National Collaborating Centre for Acute Care

Glaucoma

Diagnosis and management of chronic open angle glaucoma and ocular hypertension

METHODS, EVIDENCE & GUIDANCE

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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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APPENDICES

Appendices can be found in a separate document on the NICE website www.nice.org.uk

Guideline Development Group membership and Acknowledgments

Guideline Development Group

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> NCC-AC

Karen Head, Caroline Lawson, Kamsha Maharaj, David Wonderling

> Expert Advisors

Professor Stephen Vernon, Dr. Jofre-Bonet, Dr Jennifer Burr, Dr Steven Kymes, Ms Iris Gordon, Dr Susan Charman

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.

Mr Peter Robb (Chair)	Consultant ENT Surgeon, Epsom and St Helier University Hospitals and The Royal Surrey County Hospital NHS Trusts
Mr John Seddon	Lay member
Mr Mike Baldwin	Head of Health Technology Appraisals, Sanofi-Aventis
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Stakeholder Involvement

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
Connecting for Health
Conwy & Denbighshire NHS Trust
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Department of Health
Department of Health, Social Security and Public Safety of Northern Ireland
Derbyshire Mental Health Services NHS Trust
Dudley Group of Hospitals NHS Trust, The
East & North Herts PCT & West Herts PCT
Federation of Ophthalmic & Dispensing Opticians (FODO)
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 person'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 GPs.
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 evidence A generic term to describe methods used for summarising (comparing 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's peripheral anterior chamber depth assessment	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 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 (NCC-AC). The centre is 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.

On the 1st April 2009 the NCC-AC merged with three other NCCs (Primary Care, Chronic Conditions and Nursing and Supportive Care) to form the National Clinical Guidelines Centre for Acute and Chronic Conditions (NCGC-ACC).

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

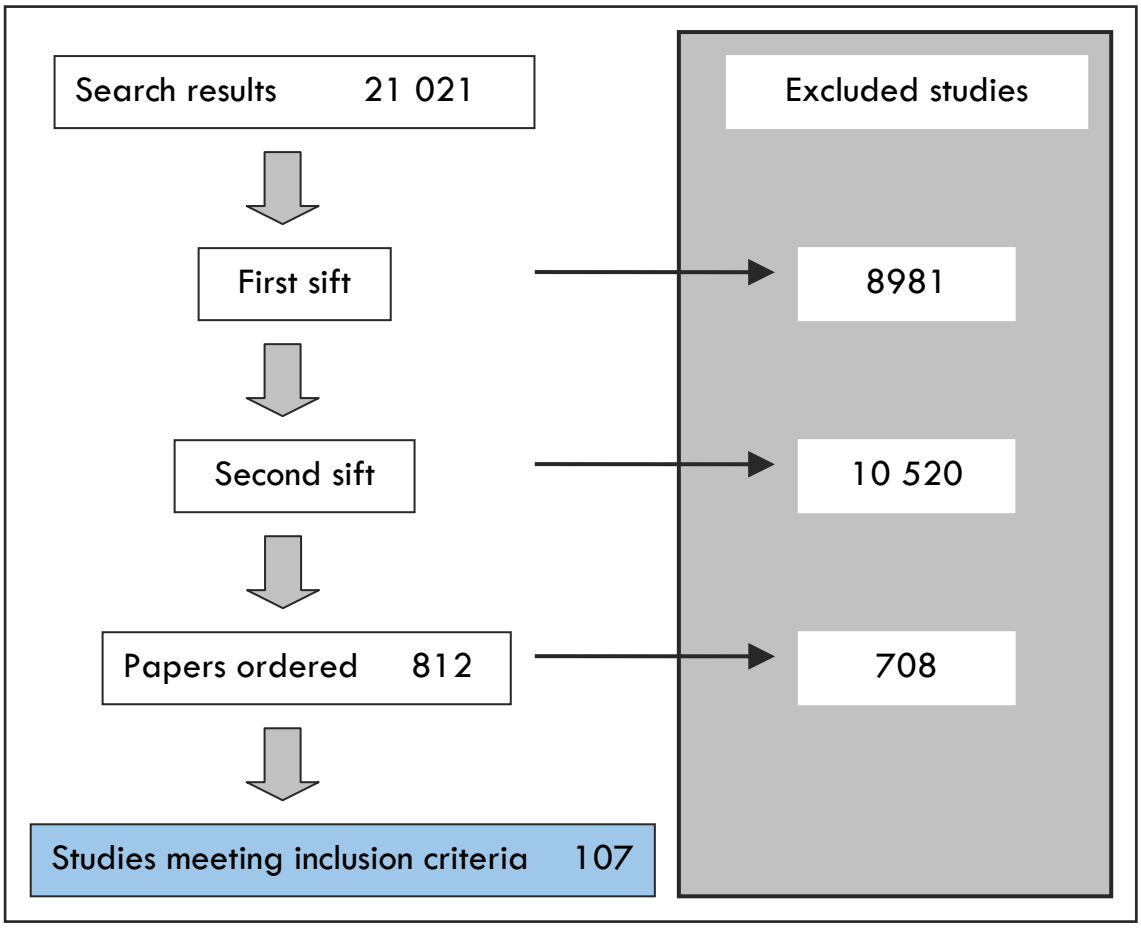
We obtained published economic evidence from a systematic search of the following databases:

- 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
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'

Level of evidence	Type of evidence
(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:

- IOP 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. 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. 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 visual field**
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 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. Implementation support: W, X, Y, Z)

➢ Monitor at regular intervals people with COAG according to their risk of progression to sight loss as illustrated by 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 in 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.*
[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 if IOP check only following treatment change.*

(Selection criteria: A, B, E. 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 by 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 (mmHg)	**>21 to 25**	**>25 tp 32**	**>21 to 25**	**>25 to 32**	**>21 to 25**	**>25 to 32**	**>32**
Age (years) [a]	**Any**	**Any**	**Any**	**Treat until 60**	**Treat until 65**	**Treat until 80**	**Any**
Treatment	No Treatment	No Treatment	No Treatment	BB [b]	PGA	PGA	PGA

[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 timescale. 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.*
The use of age thresholds is considered appropriate only where vision is currently normal (OHT with or without suspicion of COAG) and the treatment is purely preventative. Under such circumstances the threat to a person's sighted lifetime is considered negligible. In the event of COAG developing in such a person then the treatment is recommended.
[b] *If beta-blockers (BB) are contraindicated offer a prostaglandin analogue (PGA).*

(Selection criteria: A, B, C, E. 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. Offer them information on the risks and benefits associated with surgery.

**At the time of publication (April 2009), MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*

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

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

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

➢ People with a diagnosis of OHT, suspected COAG or 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. 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 COAG in the early stages and OHT and suspected COAG are symptomless
- that most people treated for COAG will not go blind
- 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
- 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 occlusion and devices) and hygiene (storage)
- the need for regular monitoring as specified by the healthcare professional
- methods of investigation during assessment
- how long each appointment is likely to take and whether the person will need any help to attend (for example, driving soon after pupil dilatation would be inadvisable)
- support groups
- compliance aids (such as dispensers) available from their GP or community pharmacist
- Letter of Vision Impairment (LVI), Referral of Vision Impairment (RVI) and Certificate of Vision 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:

- IOP 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 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 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.

➢ 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.

➢ 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 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 visual field**
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 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 to 5 years (depending on perceived risk of conversion), or before if confirmed normal, 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 by 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 in 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.*
[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 if IOP check only following treatment change.*

➢ 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 by 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 (mmHg)	>21 to 25	>25 to 32	>21 to 25	>25 to 32	>21 to 25	>25 to 32	>32
Age (years) [a]	Any	Any	Any	Treat until 60	Treat until 65	Treat until 80	Any
Treatment	No Treatment	No Treatment	No Treatment	BB [b]	PGA	PGA	PGA

[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.*
The use of age threshold is considered appropriate only where vision is currently normal (OHT with or without suspicion of COAG) and the treatment is purely preventative. Under such circumstances the threat to a person's sighted lifetime is considered negligible. In the event of COAG developing in such a person then treatment is recommended.
[b] *If beta-blockers (BB) are contraindicated offer a prostaglandin analogue (PGA)*

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

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

➢ 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.

➢ 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.

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

3.2.4 Recommendations on treatment for patients with COAG

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

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

➢ Offer people with advanced COAG surgery with pharmacological augmentation (MMC or 5FU)* as indicated. Offer them information on the risks and benefits associated with surgery.

**At the time of publication (April 2009), MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*

➢ Offer people who present with advanced 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 5-FU)*as indicated

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

**At the time of publication (April 2009, MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*

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

**At the time of publication (April 2009), MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*

➢ 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 5-FU)* as indicated or laser trabeculoplasty.

**At the time of publication (April 2009, MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*

➢ 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 cyclodiode laser treatment.

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

- pharmacological treatment (a prostaglandin analogues, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP
- laser trabeculoplasty or cyclodiode 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 repeatable visual field defect, or both to a consultant ophthalmologist for consideration of a definitive diagnosis 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
- CCT measurement.

➢ People with a diagnosis of OHT, suspected COAG or 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 sight 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
- 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:

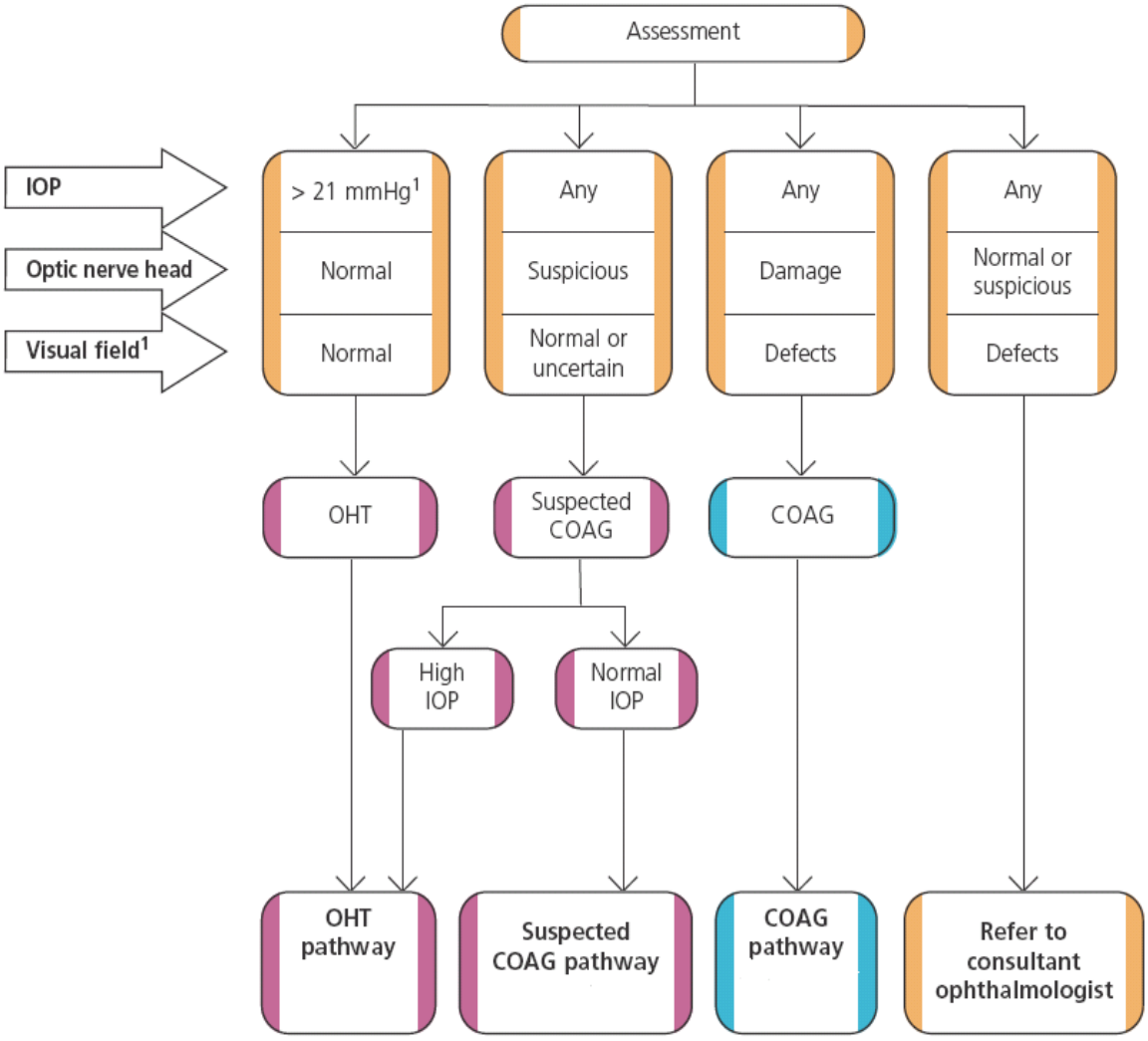
- their specific condition (OHT, suspected COAG and COAG), its life-long implications and their prognosis for retention of sight
- that COAG in the early stages and OHT and suspected COAG are symptomless
- that most people treated for COAG will not go blind
- that once lost, sight cannot be recovered
- that glaucoma can run in families and that family members may wish to be tested for the disease
- 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

- how long each appointment is likely to take and whether the person will need any help to attend (for example, driving soon after pupil dilatation would be inadvisable)
- support groups
- compliance aids (such as dispensers) available from their GP or community pharmacist
- Letter of Vision Impairment (LVI), Referral of Vision Impaired (RVI) and Certificate of Vision Impairment (CVI) registration
- Driver and Vehicle Licensing Agency (DVLA) regulations.

3.3 Algorithms

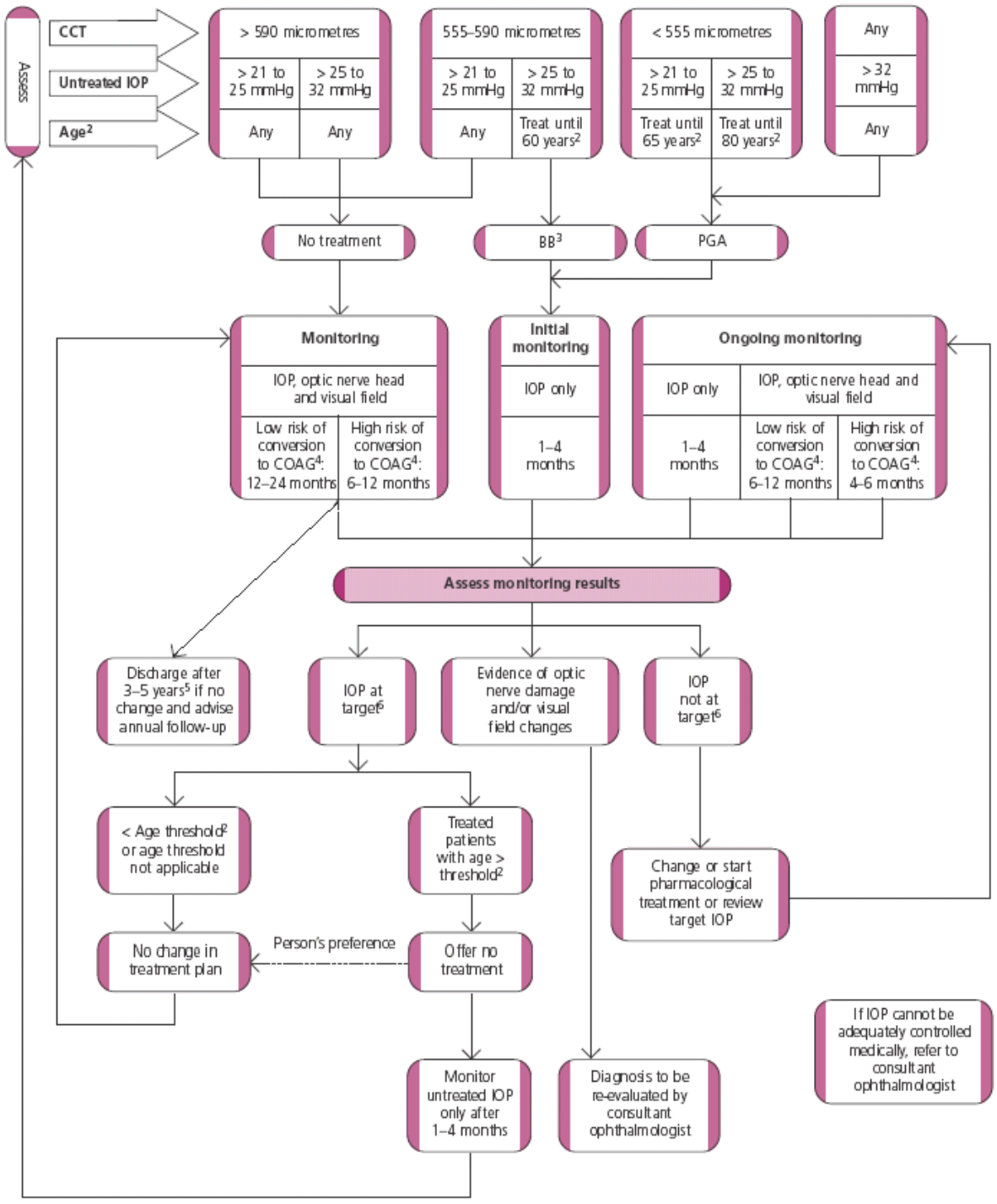
The GDG developed a care pathway algorithm according to the recommendations, where decision points are represented with boxes linked with arrows

ALGORITHM 1 – DIAGNOSIS



[1] Repeatable.

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



[2] Above the age threshold as indicated for each combination of parameters, the optimal treatment strategy changes to no treatment. The use of age thresholds is considered appropriate only where vision is currently normal (OHT with or without suspicion of COAG) and the treatment is purely preventative. Under such circumstances the threat to a person's sighted lifetime is considered negligible. In the event of COAG developing in such a person then treatment is recommended.

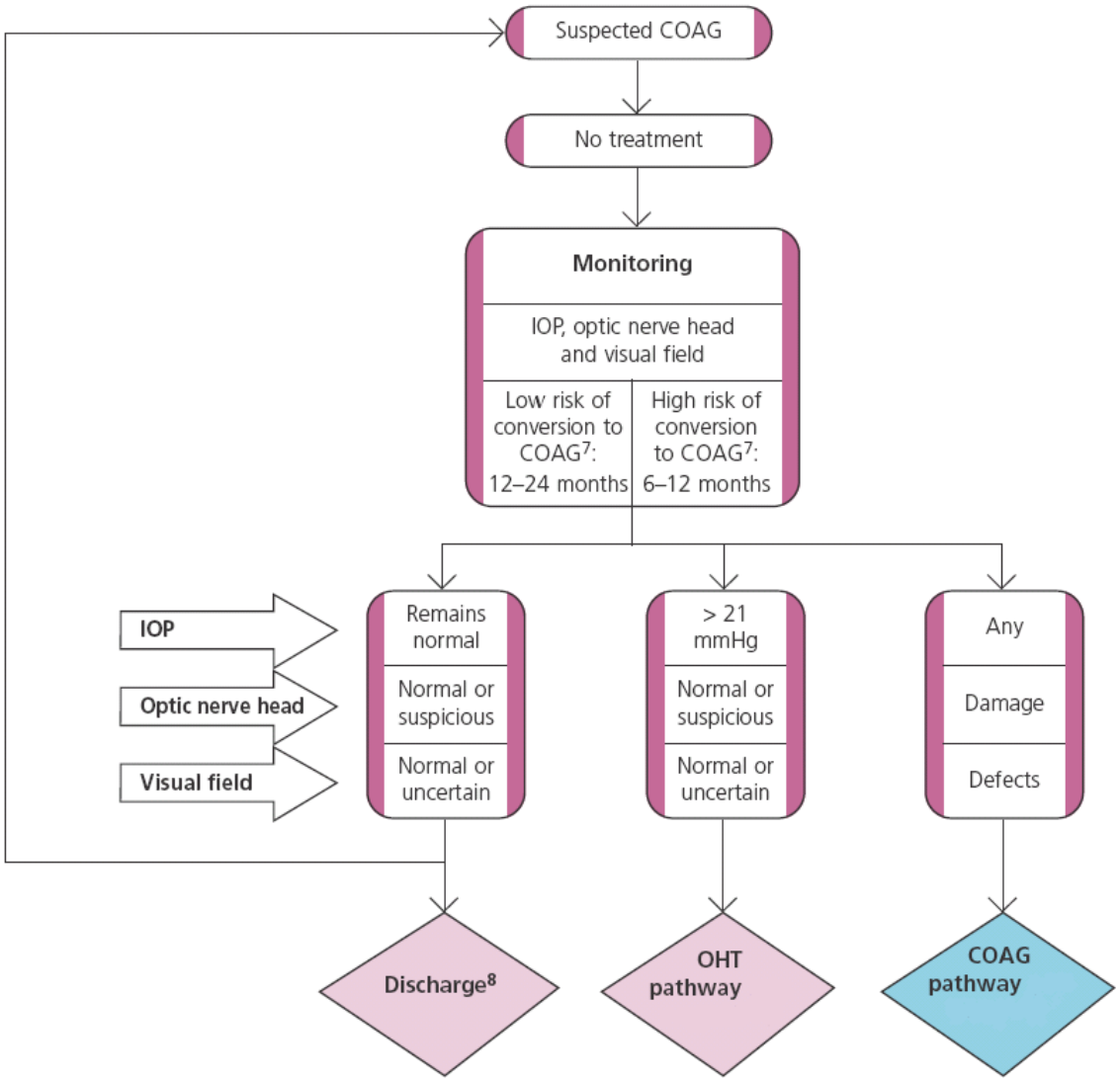
[3] If BB are contraindicated offer a PGA.

[4] To be clinically judged in terms of age, IOP, CCT, and appearance and size of optic nerve head.

[5] Or before if confirmed normal.

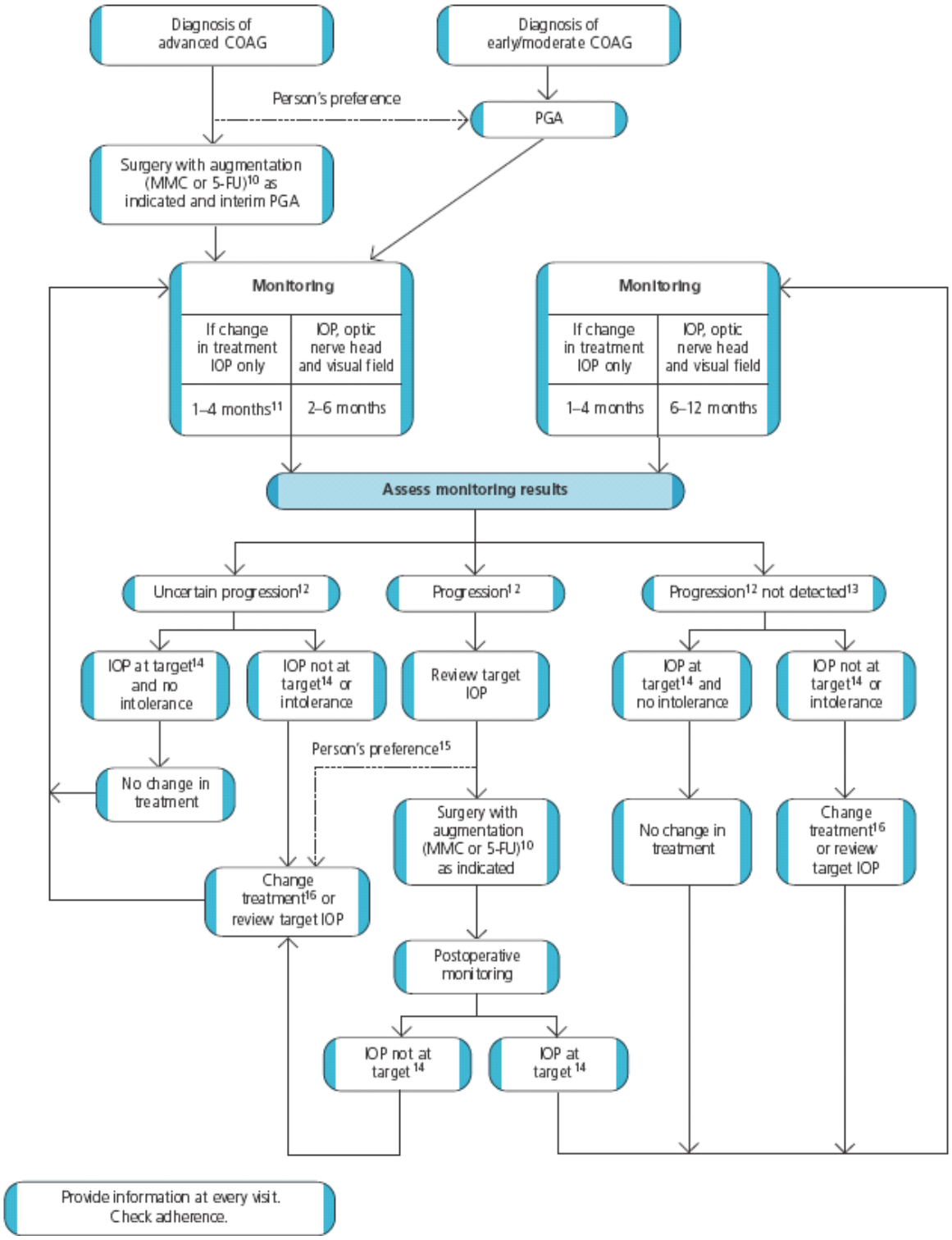
[6] Target IOP = see 'Terms and abbreviations' on page 4.

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



[7] To be clinically judged in terms of age, IOP, CCT, appearance and size of optic nerve head.
[8] After 3–5 years if no change or before if confirmed normal, and advise annual follow-up with primary care optometrist.

ALGORITHM 4 – COAG PATHWAY



[10] At the time of publication (April 2009), MMC and 5-FU did not have UK marketing authorisation for this indication. 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.
[11] Or 1–2 months if there is progression or uncertain progression.
[12] Progression = increased optic nerve damage and/or visual field change confirmed by repeated test where clinically appropriate.
[13] Or not assessed if IOP check only following treatment change.
[14] Target IOP = see 'Terms and abbreviations' on page 4.
[15] When the person prefers not to have surgery or is not suitable for surgery, offer pharmacological treatment or laser treatment.
[16] Pharmacological treatment (re-start if after surgery), surgery with augmentation (MMC or 5-FU) as indicated or laser as appropriate.

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	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	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	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	Not calculated

(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	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 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 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.**
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.**
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 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 visual field
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 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

Maintaining IOP control with reduction of risk for conversion to

clinical benefits and harms	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), or before if confirmed normal, 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 in 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.
[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 if IOP check only following treatment change.

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 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.

➢ 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.

➢ 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 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 visual field**
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 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 to 5 years (depending on perceived risk of conversion), or before if confirmed normal, 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 by 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 in 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.
[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 if IOP check only following treatment change.

➢ 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. 121						
Prostaglandin analogues (PGA)	Yes p. 123						
Topical Carbonic Anhydrase Inhibitors (CAI)	Yes p. 130	Yes p. 127					
Sympathomimetics (Symp)	Yes p. 132	Yes p. 127	No				
Miotics	Yes p. 134	No	No	No			
Combination (fixed or separate) (Comb)	Yes p. 140, 142, 148	Yes p. 135, 137, 143, 145	No	No	No	No	
No treatment (NT)	Yes p. 117	Yes p. 122	Yes P. 129	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

Neither prostaglandin analogues nor beta-blockers are cost-effective for this group (see

Table 7-37 and
(a) *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.	Not reported

(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	Not reported

(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	Not reported
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	Not reported
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	Not reported

(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	Not reported
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	Not reported

(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 (mmHg)	>21 to 25	>25 to 32	>21 to 25	>25 to 32	>21 to 25	>25 to 32	>32
Age (years) [a]	Any	Any	Any	Treat until 60	Treat until 65	Treat until 80	Any
Treatment	No Treatment	No Treatment	No Treatment	BB [b]	PGA	PGA	PGA

[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.
The use of age threshold is considered appropriate only where vision is currently normal (OHT with or without suspicion of COAG) and the treatment is purely preventative. Under such circumstances the threat to a person's sighted lifetime is considered negligible. In the event of COAG developing in such a person then treatment is recommended.
[b] If beta-blockers (BB) are contraindicated offer a prostaglandin analogue (PGA)

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

Both beta-blockers and prostaglandin analogues are effective at

benefits and harms	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 and an allergy to preservatives only if they are at high risk of conversion to COAG (IOP more than 25 and up to 32 mmHg and CCT less than 555 micrometres; or IOP more than 32 mmHg).**
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 by 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 (mmHg)	>21 to 25	>25 to 32	>21 to 25	>25 to 32	>21 to 25	>25 to 32	>32
Age (years) [a]	Any	Any	Any	Treat until 60	Treat until 65	Treat until 80	Any
Treatment	No Treatment	No Treatment	No Treatment	BB [b]	PGA	PGA	PGA

[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.*
The use of age threshold is considered appropriate only where vision is currently normal (OHT with or without suspicion of COAG) and the treatment is purely preventative. Under such circumstances the threat to a person's sighted lifetime is considered negligible. In the event of COAG developing in such a person then treatment is recommended.
[b] *If beta-blockers (BB) are contraindicated offer a prostaglandin analogue (PGA)*

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

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

➢ 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.

➢ 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.

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

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	PGA	CAI	Symp.	Miotics	Comb.	Any pharm.	Any	ALT	SLT	Trab.	N-P Surg.	Surg + Aug.	Laser irid (PDS)	NT
BB	Yes 162														
PGA	Yes 164														
CAI	Yes 170	Yes 167													
Symp.	Yes 172	Yes 168	No												
Miotics	Yes 174	No	No	No											
Comb.	Yes 180 182 188	Yes 1751 7718 3185	No	No	No	No									
Any pharm.	No	No	No	No	No	No									
Any (pharm, surg or laser)	No	No	No	No	No	No	Yes 195								
ALT	No	No	No	No	No	No	Yes* 194	No							
SLT	No	Yes* 194	No	No	No	No	No	No	Yes 192						
Trab.	Yes 199	Yes 199	No	No	No	No	Yes 198	No	Yes 196	No					
N-P Surg.	No	No	No	No	No	No	No	No	No	No	Yes 206	Yes 205			
Surg + Aug.	No	No	No	No	No	No	No	No	No.	No	Yes 201	Yes 208	Yes 203		
Laser Irid (PDS)															
NT	Yes 161	Yes 163	Yes 169	No.	No	No	No.	Yes 111	No	No	No	No	No	No	

Numbers relate to page numbers. 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	Not reported

(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.	Not reported

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	Not reported

(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	Not reported
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	Not reported
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	Not reported

(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	Not reported
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	Not reported

(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)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
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
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)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
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)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
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. Offer them information on the risks and benefits associated with surgery.** **At the time of publication (April 2009, MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*
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 advanced COAG surgery with pharmacological augmentation (MMC or 5FU)* as indicated. Offer them information on the risks and benefits associated with surgery.** **At the time of publication (April 2009, MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*
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.** **At the time of publication (April 2009, MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*
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 advanced 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.** **At the time of publication (April 2009, MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*
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:** • **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 cyclodiode laser treatment.**
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 cyclodiode 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.

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

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

➢ Offer people with advanced COAG surgery with pharmacological augmentation (MMC or 5FU)* as indicated. Offer them information on the risks and benefits associated with surgery.

**At the time of publication (April 2009, MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*

➢ Offer people who present with advanced 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 5-FU)*as indicated

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

**At the time of publication (April 2009, MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*

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

**At the time of publication (April 2009, MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*

➢ 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 5-FU)* as indicated or laser trabeculoplasty.

**At the time of publication (April 2009, MMC and 5-FU did not have UK marketing authorisation for this indication. 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.*

➢ 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 cyclodiode laser treatment.

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

- pharmacological treatment (a prostaglandin analogues, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP
- laser trabeculoplasty or cyclodiode 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. 225					
Certified optometrist with specialist interest	Yes p. 226	No				
Non specialist optometrist	Yes p. 222	Yes p. 223	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. 229	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 interest	Non specialist optometrist	Orthoptist with specialist interest + training	Nurse with specialist interest + training

Matrix 3: Effectiveness of treatment by different healthcare professionals

General ophthalmologist						
Specialist ophthalmologist	Yes p. 236					
Certified optometrist with specialist interest	No	Yes p. 238				
Non specialist optometrist	Yes p. 234	Yes p. 236	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	
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)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
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 repeatable visual field defect, or both, 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** • **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** • **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)
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)
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 a diagnosis of OHT, suspected COAG or 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 repeatable visual field defect, or both to a consultant ophthalmologist for consideration of a definitive diagnosis 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
- CCT measurement.

➢ People with a diagnosis of OHT, suspected COAG or 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 sight 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
- 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 COAG in the early stages and OHT and suspected COAG are symptomless** • **that most people treated for COAG will not go blind** • **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** • **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** • **how long each appointment is likely to take and whether the person will need any help to attend (for example, driving soon after pupil dilatation would be inadvisable)** • **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 Vision 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 COAG in the early stages and OHT and suspected COAG are symptomless
- that most people treated for COAG will not go blind
- 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
- 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
- how long each appointment is likely to take and whether the person will need any help to attend (for example, driving soon after pupil dilatation would be inadvisable)
- support groups
- compliance aids (such as dispensers) available from their GP or community pharmacist
- Letter of Vision Impairment (LVI), Referral of Vision Impaired (RVI) and Certificate of Vision 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.

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)*