. *(Guideline Ref ID: EGRILMEZ2004)*

41. El Sayyad F, Helal M, El Kholify H, Khalil M, El Maghraby A. Nonpenetrating deep sclerectomy versus trabeculectomy in bilateral primary open-angle glaucoma. *Ophthalmology* 2000, **107**(9):1671-4. *(Guideline Ref ID: ELSAYYAD2000)*

42. Epstein DL, Krug JH, Jr., Hertzmark E, Remis LL, Edelstein DJ. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. *Ophthalmology* 1989, **96**(10):1460-7. *(Guideline Ref ID: EPSTEIN1989)*

43. European Glaucoma Society. (2003) Terminology and guidelines for glaucoma. Savona: European Glaucoma Society. *(Guideline Ref ID: EGS2003)*

44. Fellman RL, Sullivan EK, Ratliff M, Silver LH, Whitson JT, Turner FD *et al*. Comparison of travoprost 0.0015% and 0.004% with timolol 0.5% in patients with elevated intraocular pressure: a 6-month, masked, multicenter trial. *Ophthalmology* 2002, **109**(5):998-1008. *(Guideline Ref ID: FELLMAN2002)*

45. Gandolfi SA, Chetta A, Cimino L, Mora P, Sangermani C, Tardini MG. Bronchial reactivity in healthy individuals undergoing long-term topical treatment with beta-blockers. *Archives of Ophthalmology* 2005, **123**(1):35-8. *(Guideline Ref ID: GANDOLFI2005)*

46. Glynn RJ, Seddon JM, Krug JH, Jr., Sahagian CR, Chiavelli ME, Campion EW. Falls in elderly patients with glaucoma. *Arch Ophthalmol* 1991, **109**(2):205-10. *(Guideline Ref ID: GLYNN1991)*

47. Goldberg I, Cunha-Vaz J, Jakobsen JE, Nordmann JP, Trost E, Sullivan EK *et al*. Comparison of topical travoprost eye drops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension.[see comment]. *Journal of Glaucoma* 2001, **10**(5):414-22. *(Guideline Ref ID: GOLDBERG2001)*

48. Goldberg LD, Walt J. Cost considerations in the medical management of glaucoma in the US: estimated yearly costs and cost effectiveness of bimatoprost compared with other medications. *Pharmacoeconomics* 2006, **24**(3):251-64. *(Guideline Ref ID: GOLDBERG2006)*

49. Goldenfeld M, Krupin T, Ruderman JM, Wong PC, Rosenberg LF, Ritch R *et al*. 5-Fluorouracil in initial trabeculectomy: A prospective, randomized multicenter study. *Ophthalmology* 1994, **101**(6):1024-9. *(Guideline Ref ID: GOLDENFELD1994)*

50. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA *et al*. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of

primary open-angle glaucoma. *Archives of Ophthalmology* 2002, **120**(6):714-20. *(Guideline Ref ID: GORDON2002)*

51. Gordon MO, Torri V, Miglior S, Beiser JA, Floriani I, Miller JP *et al*. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. *Ophthalmology* 2007, **114**(1):10-9. *(Guideline Ref ID: GORDON2007)*

52. Gray SF, Spry PG, Brookes ST, Peters TJ, Spencer IC, Baker IA *et al*. The Bristol shared care glaucoma study: outcome at follow up at 2 years. *British Journal of Ophthalmology* 2000, **84**(5):456-63. *(Guideline Ref ID: GRAY2000)*

53. Gupta V, Srinivasan G, Mei SS, Gazzard G, Sihota R, Kapoor KS. Utility values among glaucoma patients: an impact on the quality of life. *Br J Ophthalmol* 2005, **89**(10):1241-4. *(Guideline Ref ID: GUPTA2005)*

54. Halpern MT, Covert DW, Robin AL. Projected impact of travoprost versus both timolol and latanoprost on visual field deficit progression and costs among black glaucoma subjects. *Transactions of the Ophthalmological Societies of the United Kingdom* 2002, **100**:109-18. *(Guideline Ref ID: HALPERN2002)*

55. Harper R, Radi N, Reeves BC, Fenerty C, Spencer AF, Batterbury M. Agreement between ophthalmologists and optometrists in optic disc assessment: training implications for glaucoma co-management. *Graefes Archive for Clinical & Experimental Ophthalmology* 2001, **239**(5):342-50. *(Guideline Ref ID: HARPER2001)*

56. Harper R, Reeves B. The sensitivity and specificity of direct ophthalmoscopic optic disc assessment in screening for glaucoma: A multivariate analysis. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2000, **238**(12):949-55. *(Guideline Ref ID: HARPER2000)*

57. Harper R, Reeves B, Smith G. Observer variability in optic disc assessment: implications for glaucoma shared care. *Ophthalmic & Physiological Optics* 2000, **20**(4):265-73. *(Guideline Ref ID: HARPER2000A)*

58. Heijl A, Bengtsson B. Long-term effects of timolol therapy in ocular hypertension: a double-masked, randomised trial. *Graefes Arch Clin Exp Ophthalmol* 2000, **238**(11):877-83. *(Guideline Ref ID: HEIJL2000)*

59. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002, **120**(10):1268-79. *(Guideline Ref ID: HEIJL2002)*

60. Henson DB, Spencer AF, Harper R, Cadman EJ. Community refinement of glaucoma referrals. *Eye* 2003, **17**(1):21-6. *(Guideline Ref ID: HENSON2003)*

61. Higginbotham EJ, Feldman R, Stiles M, Dubiner H, Fixed Combination Investigative Group. Latanoprost and timolol combination therapy vs monotherapy: one-year randomized trial. *Archives of Ophthalmology* 2002, **120**(7):915-22. *(Guideline Ref ID: HIGGINBOTHAM2002A)*

62. Higginbotham EJ, Schuman JS, Goldberg I, Gross RL, VanDenburgh AM, Chen K *et al*. One-year, randomized study comparing bimatoprost and timolol in glaucoma and

ocular hypertension. *Archives of Ophthalmology* 2002, **120**(10):1286-93. *(Guideline Ref ID: HIGGINBOTHAM2002)*

63. Hodapp E, Parrish RG, Anderson DR. Clinical decisions in glaucoma. St Louis: Mosby, 1993.*(Guideline Ref ID: HODAPP1993)*

64. Jampel HD, Musch DC, Gillespie BW, Lichter PR, Wright MM, Guire KE *et al*. Perioperative complications of trabeculectomy in the collaborative initial glaucoma treatment study (CIGTS). *American Journal of Ophthalmology* 2005, **140**(1):16-22. *(Guideline Ref ID: JAMPEL2005)*

65. Jay JL, Murray SB. Early trabeculectomy versus conventional management in primary open angle glaucoma. *British Journal of Ophthalmology* 1988, **72**(12):881-9. *(Guideline Ref ID: JAY1988)*

66. Jones SJ, Vernon SA, Cater L, Henry DJ. Costing a community based screening programme for the detection of glaucoma. *Eye* 1990, **4 (Pt 1)**:98-102. *(Guideline Ref ID: JONES1990)*

67. Jonescu-Cuypers C, Jacobi P, Konen W, Krieglstein G. Primary viscocanalostomy versus trabeculectomy in white patients with open-angle glaucoma: A randomized clinical trial. *Ophthalmology* 2001, **108**(2):254-8. *(Guideline Ref ID: JONESCUCUYPERS2001)*

68. Kaiserman I, Kaiserman N, Elhayany A, Vinker S. Topical beta-blockers are not associated with an increased risk of treatment for depression. *Ophthalmology* 2006, **113**(7):1077-80. *(Guideline Ref ID: KAISERMAN2006)*

69. Kamal D, Garway-Heath D, Ruben S, O'Sullivan F, Bunce C, Viswanathan A *et al*. Results of the betaxolol versus placebo treatment trial in ocular hypertension. *Graefes Arch Clin Exp Ophthalmol* 2003, **241**(3):196-203. *(Guideline Ref ID: KAMAL2003)*

70. Kampik A, Arias-Puente A, O'Brart DP, Vuori ML, European latanoprost study group. Intraocular pressure-lowering effects of latanoprost and brimonidine therapy in patients with open-angle glaucoma or ocular hypertension: a randomized observer-masked multicenter study. *Journal of Glaucoma* 2002, **11**(2):90-6. *(Guideline Ref ID: KAMPIK2002)*

71. Kanski JJ. Clinical ophthalmology. Oxford: Butterworth-Heinemann, 2003.*(Guideline Ref ID: KANSKI2003)*

72. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP *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. *Archives of Ophthalmology* 2002, **120**(6):701-13. *(Guideline Ref ID: KASS2002)*

73. Kaushik S, Pandav SS, Ram J. Neuroprotection in glaucoma. *J Postgrad Med* 2003, **49**(1):90-5. *(Guideline Ref ID: KAUSHIK2003)*

74. Kirwan JF, Nightingale JA, Bunce C, Wormald R. Beta blockers for glaucoma and excess risk of airways obstruction: population based cohort study. *BMJ* 2002, **325**(7377):1396-7. *(Guideline Ref ID: KIRWAN2002A)*

75. Kirwan JF, Nightingale JA, Bunce C, Wormald R. Do selective topical beta antagonists for glaucoma have respiratory side effects? *Br J Ophthalmol* 2004, **88**(2):196-8. *(Guideline Ref ID: KIRWAN2004A)*

76. Kitazawa Y. The effect of timolol on topographic features of the optic disk in ocular hypertension. *Chibret International Journal of Ophthalmology* 1990, **7**(1):14-7. *(Guideline Ref ID: KITAZAWA1990)*

77. Kobayashi H, Kobayashi K, Okinami S. A comparison of the intraocular pressure-lowering effect and safety of viscocanalostomy and trabeculectomy with mitomycin C in bilateral open-angle glaucoma. *Graefes Archive for Clinical & Experimental Ophthalmology* 2003, **241**(5):359-66. *(Guideline Ref ID: KOBAYASHI2003)*

78. Kobelt G, Jonsson B, Bergstrom A, Chen E, Linden C, Alm A. Cost-effectiveness analysis in glaucoma: What drives utility? Results from a pilot study in Sweden. *Acta Ophthalmologica Scandinavica* 2006, **84**(3):363-71. *(Guideline Ref ID: KOBELT2006)*

79. Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D. The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma. *Health Technology Assessment* 2005, **9**(46). *(Guideline Ref ID: KWARTZ2005)*

80. Kymes SM, Kass MA, Anderson DR, Miller JP, Gordon MO. Management of ocular hypertension: a cost-effectiveness approach from the Ocular Hypertension Treatment Study. *Am J Ophthalmol* 2006, **141**(6):997-1008. *(Guideline Ref ID: KYMES2006)*

81. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977, **33**(1):159-74. *(Guideline Ref ID: LANDIS1977)*

82. Le Pen C, Ligier M, Berdeaux G. Cost-effectiveness and cost-utility analysis of travoprost versus latanoprost and timolol in the treatment of advanced glaucoma in five European countries: Austria, France, Germany, The Netherlands and the United Kingdom. *Journal of Medical Economics* 2005, **8**:67-84. *(Guideline Ref ID: LEPEN2005)*

83. Leblanc RP. Twelve-month results of an ongoing randomized trial comparing brimonidine tartrate 0.2% and timolol 0.5% given twice daily in patients with glaucoma or ocular hypertension. Brimonidine Study Group 2. *Ophthalmology* 1998, **105**(10):1960-7. *(Guideline Ref ID: LEBLANC1998)*

84. Lee BS, Kymes SM, Nease RF, Jr., Sumner W, Siegfried CJ, Gordon MO. The impact of anchor point on utilities for 5 common ophthalmic diseases. *Ophthalmology* 2008, **115**(5):898-903. *(Guideline Ref ID: LEE2008)*

85. Lee PP, Walt JG, Doyle JJ, Kotak SV, Evans SJ, Budenz DL *et al*. A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. *Archives of Ophthalmology* 2006, **124**(1):12-9. *(Guideline Ref ID: LEE2006)*

86. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: The Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2003, **121**(1):48-56. *(Guideline Ref ID: LESKE2003)*

87. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of Long-term Progression in the Early Manifest Glaucoma Trial. *Ophthalmology* 2007, **114**(11):1965-72. *(Guideline Ref ID: LESKE2007)*

88. Leyland M, Bloom P, Zinicola E, McAlister J, Rassam S, Migdal C. Single intraoperative application of 5-Fluorouracil versus placebo in low-risk trabeculectomy surgery: a randomized trial. *Journal of Glaucoma* 2001, **10**(6):452-7. *(Guideline Ref ID: LEYLAND2001)*

89. Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA *et al*. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001, **108**(11):1943-53. *(Guideline Ref ID: LICHTER2001)*

90. Luke C, Dietlein TS, Jacobi PC, Konen W, Krieglstein GK. A prospective randomized trial of viscocanalostomy versus trabeculectomy in open-angle glaucoma: a 1-year follow-up study. *Journal of Glaucoma* 2002, **11**(4):294-9. *(Guideline Ref ID: LUKE2002)*

91. Manni G, Centofanti M, Parravano M, Oddone F, Bucci MG. A 6-month randomized clinical trial of bimatoprost 0.03% versus the association of timolol 0.5% and latanoprost 0.005% in glaucomatous patients. *Graefes Archive for Clinical & Experimental Ophthalmology* 2004, **242**(9):767-70. *(Guideline Ref ID: MANNI2004)*

92. March WF, Ochsner KI. The long-term safety and efficacy of brinzolamide 1.0% (azopt) in patients with primary open-angle glaucoma or ocular hypertension. The Brinzolamide Long-Term Therapy Study Group. *American Journal of Ophthalmology* 2000, **129**(2):136-43. *(Guideline Ref ID: MARCH2000)*

93. Martin E, Martinez-de-la-Casa JM, Garcia-Feijoo J, Troyano J, Larrosa JM, Garcia-Sanchez J. A 6-month assessment of bimatoprost 0.03% vs timolol maleate 0.5%: hypotensive efficacy, macular thickness and flare in ocular-hypertensive and glaucoma patients. *Eye* 2007, **21**(2):164-8. *(Guideline Ref ID: MARTIN2007)*

94. Martini E, Laffi GL, Sprovieri C, Scorolli L. Low-dosage mitomycin C as an adjunct to trabeculectomy. A prospective controlled study. *European Journal of Ophthalmology* 1997, **7**(1):40-8. *(Guideline Ref ID: MARTINI1997)*

95. Mastropasqua L, Carpineto P, Ciancaglini M, Gallenga PE. A 12-month, randomized, double-masked study comparing latanoprost with timolol in pigmentary glaucoma. *Ophthalmology* 1999, **106**(3):550-5. *(Guideline Ref ID: MASTROPASQUA1999)*

96. Meads C, Hyde C. What is the cost of blindness? *Br J Ophthalmol* 2003, **87**(10):1201-4. *(Guideline Ref ID: MEADS2003)*

97. Medicines and Healthcare products Regulatory Agency. MAC manual part 3: procedures. Sterilization, disinfection and cleaning of medical equipment: guidance on decontamination from the Microbiology Advisory Committee to Department of Health http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007441&RevisionSelectionMethod=LatestReleased [accessed 15-9-2008]. *(Guideline Ref ID: MHRA2006)*

98. Migdal C, Gregory W, Hitchings R. Long-term functional outcome after early surgery compared with laser and medicine in open-angle glaucoma. *Ophthalmology* 1994, **101**(10):1651-6. *(Guideline Ref ID: MIGDAL1994)*

99. Miglior S, Zeyen T, Pfeiffer N, Cunha-Vaz J, Torri V, Adamsons I *et al*. Results of the European Glaucoma Prevention Study. *Ophthalmology* 2005, **112**(3):366-75. *(Guideline Ref ID: MIGLIOR2005)*

100. Millodot M, Laby DM. Dictionary of ophthalmology. Woburn, MA: Reed Educational and Professional Publishing Ltd, 2002.*(Guideline Ref ID: MILLODOT2002)*

101. Mills KB. Blind randomised non-crossover long-term trial comparing topical timolol 0.25% with timolol 0.5% in the treatment of simple chronic glaucoma. *British Journal of Ophthalmology* 1983, **67**(4):216-9. *(Guideline Ref ID: MILLS1983)*

102. Moriarty BJ, Char JN, Acheson RW, Dunn DT. Argon laser trabeculoplasty in primary open-angle glaucoma--results in black Jamaican population. *International Ophthalmology* 1988, **12**(4):217-21. *(Guideline Ref ID: MORIARTY1988)*

103. Muller ME, van d, V, Krulder JW, van der Cammen TJ. Syncope and falls due to timolol eye drops. *BMJ* 2006, **332**(7547):960-1. *(Guideline Ref ID: MULLER2006)*

104. Nagar M, Ogunyomade A, O'Brart DP, Howes F, Marshall J. A randomised, prospective study comparing selective laser trabeculoplasty with latanoprost for the control of intraocular pressure in ocular hypertension and open angle glaucoma. *British Journal of Ophthalmology* 2005, **89**(11):1413-7. *(Guideline Ref ID: NAGAR2005)*

105. National Collaborating Centre for Primary Care. Medicines concordance and adherence: involving adults and carers in decisions about prescribed medicines: draft for consultation. http://www.nice.org.uk/nicemedia/pdf/MedicinesConcordanceDraftFullGuidelineForConsultation.doc [accessed 15-9-2008]. *(Guideline Ref ID: NCCPC2008)*

106. National Institute for Health and Clinical Excellence. (2007) The guidelines manual. London: National Institute for Health and Clinical Excellence. *(Guideline Ref ID: NICE2007)*

107. National Institute for Health and Clinical Excellence. (2008) Canaloplasty for primary open-angle glaucoma: guidance. London: National Institute for Health and Clinical Excellence. *(Guideline Ref ID: NICE2008)*

108. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisals http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf [accessed 19-12-2008]. *(Guideline Ref ID: NATIONALINSTITU2008)*

109. Nelson WL, Fraunfelder FT, Sills JM, Arrowsmith JB, Kuritsky JN. Adverse respiratory and cardiovascular events attributed to timolol ophthalmic solution, 1978-1985. *Am J Ophthalmol* 1986, **102**(5):606-11. *(Guideline Ref ID: NELSON1986)*

110. Netland PA, Landry T, Sullivan EK, Andrew R, Silver L, Weiner A *et al*. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *American Journal of Ophthalmology* 2001, **132**(4):472-84. *(Guideline Ref ID: NETLAND2001)*

111. Neudorfer M, Sadetzki S, Anisimova S, Geyer O. Nonpenetrating Deep Sclerectomy with the Use of Adjunctive Mitomycin C. *Ophthalmic Surgery, Lasers & Imaging* 2004, **35**(1):6-12. *(Guideline Ref ID: NEUDORFER2004)*

112. Nolan WP, See JL, Chew PTK, Friedman DS, Smith SD, Radhakrishnan S *et al*. Detection of Primary Angle Closure Using Anterior Segment Optical Coherence Tomography in Asian Eyes. *Ophthalmology* 2007, **114**(1):33-9. *(Guideline Ref ID: NOLAN2007)*

113. Ophir A, Ticho U. A randomized study of trabeculectomy and subconjunctival administration of fluorouracil in primary glaucomas. *Archives of Ophthalmology* 1992, **110**(8):1072-5. *(Guideline Ref ID: OPHIR1992)*

114. Orengo-Nania S, Landry T, Von Tress M, Silver LH, Weiner A, Davis AA *et al*. Evaluation of travoprost as adjunctive therapy in patients with uncontrolled intraocular pressure while using timolol 0.5%. *American Journal of Ophthalmology* 2001, **132**(6):860-8. *(Guideline Ref ID: ORENGONANIA2001)*

115. Ozturk F, Ermis SS, Inan UU. Comparison of the ocular hypotensive effects of bimatoprost and timolol-dorzolamide combination in patients with elevated intraocular pressure: a 6-month study. *Acta Ophthalmologica Scandinavica* 2007, **85**(1):80-3. *(Guideline Ref ID: OZTURK2007)*

116. Pfeiffer N, European Latanoprost Fixed Combination Study Group. A comparison of the fixed combination of latanoprost and timolol with its individual components. *Graefes Archive for Clinical & Experimental Ophthalmology* 2002, **240**(11):893-9. *(Guideline Ref ID: PFEIFFER2002)*

117. Polo V, Larrosa JM, Ferreras A, Honrubia FM. Latanoprost vs combined therapy with timolol plus dorzolamide in open-angle glaucoma: A 24-month study. *Annals of Ophthalmology* 2005, **37**(1):33-6. *(Guideline Ref ID: POLO2005)*

118. Rasheed e. Initial trabeculectomy with intraoperative mitomycin-C application in primary glaucomas. *Ophthalmic Surgery & Lasers* 1999, **30**(5):360-6. *(Guideline Ref ID: RASHEED1999)*

119. Rein DB, Wirth KE, Johnson CA, Lee PP. Estimating quality-adjusted life year losses associated with visual field deficits using methodological approaches. *Ophthalmic Epidemiol* 2007, **14**(4):258-64. *(Guideline Ref ID: REIN2007)*

120. Rhee DJ, Katz LJ, Spaeth GL, Myers JS. Complementary and alternative medicine for glaucoma. *Surv Ophthalmol* 2001, **46**(1):43-55. *(Guideline Ref ID: RHEE2001)*

121. Rismanchian A, Eslami F, Moeini H, Attarzade H, Naderibeni A. Efficacy of the latanoprost versus timolol/dorzolamide combination therapy in patients with primary open angle glaucoma. *Saudi Med J* 2008, **29**(3):384-7. *(Guideline Ref ID: RISMANCHIAN2008)*

122. Ritch R. Complementary therapy for the treatment of glaucoma: a perspective. *Ophthalmol Clin North Am* 2005, **18**(4):597-609. *(Guideline Ref ID: RITCH2005)*

123. Robin AL, Ramakrishnan R, Krishnadas R, Smith SD, Katz JD, Selvaraj S *et al*. A long-term dose-response study of mitomycin in glaucoma filtration surgery.[see comment]. *Archives of Ophthalmology* 1997, **115**(8):969-74. *(Guideline Ref ID: ROBIN1997)*

124. Rolim dM, Paranhos JA. Laser trabeculoplasty for open angle glaucoma. *Cochrane Database of Systematic Reviews* 2007, **Issue 4**:CD003919. *(Guideline Ref ID: ROLIM2007)*

125. Rouland JF, Le Pen C, Ophthalmologists of the Glaucoma Study. Naturalistic, prospective study of glaucoma and ocular hypertension treatment in France: strategies, clinical outcomes, and costs at 1 year. *European Journal of Ophthalmology* 2003, **13 Suppl 4**:S5-20. *(Guideline Ref ID: ROULAND2003A)*

126. Rouland J-F, Le Pen C, Benhaddi H, Piriou E, Lilliu H, Kenigsberg P-A. Naturalistic, prospective study of glaucoma and ocular hypertension treatment in France: Strategies, clinical outcomes, and costs at 2 years. *European Journal of Ophthalmology* 2005, **15**(5):562-80. *(Guideline Ref ID: ROULAND2005A)*

127. Royal College of Ophthalmologists. Creutzfeldt-Jakob Disease (CJD) and ophthalmology http://www.rcophth.ac.uk/docs/publications/CollegeCJDNov2003.pdf *(Guideline Ref ID: RCO2004A)*

128. Royal College of Ophthalmologists. Certificate of vision impairment: explanatory notes for consultant ophthalmologists and hospital eye clinic staff http://www.rcophth.ac.uk/docs/profstands/ExplanatoryNotesForCounsultants&EyeClinicStaff.pdf [accessed 15-9-2008]. *(Guideline Ref ID: RCO2005)*

129. Royal College of Ophthalmologists. Ophthalmic instrument decontamination http://www.rcophth.ac.uk/docs/profstands/ophthalmic-services/DecontaminationApril2008.pdf [accessed 15-9-2008]. *(Guideline Ref ID: RC02008)*

130. Schermer TR, Thoonen BP, van den BG, Akkermans RP, Grol RP, Folgering HT *et al.* Randomized controlled economic evaluation of asthma self-management in primary health care. *Am J Respir Crit Care Med* 2002, **166**(8):1062-72. *(Guideline Ref ID: SCHERMER2002)*

131. Schulzer M, Drance SM, Douglas GR. A comparison of treated and untreated glaucoma suspects. *Ophthalmology* 1991, **98**(3):301-7. *(Guideline Ref ID: SCHULZER1991)*

132. Schuman JS. Clinical experience with brimonidine 0.2% and timolol 0.5% in glaucoma and ocular hypertension. *Survey of Ophthalmology* 1996, **41 Suppl 1**:S27-S37. *(Guideline Ref ID: SCHUMAN1996)*

133. Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K. A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group.[see comment]. *Archives of Ophthalmology* 1997, **115**(7):847-52. *(Guideline Ref ID: SCHUMAN1997)*

134. Schwartz B, Lavin P, Takamoto T, Araujo DF, Smits G. Decrease of optic disc cupping and pallor of ocular hypertensives with timolol therapy. *Acta Ophthalmologica Scandinavica Supplement* 1995, **73**(Suppl 215):5-21. *(Guideline Ref ID: SCHWARTZ1995)*

135. Sherwood MB, Craven ER, Chou C, DuBiner HB, Batoosingh AL, Schiffman RM *et al.* Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. *Archives of Ophthalmology* 2006, **124**(9):1230-8. *(Guideline Ref ID: SHERWOOD2006)*

136. Sherwood MB, Lattimer J, Hitchings RA. Laser trabeculoplasty as supplementary treatment for primary open angle glaucoma. *British Journal of Ophthalmology* 1987, **71**(3):188-91. *(Guideline Ref ID: SHERWOOD1987)*

137. Shore JH, Fraunfelder FT, Meyer SM. Psychiatric side effects from topical ocular timolol, a beta-adrenergic blocker. *J Clin Psychopharmacol* 1987, **7**(4):264-7. *(Guideline Ref ID: SHORE1987)*

138. Singh K, Egbert PR, Byrd S, Budenz DL, Williams AS, Decker JH *et al*. Trabeculectomy with intraoperative 5-fluorouracil vs mitomycin C. *American Journal of Ophthalmology* 1997, **123**(1):48-53. *(Guideline Ref ID: SINGH1997)*

139. Snape JP, Waldock A. Spirometry for patients prescribed topical beta-blockers. *Nursing Standard* 2000, **15**(4):35-8. *(Guideline Ref ID: SNAPE2000)*

140. Spencer IC, Spry PG, Gray SF, Baker IA, Menage MJ, Easty DL *et al*. The Bristol Shared Care Glaucoma Study: study design. *Ophthalmic and Physiological Optics* 1995, **15**(5):391-4. *(Guideline Ref ID: SPENCER1995)*

141. Sponsel WE. Timolol Vs pilocarpine in open angle glaucoma: The observation of significant differences in visual field response in patients with clinically equivalent IOP control. *Chibret International Journal of Ophthalmology* 1987, **5**(3):50-6. *(Guideline Ref ID: SPONSEL1987)*

142. Spry PG, Spencer IC, Sparrow JM, Peters TJ, Brookes ST, Gray S *et al*. The Bristol Shared Care Glaucoma Study: reliability of community optometric and hospital eye service test measures. *British Journal of Ophthalmology* 1999, **83**(6):707-12. *(Guideline Ref ID: SPRY1999)*

143. Stewart WC, Leech J, Sharpe ED, Kulze J, Ellyn J, Day DG. An economic analysis of switching to latanoprost from a beta-blocker or adding brimonidine or latanoprost to a beta-blocker in open-angle glaucoma or ocular hypertension. *American Journal of Managed Care* 2002, **8**:S240-S248. *(Guideline Ref ID: STEWART2002)*

144. Stewart WC, Stewart JA, Nassar QJ, Mychaskiw MA. Cost-effectiveness of treating ocular hypertension. *Ophthalmology* 2008, **115**(1):94-8. *(Guideline Ref ID: STEWART2008)*

145. Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. International Dorzolamide Study Group.[see comment]. *Archives of Ophthalmology* 1995, **113**(8):1009-16. *(Guideline Ref ID: STRAHLMAN1995)*

146. Sycha T, Vass C, Findl O, Bauer P, Groke I, Schmetterer L *et al*. Interventions for normal tension glaucoma. *Cochrane Database of Systematic Reviews* 2003, **Issue 4**:CD002222. *(Guideline Ref ID: SYCHA2003)*

147. Szymanski A, Gierek-Lapinska A, Koziak M, Gierek-Ciaciura S. A fluorophotometric study of corneal endothelium after trabeculectomy using different concentrations of Mitomycin-C. *International Ophthalmology* 1997, **20**(1-3):95-9. *(Guideline Ref ID: SZYMANSKI1997)*

148. Theodossiades J, Murdoch I. What optic disc parameters are most accurately assessed using the direct ophthalmoscope? *Eye* 2001, **15**(Pt 3):283-7. *(Guideline Ref ID: THEODOSSIADES2001)*

149. Thomas R, George T, Braganza A, Muliyil J. The flashlight test and van Herick's test are poor predictors for occludable angles. *Australian and New Zealand Journal of Ophthalmology* 1996, **24**(3):251-6. *(Guideline Ref ID: THOMAS1996)*

150. Tomita G, Araie M, Kitazawa Y, Tsukahara S. A three-year prospective, randomized and open comparison between latanoprost and timolol in Japanese normal-tension glaucoma patients. *Eye* 2004, **18**(10):984-9. *(Guideline Ref ID: TOMITA2004)*

151. Traverso CE, Walt JG, Kelly SP, Hommer AH, Bron AM, Denis P *et al*. Direct costs of glaucoma and severity of the disease: a multinational, long-term study of resource utilization in Europe. *Evidence-Based Ophthalmology* 2006, **7**(1):47-8. *(Guideline Ref ID: TRAVERSO2006)*

152. Tsai J-C, Chang H-W. Comparison of the effects of brimonidine 0.2% and timolol 0.5% on retinal nerve fiber layer thickness in ocular hypertensive patients: A prospective, unmasked study. *Journal of Ocular Pharmacology & Therapeutics* 2005, **21**(6):475-82. *(Guideline Ref ID: TSAI2005)*

153. Tuck MW, Crick RP. The cost-effectiveness of various modes of screening for primary open angle glaucoma. *Ophthalmic Epidemiology* 1997, **4**(1):3-17. *(Guideline Ref ID: TUCK1997)*

154. Tuck MW, Crick RP. The age distribution of primary open angle glaucoma. *Ophthalmic Epidemiology* 1998, **5**(4):173-83. *(Guideline Ref ID: TUCK1998)*

155. Vass C, Findl O, Sycha T, Bauer P, Schmetterer L. Medical interventions for primary open angle glaucoma and ocular hypertension. *Cochrane Database of Systematic Reviews* 2004, **Issue 3**:CD003167. *(Guideline Ref ID: VASS2007)*

156. Vetrugno M, Cardascia N, Cantatore F, Sborgia C. Comparison of the effects of bimatoprost and timolol on intraocular pressure and pulsatile ocular blood flow in patients with primary open-angle glaucoma: A prospective, open-label, randomized, two-arm, parallel-group study. *Current Therapeutic Research, Clinical & Experimental* 2004, **65**(6):444-54. *(Guideline Ref ID: VETRUGNO2004)*

157. Vogel R, Crick RP, Mills KB, Reynolds PM, Sass W, Clineschmidt CM *et al*. Effect of timolol versus pilocarpine on visual field progression in patients with primary open-angle glaucoma. *Ophthalmology* 1992, **99**(10):1505-11. *(Guideline Ref ID: VOGEL1992)*

158. Watson P, Stjernschantz J. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. The Latanoprost Study Group. *Ophthalmology* 1996, **103**(1):126-37. *(Guideline Ref ID: WATSON1996)*

159. Watson PG, Allen ED, Graham CM, Porter GP, Pickering MS. Argon laser trabeculoplasty or trabeculectomy a prospective randomised block study. *Transactions of the Ophthalmological Societies of the United Kingdom* 1985, **104**(Pt 1):55-61. *(Guideline Ref ID: WATSON1984)*

160. Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol* 2001, **107**(1):3-8. *(Guideline Ref ID: WEISS2001)*

161. Wilkins M, Indar A, Wormald R. Intra-operative mitomycin C for glaucoma surgery. *Cochrane Database of Systematic Reviews* 2005, **Issue 4**:CD002897. *(Guideline Ref ID: WILKINS2005)*

162. Wormald R, Wilkins MR, Bunce C. Post-operative 5-Fluorouracil for glaucoma surgery. *Cochrane Database of Systematic Reviews* 2001, **Issue 3**:CD001132. *(Guideline Ref ID: WORMALD2001)*

163. Yalvac IS, Sahin M, Eksioglu U, Midillioglu IK, Aslan BS, Duman S. Primary viscocanalostomy versus trabeculectomy for primary open-angle glaucoma: three-year prospective randomized clinical trial.[see comment]. *Journal of Cataract & Refractive Surgery* 2004, **30**(10):2050-7. *(Guideline Ref ID: YALVAC2004)*

164. Yarangumeli A, Gureser S, Koz OG, Elhan AH, Kural G. Viscocanalostomy versus trabeculectomy in patients with bilateral high-tension glaucoma. *International Ophthalmology* 2005, **25**(4):207-13. *(Guideline Ref ID: YARANGUMELI2005)*

165. Zadok D, Zadok J, Turetz J, Krakowski D, Nemet P. Intraoperative mitomycin versus postoperative 5-fluorouracil in primary glaucoma filtering surgery. *Annals of Ophthalmology Glaucoma* 1995, **27**(6):336-40. *(Guideline Ref ID: ZADOK1995)*

166. Zhou Z, Althin R, Sforzolini BS, Dhawan R. Persistency and treatment failure in newly diagnosed open angle glaucoma patients in the United Kingdom. *British Journal of Ophthalmology* 2004, **88**(11):1391-4. *(Guideline Ref ID: ZHOU2004)*